environmental microbiology

Environmental Microbiology (2018) **20**(4), 1299–1301 doi:10.1111/1462-2920.14055

Highlight

Emergence of azole resistant *Aspergillus fumigatus* and One Health: time to implement environmental stewardship

Anuradha Chowdhary [1] **and Jacques F. Meis** [2,3*]

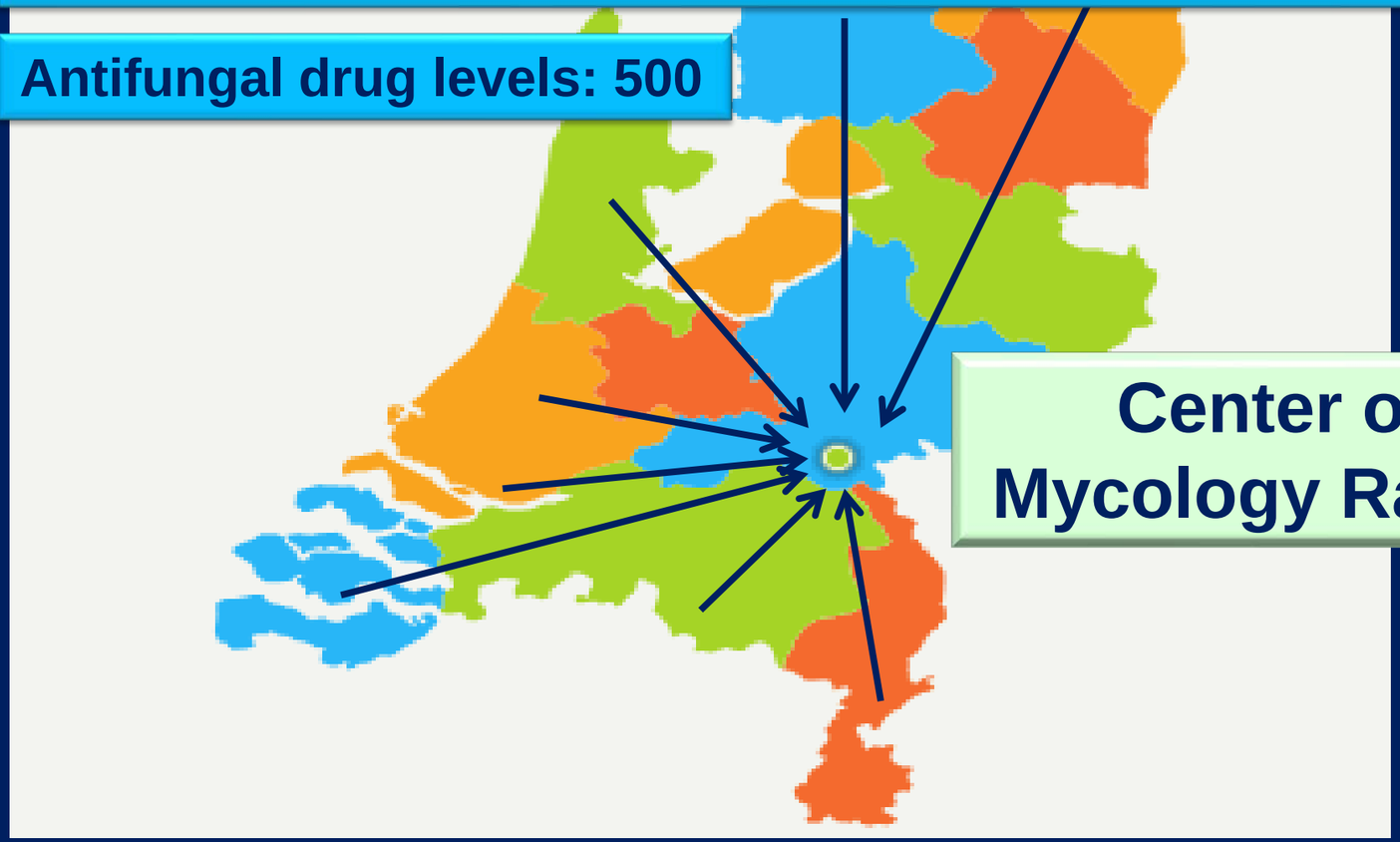
difenoconazole (in use since 1987 and 1993 respectively)

Jacques F. Meis MD, PhD
ECMM Centre of Expertise in Mycology Radboudumc/CWZ
Nijmegen, The Netherlands

Clinical Consultations: >200

Diagnostics: **2500 Fungus identification/ MIC-tests**
>2000 Antigen / PCR / serology

