The necessity and benefits of taking a One Health approach in AMR surveillance and mitigation measures

P.E. Verweij
Radboudumc-CWZ Center of Expertise for Mycology
Center for Infectious Diseases Research, Diagnostics and Laboratory Surveillance

WAGENINGEN
UNIVERSITY & RESEARCH

Center for Infectious Diseases
Radboudumc

2007
First case series
Azole R IA

"Houston we have a problem……"

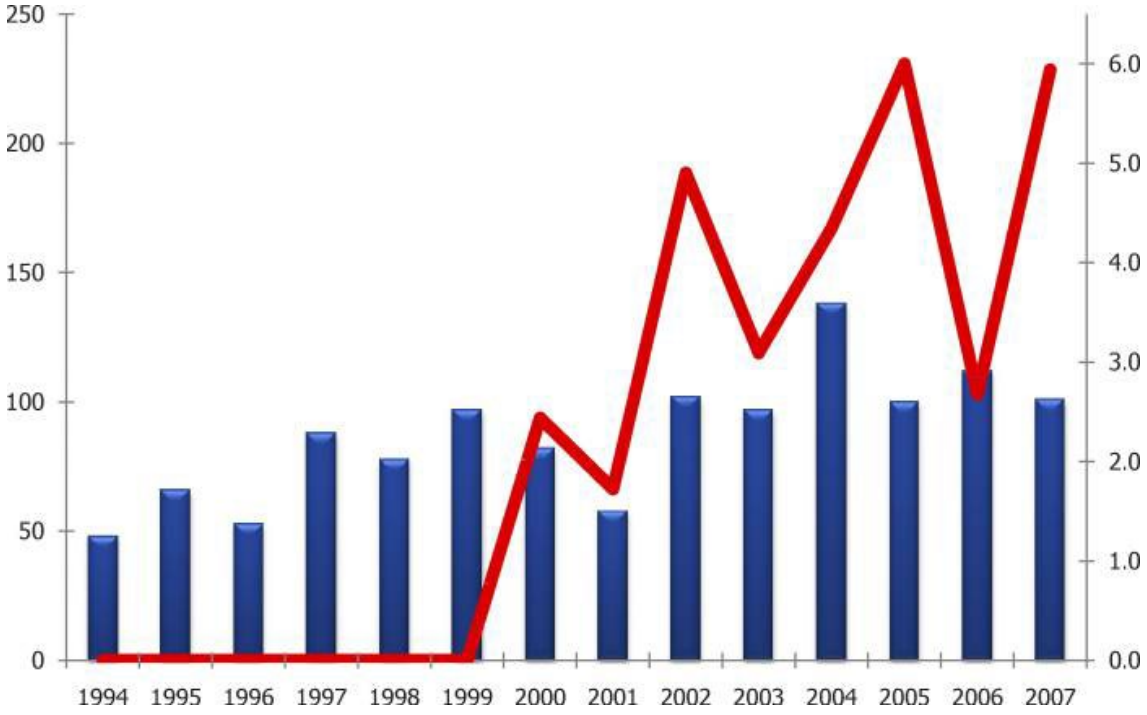
Table 1. Characteristics of Nine Patients from Whom *A. fumigatus* Resistant to Multiple Triazoles Was Cultured.

Sex	Yr of Age	Underlying Disease	Date of Isolation	Site of Isolation	Disease Classification*	Previous Azole Exposure	Treatment	Outcome
Male†	15	X-linked chronic granulomatous disease	April 4, 2002	Sputum	Breakthrough invasive pulmonary aspergillosis, proven	Prophylaxis with itraconazole (for 6 yr)	Voriconazole (high-dose)	Survived
Male	73	None	Dec. 3, 2003	Ear swab	Invasive aspergillosis of mastoid cavity, proven	None	Surgery and topical therapy	Survived
Male	16	Hyper-IgE syndrome	Nov. 19, 2004	Bronchoalveolar-lavage fluid	Breakthrough invasive pulmonary aspergillosis, proven	Treatment with voriconazole (for 2 yr)	Surgery and posaconazole	Survived
Female	76	Pulmonary fibrosis	June 26, 2005	Sputum	Invasive pulmonary aspergillosis, possible	None	Voriconazole	Survived
Male	31	Chronic granulomatous disease	Nov. 1, 2005	Lung aspirate	Breakthrough invasive pulmonary aspergillosis, probable	Prophylaxis with itraconazole (for >10 yr)	Caspofungin and posaconazole	Survived
Female	68	Acute myeloid leukemia	Feb. 14, 2006	Bronchoalveolar-lavage fluid	Disseminated invasive aspergillosis, probable	None	Voriconazole	Died
Female	62	Chronic obstructive pulmonary disease	April 5, 2006	Bronchoalveolar-lavage fluid	Invasive pulmonary aspergillosis, possible	None	Voriconazole, amphotericin B, and posaconazole	Survived
Male	19	Chronic granulomatous disease	April 15, 2006	Bone	Breakthrough aspergillus osteomyelitis, proven	Prophylaxis with itraconazole (for >2 yr)	Voriconazole, caspofungin, and posaconazole	Survived
Male	45	Acute myeloid leukemia and allogeneic hematopoietic stem-cell transplantation	May 11, 2006	Nose swab	Breakthrough aspergillus sinusitis, proven	Prophylaxis with itraconazole (for 4 wk)	Posaconazole	Died

* Diseases were classified according to consensus criteria defined by the European Organisation for Research and Treatment of Cancer and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.
† Information about this patient is from Warris et al.[3]

N Engl J Med 2007;356:1481-3

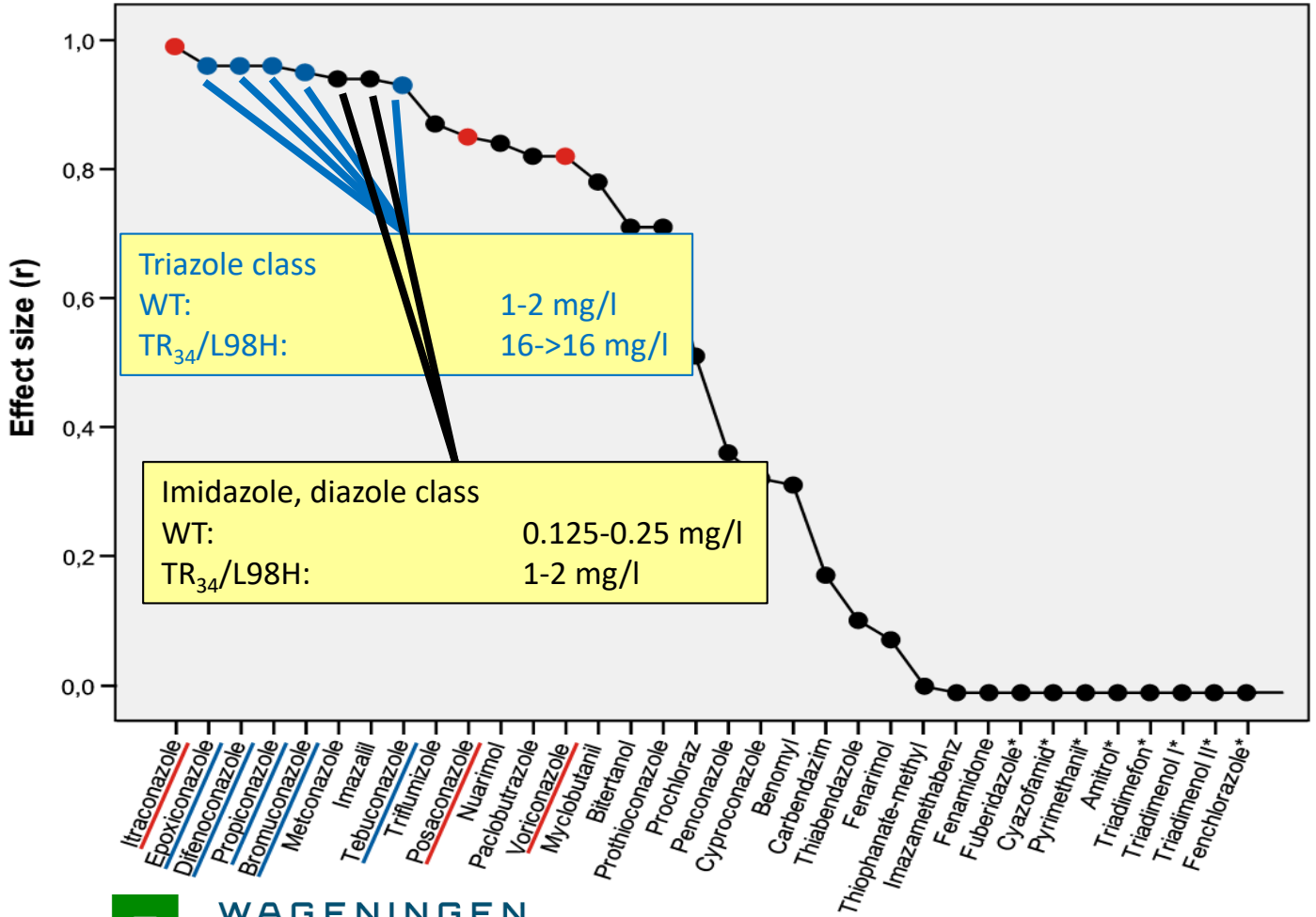
2008 Emergence of TR_{34}



30 of 32 (94%) pts TR_{34}/L98H

PLoS Med 20085:e219

2012
Activity of fungicides against *A. fumigatus*



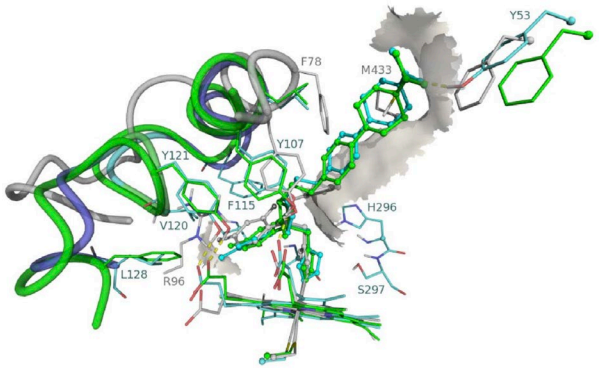
PLoS One 2012;7:e31801

WAGENINGEN UNIVERSITY & RESEARCH

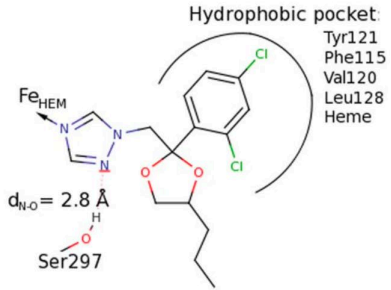
DMIs and medical triazoles

2012
Activity of fungicides against *A. fumigatus*

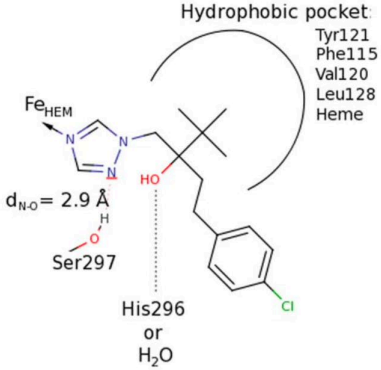
Docking poses of fungicides similar to medical triazoles