Antifungal drug levels: 500



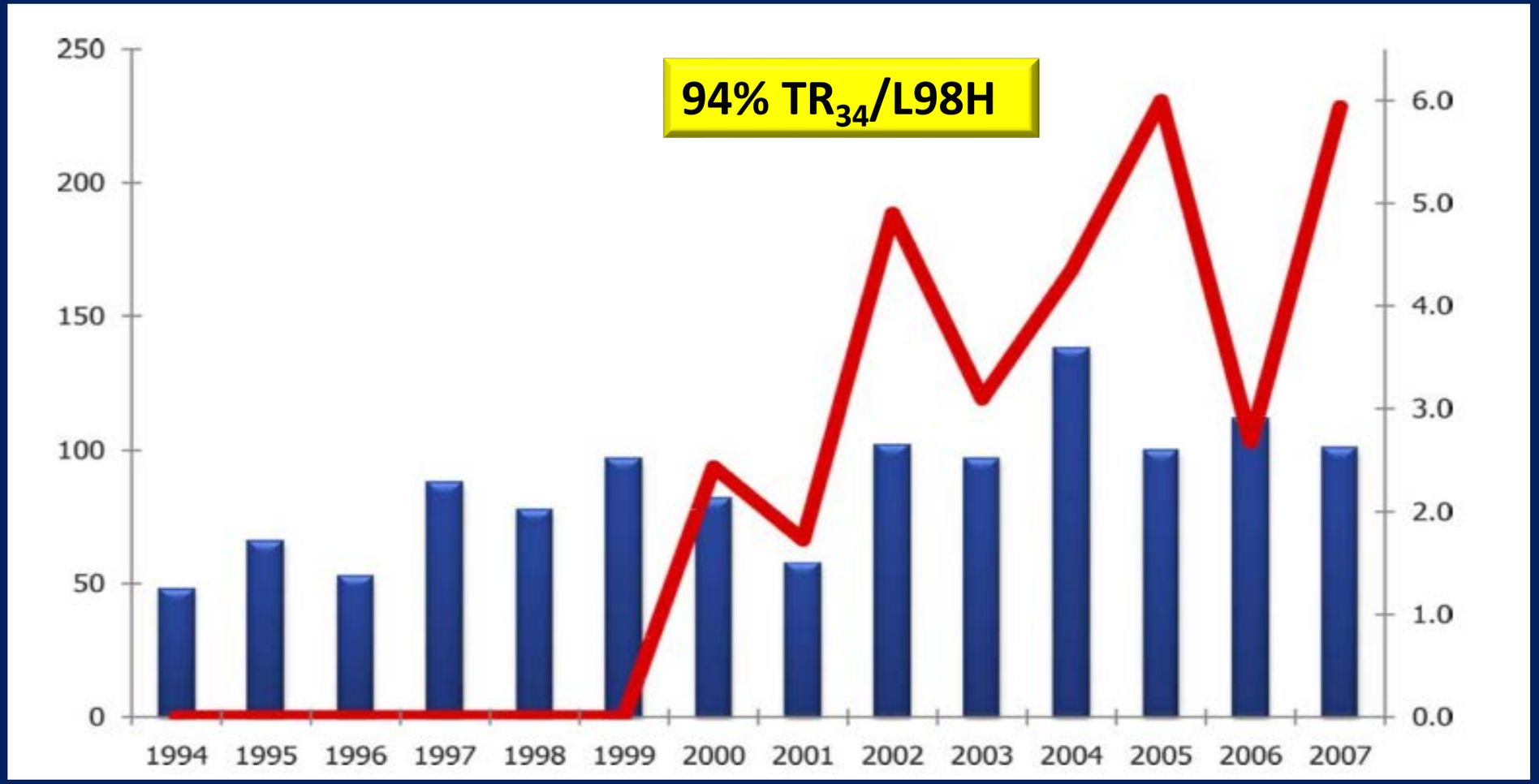
Center of Expertise in Mycology Radboudumc/CWZ

Teaching Hospital
University Medical center
Total 1200 beds

Potential conflicts of interest

- Grant support: F2G, Pulmozyme
- Consultant: Scynexis
- Speaker fees: Gilead, United Medical, TEVA

Acquired resistance in *A. fumigatus* at the Radboudumc, Nijmegen, NL



10.5%

2018

PLoS Med 2008;5:e219

OPEN ACCESS Freely available online

PLOS MEDICINE

Emergence of Azole Resistance in *Aspergillus fumigatus* and Spread of a Single Resistance Mechanism

Eveline Snelders[1,2], Henrich A. L. van der Lee[1,2], Judith Kuijpers[1,2], Anthonius J. M. M. Rijs[1,2], János Varga[3,4], Robert A. Samson[3], Emilia Mellado[5], A. Rogier T. Donders[6], Willem J. G. Melchers[1,2], Paul E. Verweij[1,2*]