Itraconazole
Posaconazole



Voriconazole



Propiconazole
Bromuconazole

Tebuconazole
Epoxiconazole

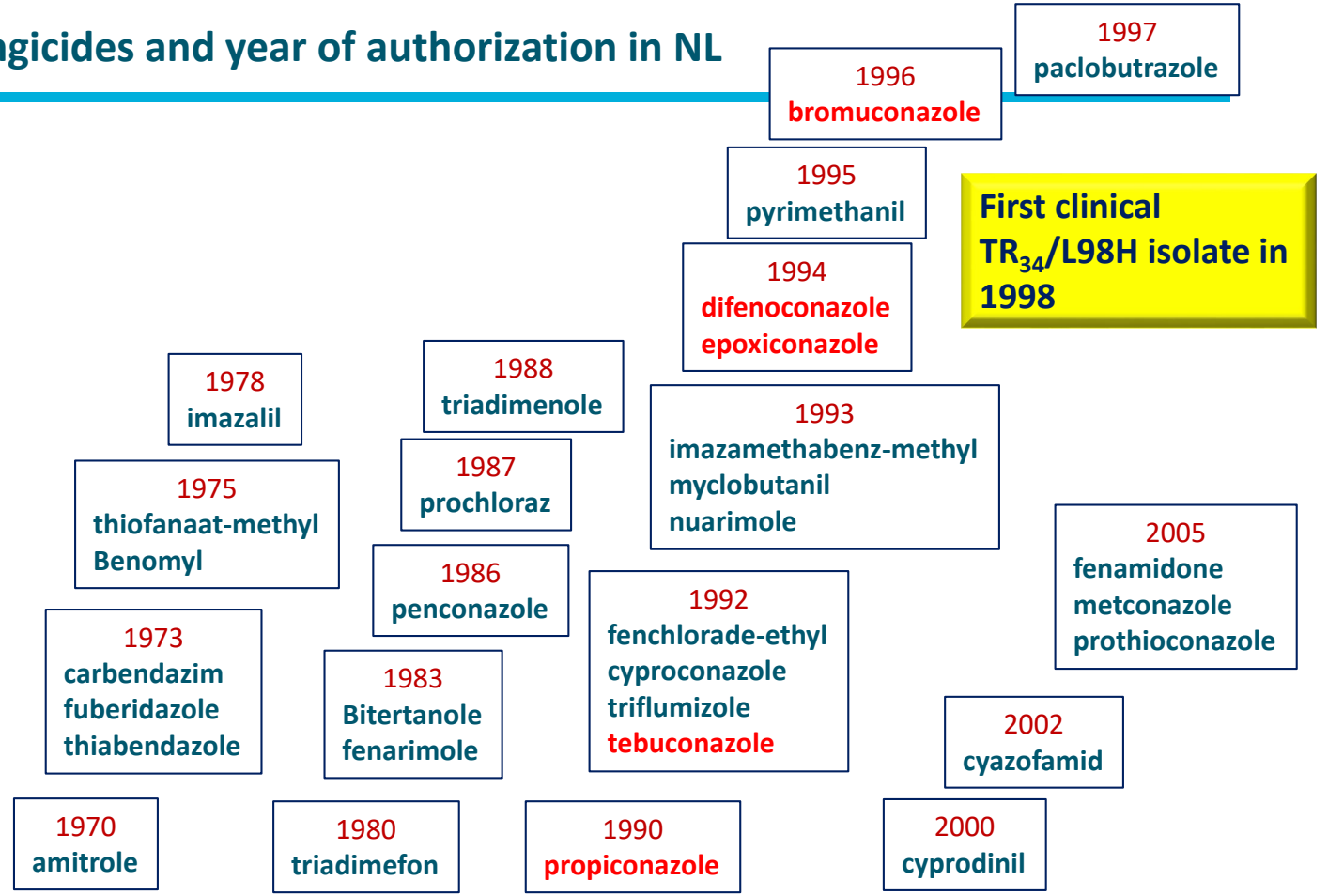
Difenoconazole

PLoS One 2012;7:e31801

Center for Infectious Diseases
Radboudumc

2012
Activity of fungicides against *A. fumigatus*

Fungicides and year of authorization in NL

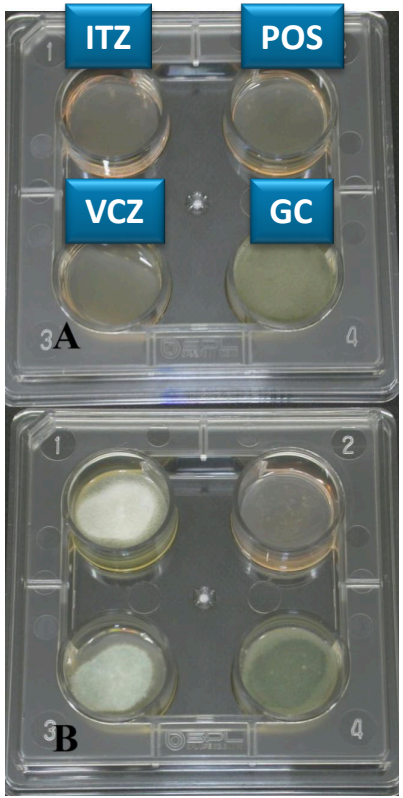


First clinical TR_{34}/L98H isolate in 1998

PLoS One 2012;7:e31801

2015
PCR detection of resistance

VIPcheck

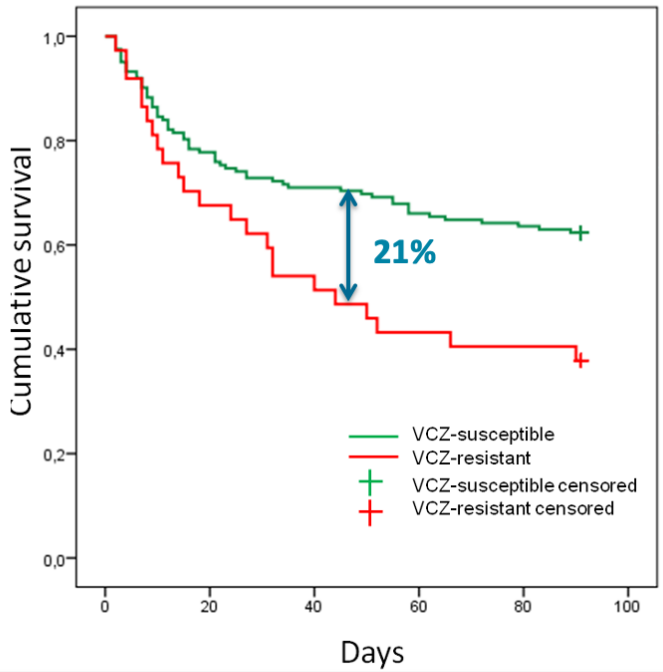


J Clin Microbiol. 2015;53:868-74; Antimicrob Agents Chemother. 2017;61:e01250-17.

Center for Infectious Diseases
Radboudumc

2019
Mortality IA S versus R
Clin Infect Dis

Overall mortality in vori R versus vori S (hospital wide study)



Mortality

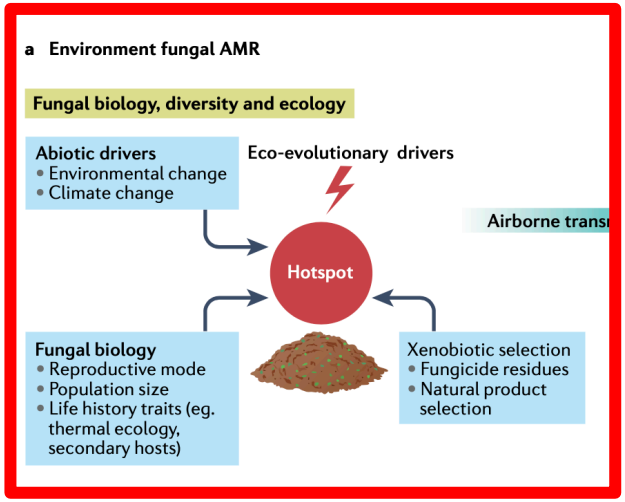
Day 42

VCZ-S 28%
VCZ-R 49%
p=0.017

Day 90

VCZ-S 37%
VCZ-R 62%
p=0.0038

P. Lestrade et al. Clin Infect Dis 2019;68:1463–1471.



A. fumigatus **is able to complete its life cycle**

presence of azole residues

Flower bulb waste

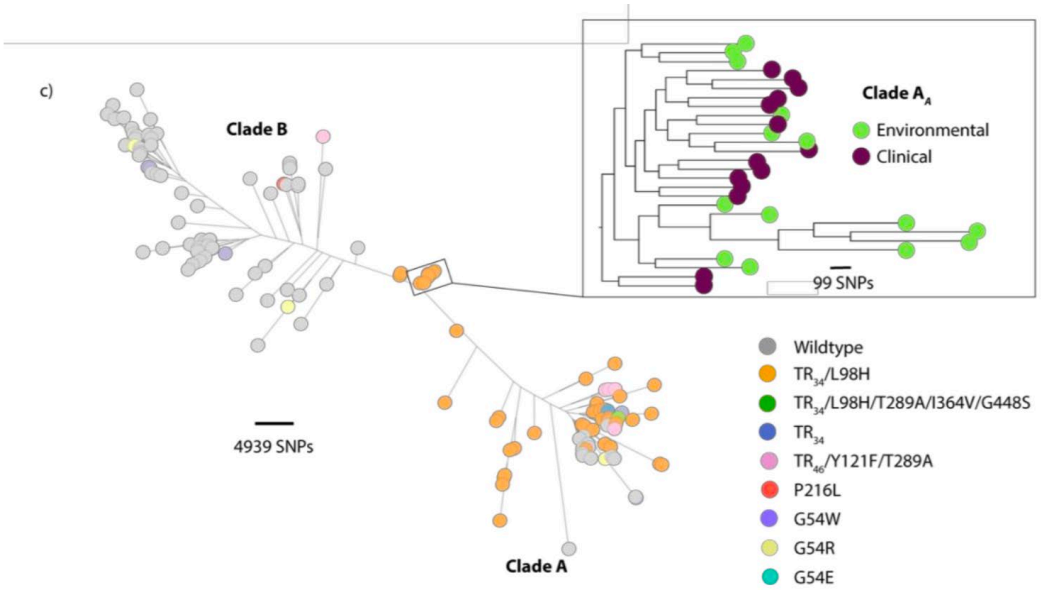
Green waste

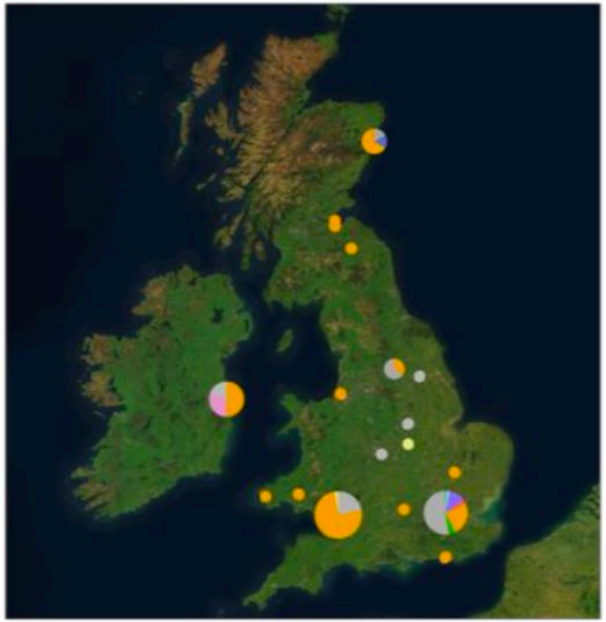
Wood chippings waste

Strawberry waste

Emerg Infect Dis 2019;25:1347-1353.