1 Department of Medical Microbiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, **2** Nijmegen Institute for Infectious Diseases, Inflammation and Immunity, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands, **3** Centraalbureau voor Schimmelcultures (CBS), Fungal Biodiversity Centre, Utrecht, The Netherlands, **4** Department of Microbiology, Faculty of Science and Informatics, University of Szeged, Hungary, **5** Servicio de Micologia, Centro Nacional de Microbiologia, Instituto de Salud Carlos III, Madrid, Spain, **6** Department of Epidemiology and Biostatistics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

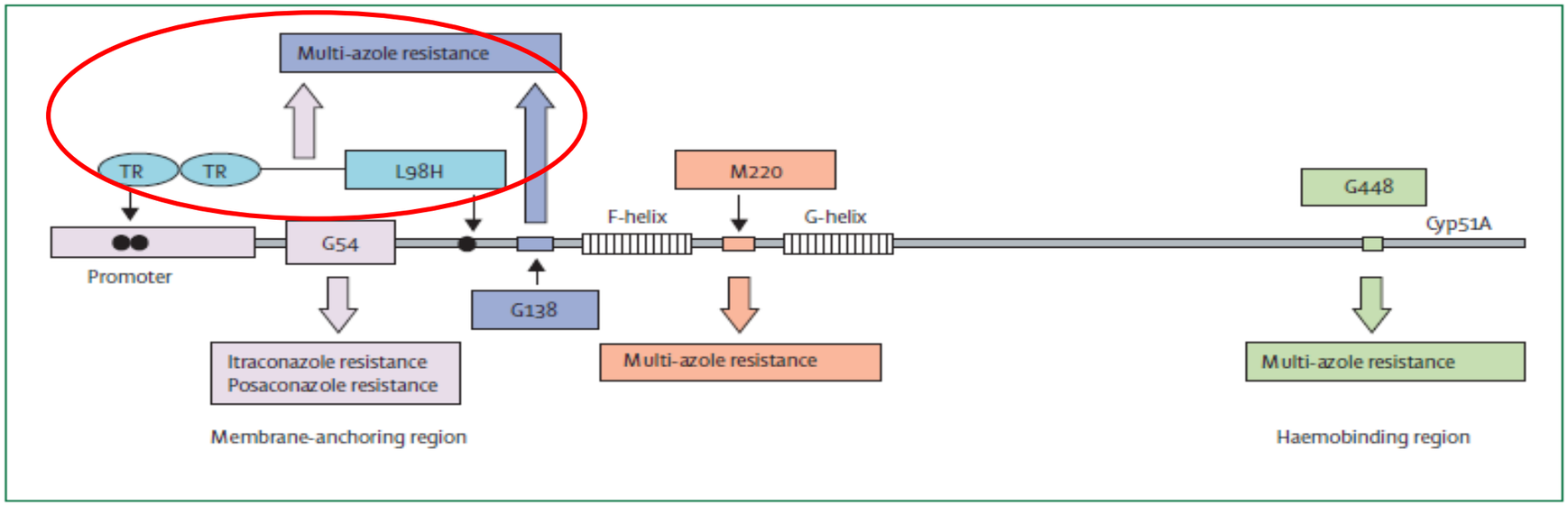


***Figure 3: Aspergillus fumigatus* cyp51A-related resistance mechanisms to azole antifungals**
The position of the different mutations are shown with the associated phenotypes. MIC=minimum inhibitory concentration. TR=tandem repeat.

A. fumigatus azole resistance surveillance 2013 - 2018

NethMap 2019

Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands

Aspergillus is included but only clinical isolates!