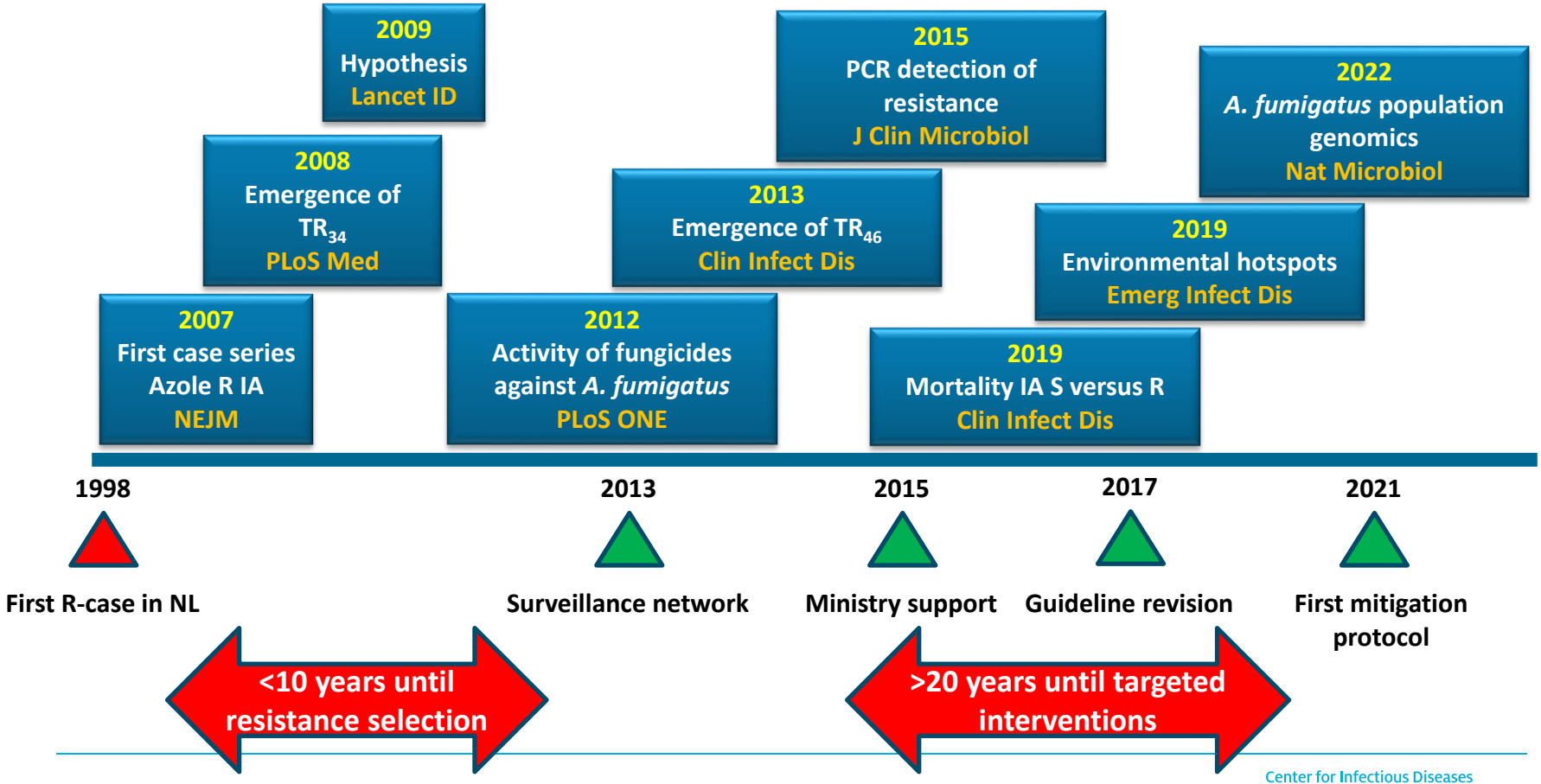
2022
A. fumigatus population genomics



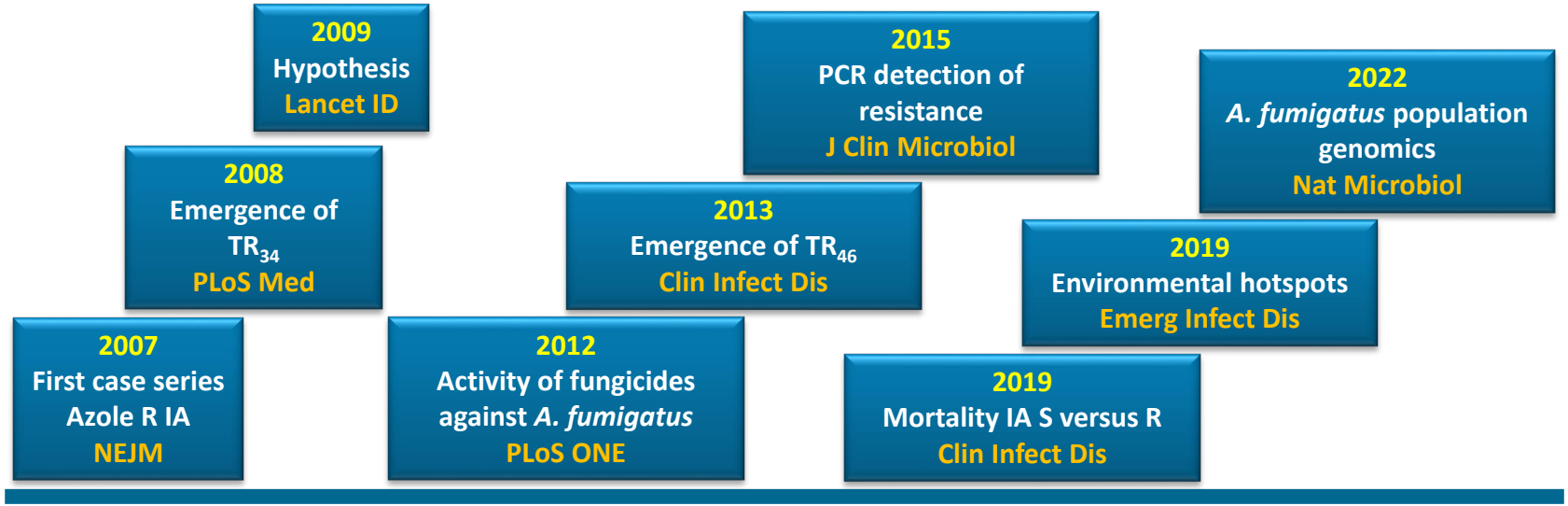


bioRxiv preprint doi: https://doi.org/10.1101/2021.04.07.438821

The Process: Time to actions….



The Process: Challenges



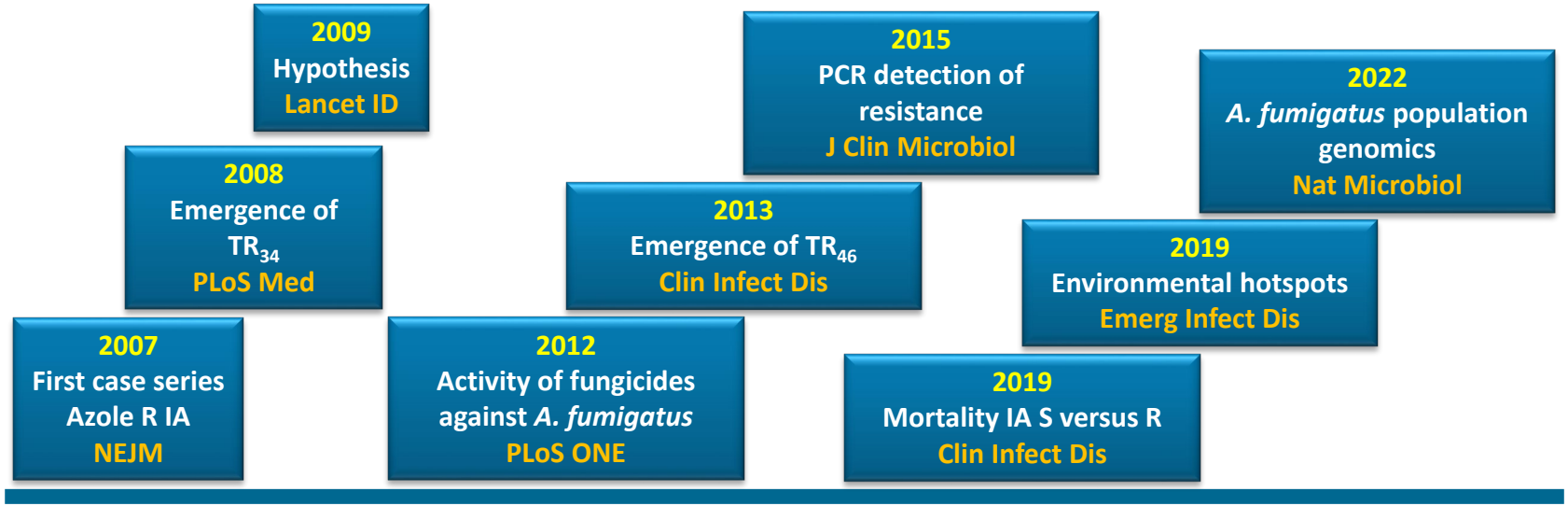
Unbelief

Grant reviewer: I don't believe this

Lancet ID: insufficient evidence

Local problem

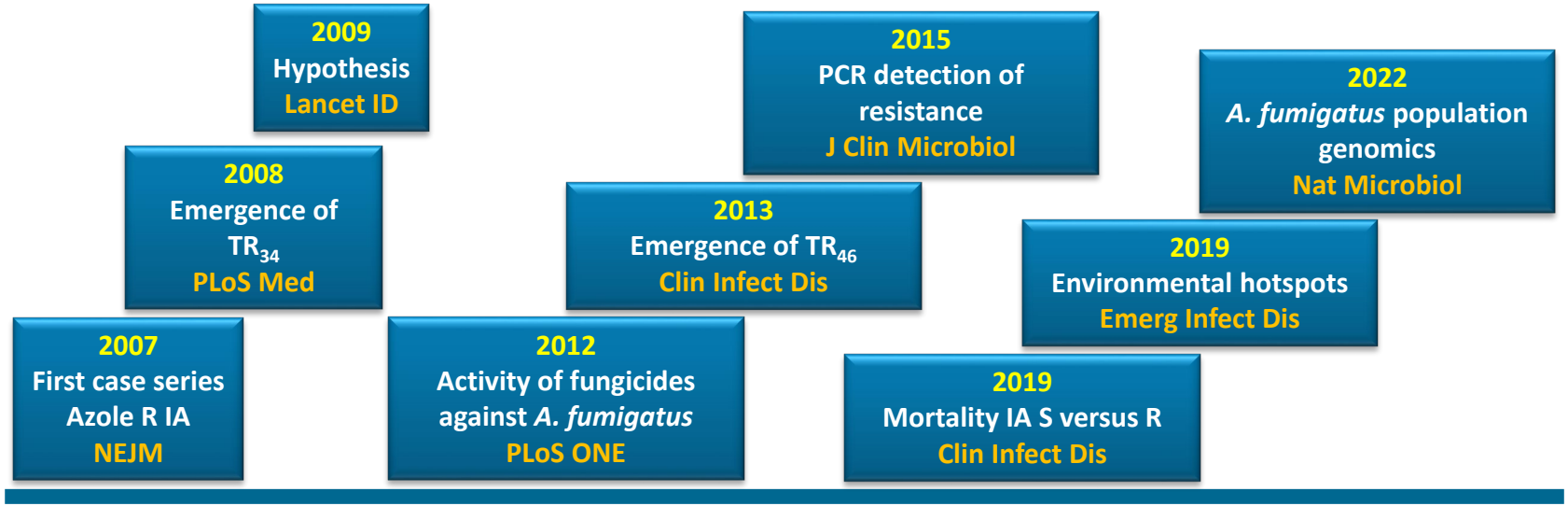
The Process: Challenges



Agricultural partner

***A. fumigatus* is not plant pathogen**

The Process: Challenges

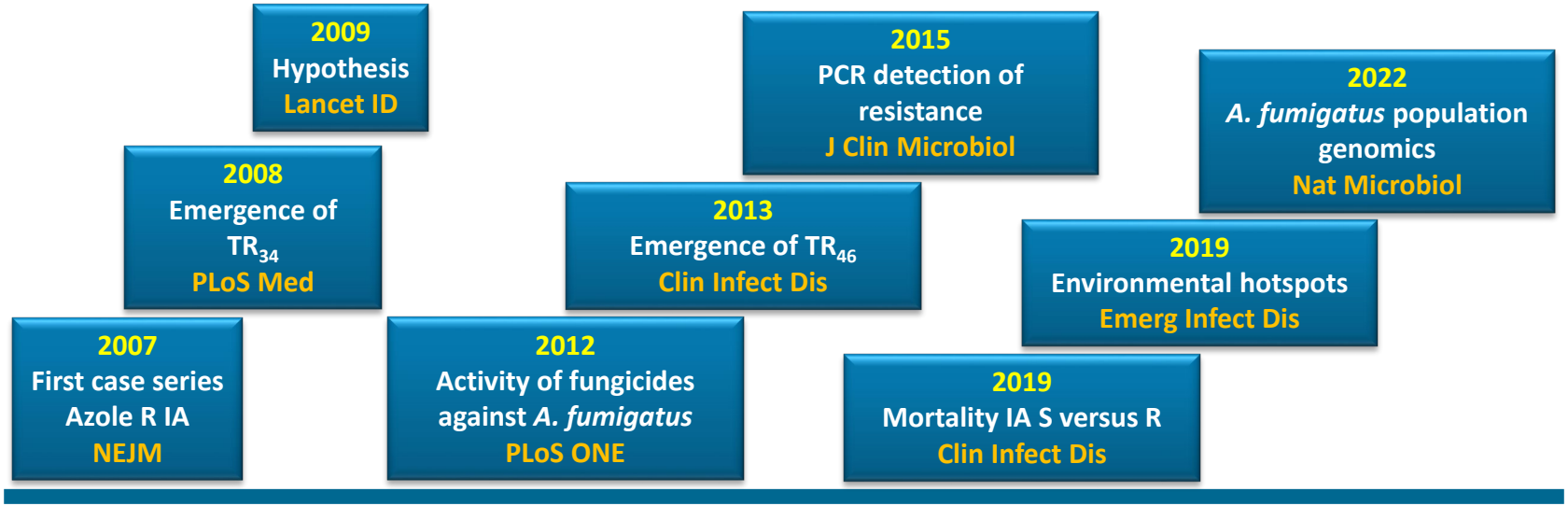


Public health problem?

Invasive mycoses are not a public health problem

Most public health institutes do not have a mycotic branch

The Process: Challenges

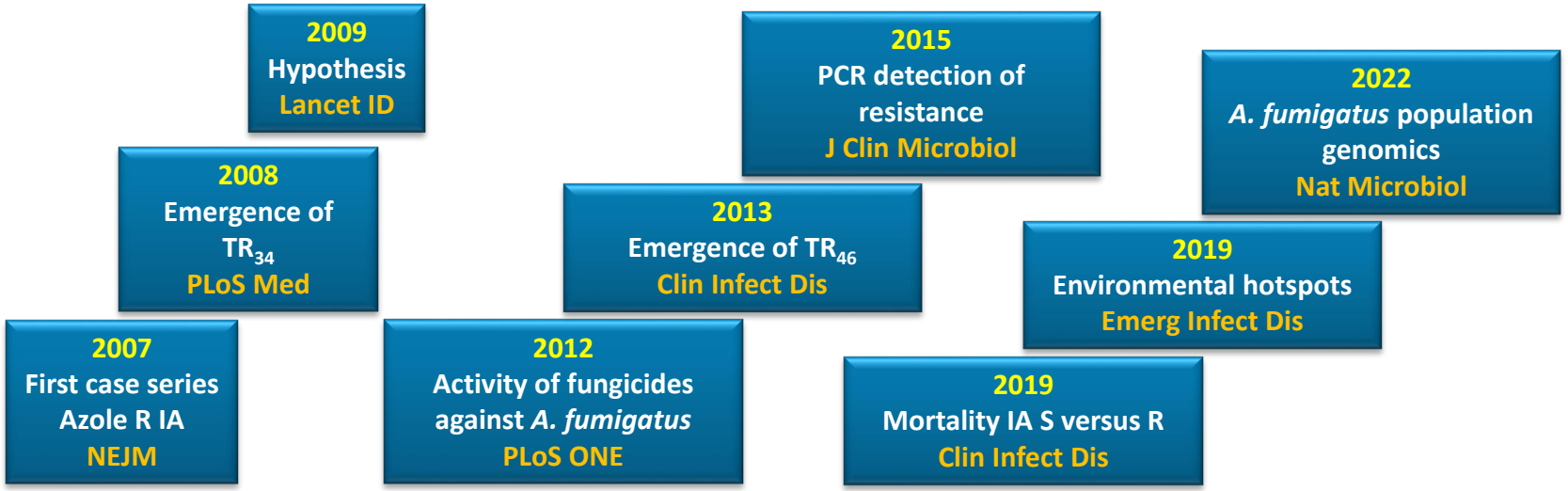


AMR excludes fungal resistance

Low priority **Prioritization in competition with bacterial resistance**

Dutch Medical Research Council 2006-2023: 129 projects ($66.5M)

The Process: Challenges

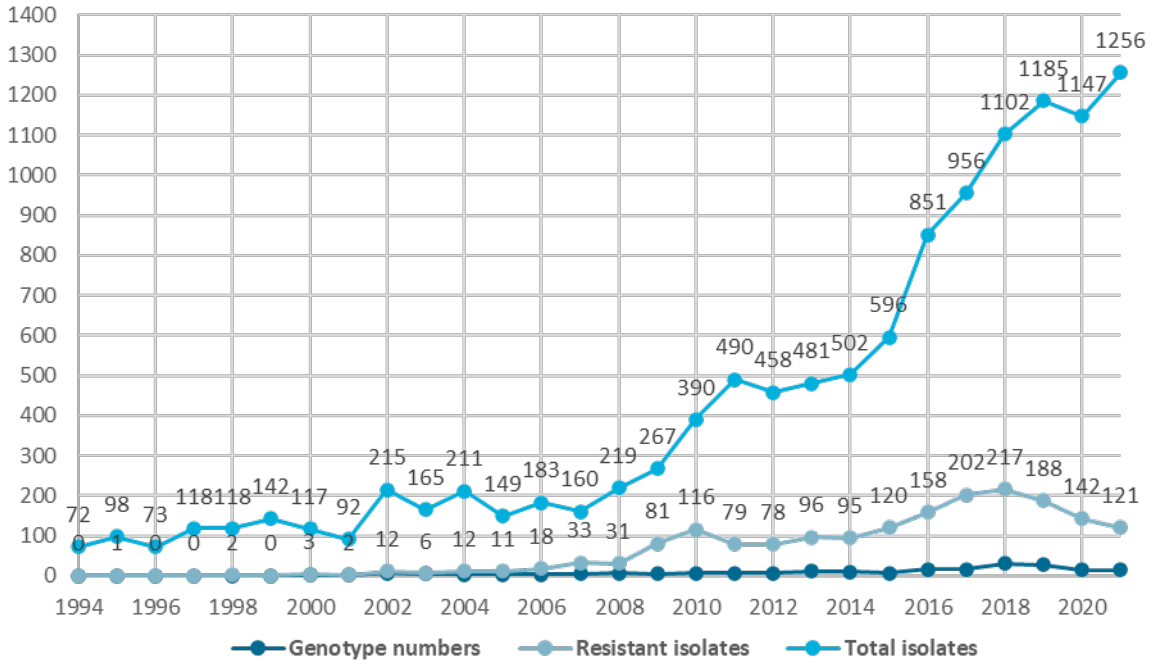


Multiple stakeholders

- Ministry of Health
- Ministry of Agriculture
- Ministry of Infrastructure
- Fungicide authorization board
- Fungicide producers
- Fungicide users
- Medical researchers
- Agricultural researchers

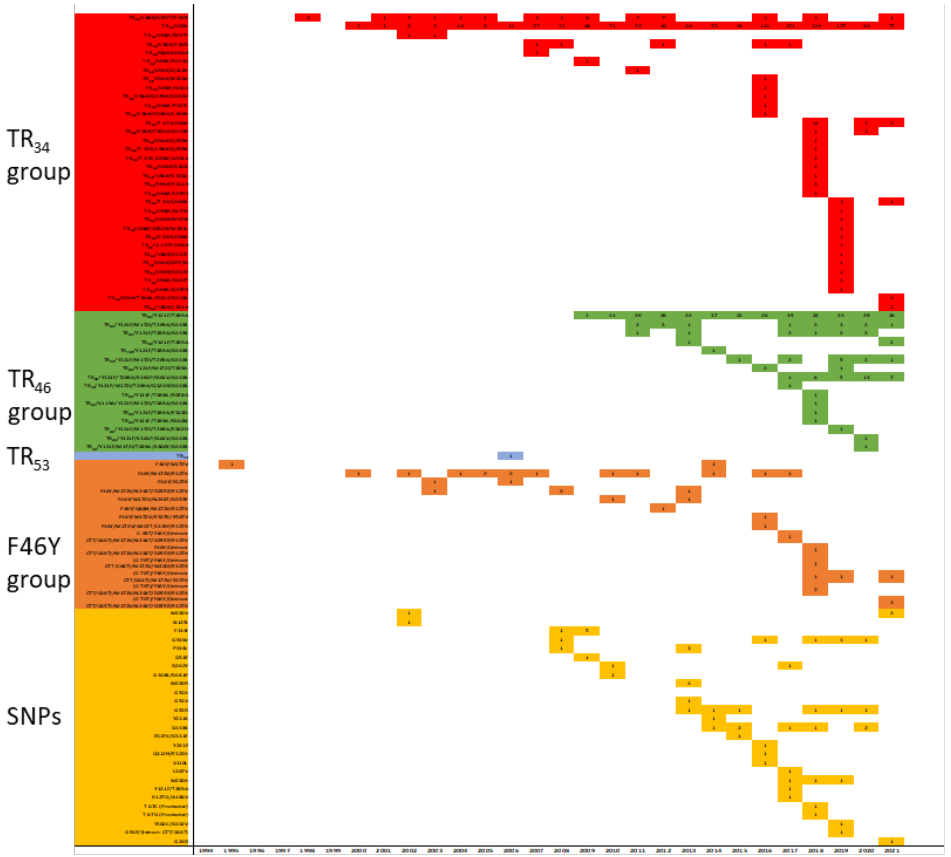
28 years of azole resistance selection: new challenges

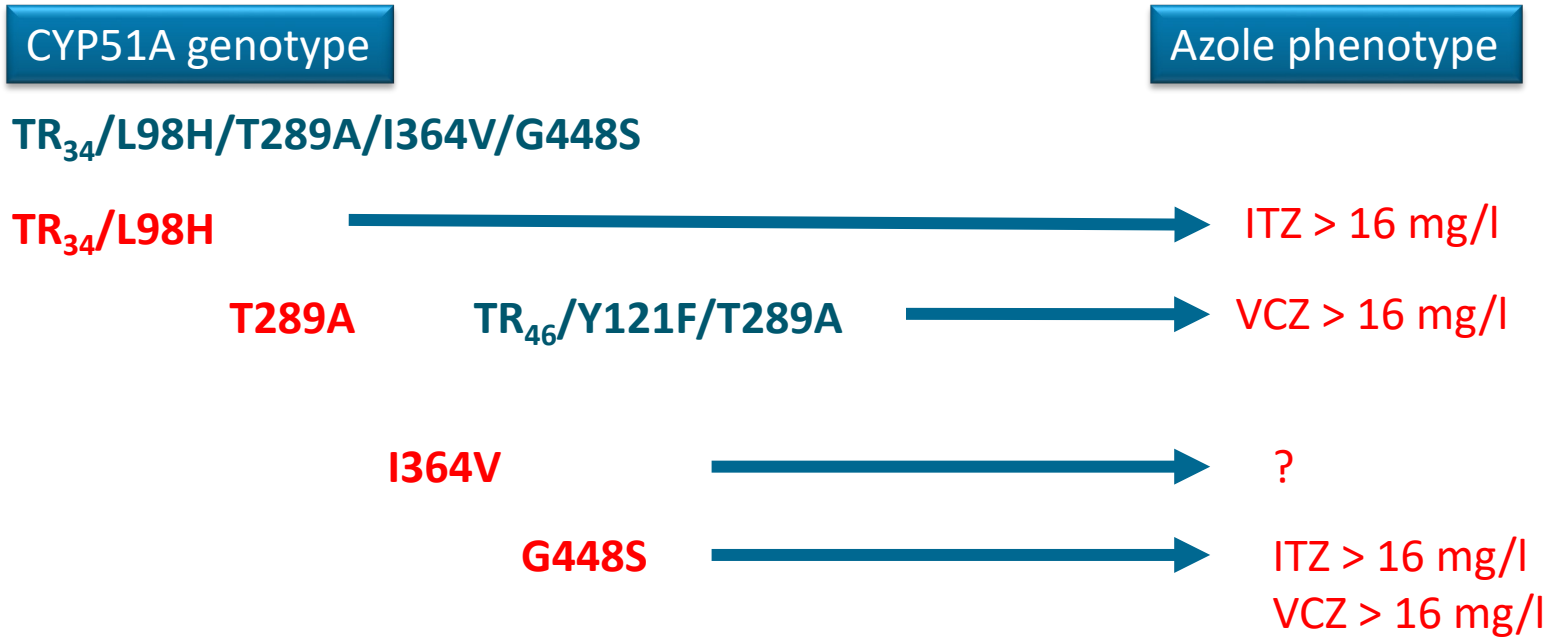
- **11,813 clinical isolates**
- **1,809 resistant isolates**
- ***cyp51A* Sanger sequencing**



Number of cyp51A variants over time

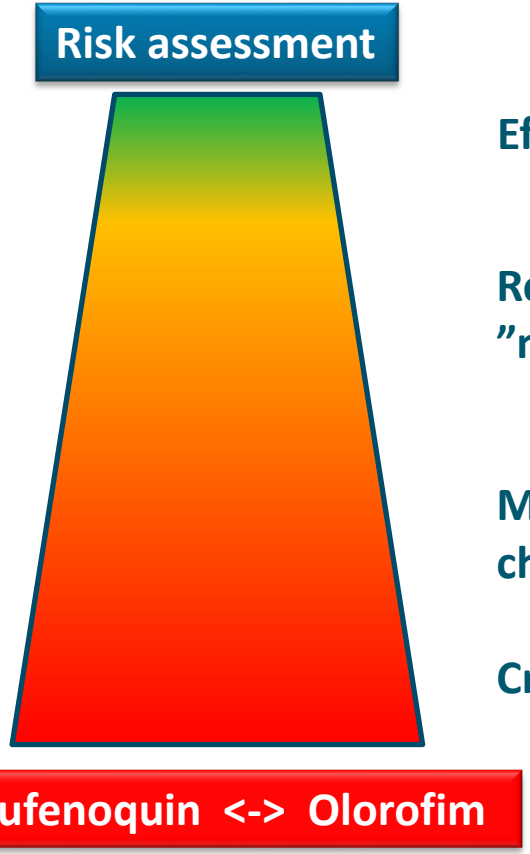
91 different genotypes





ITZ: 2	VCZ: > 16	POS: 1	ISA: > 16

Managing resistance selection in *A. fumigatus* – finding a balance



No activity against *A. fumigatus*

Effects on microbiome?

Activity against *A. fumigatus,* but class not used in medicine

Resistance selection + ”mutator” genotype?

Same class, different molecule

May cause SNPs and changes of phenotype

Same class, similar core structure

Cross resistance