The Environment, Third pilar of One Health, is neglected

https://rivm.openrepository.com/handle/10029/623134

NethMap 2019

Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands

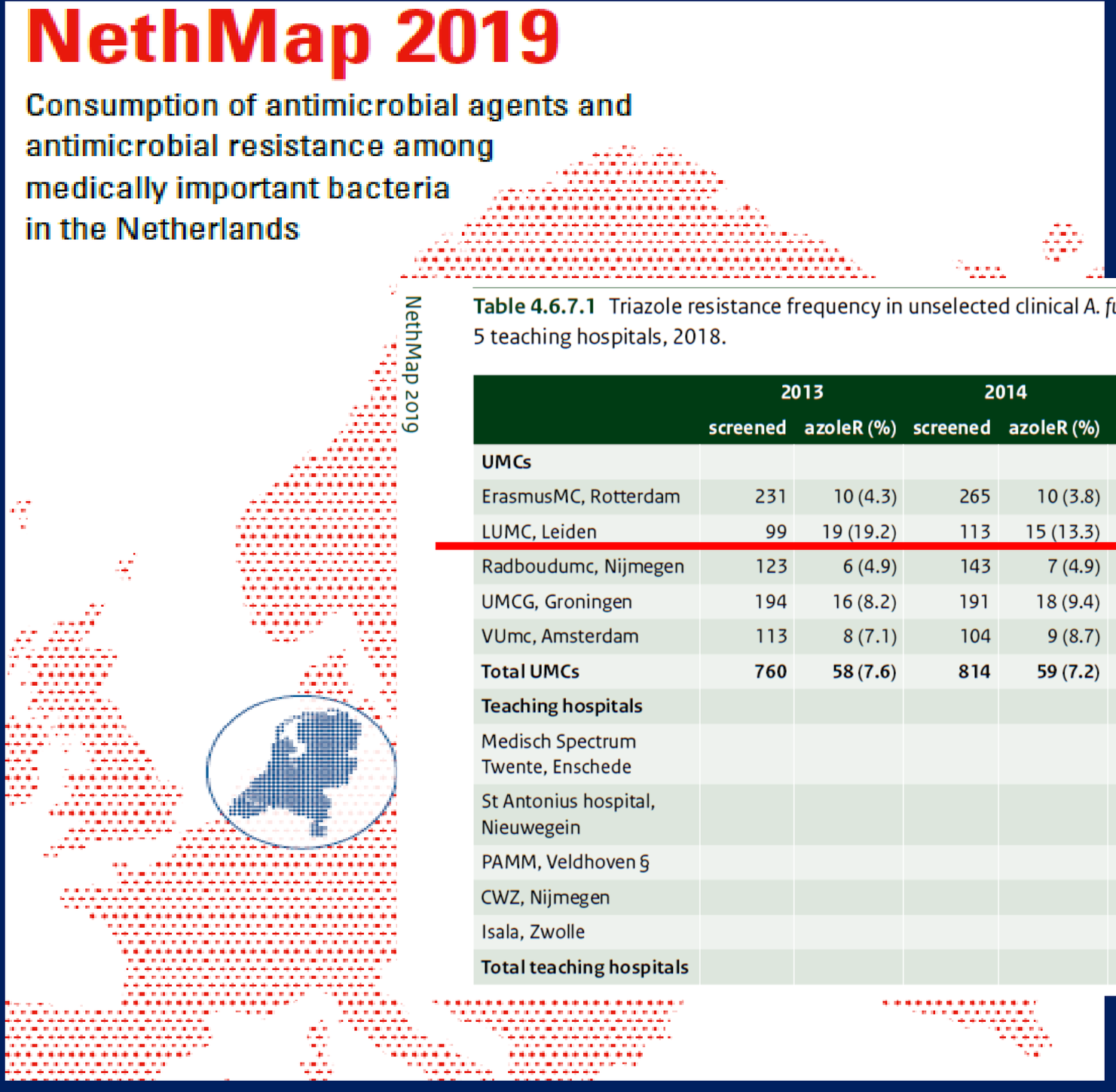


Table 4.6.7.1 Triazole resistance frequency in unselected clinical *A. fumigatus* isolates in 5 University Medical Centers, 2013 to 2018, and 5 teaching hospitals, 2018.

	2013		2014		2015		2016		2017		2018	
	screened	azoleR (%)	screened	azoleR (%)	screened	azoleR (%)	screened	azoleR (%)	screened	azoleR (%)	screened	azoleR (%)
UMCs												
ErasmusMC, Rotterdam	231	10 (4.3)	265	10 (3.8)	22	7 (31.8)*	186	24 (12.9)	147	19 (12.9)	129	17 (13.2)
LUMC, Leiden	99	19 (19.2)	113	15 (13.3)	141	23 (16.3)	88	18 (20.5)	114	27 (23.7)	120	25 (20.8)
Radboudumc, Nijmegen	123	6 (4.9)	143	7 (4.9)	145	12 (8.3)	210	20 (9.5)	198	21 (10.6)	196	23 (11.7)
UMCG, Groningen	194	16 (8.2)	191	18 (9.4)	225	15 (6.7)	215	26 (12.1)	240	35 (14.6)	238	34 (14.3)
VUmc, Amsterdam	113	8 (7.1)	104	9 (8.7)	89	14 (15.7)	85	13 (15.3)	75	12 (16)	81	13 (16)
Total UMCs	**760**	**58 (7.6)**	**814**	**59 (7.2)**	**600**	**64 (10.7)****	**784**	**101 (12.9)**	**774**	**114 (14.7)**	**764**	**112 (14.7)**
Teaching hospitals												
Medisch Spectrum Twente, Enschede											88	5 (5.7)
St Antonius hospital, Nieuwegein											265	28 (10.6)
PAMM, Veldhoven §											81	4 (4.9)
CWZ, Nijmegen											155	11 (7.1)
Isala, Zwolle											195	13 (6.7)
Total teaching hospitals											**784**	**50 (7.8)**

Possible environmental origin of resistance of *A. fumigatus* to medical triazoles (azole fungicides;demethylase inhibitors DMIs)

Material protection

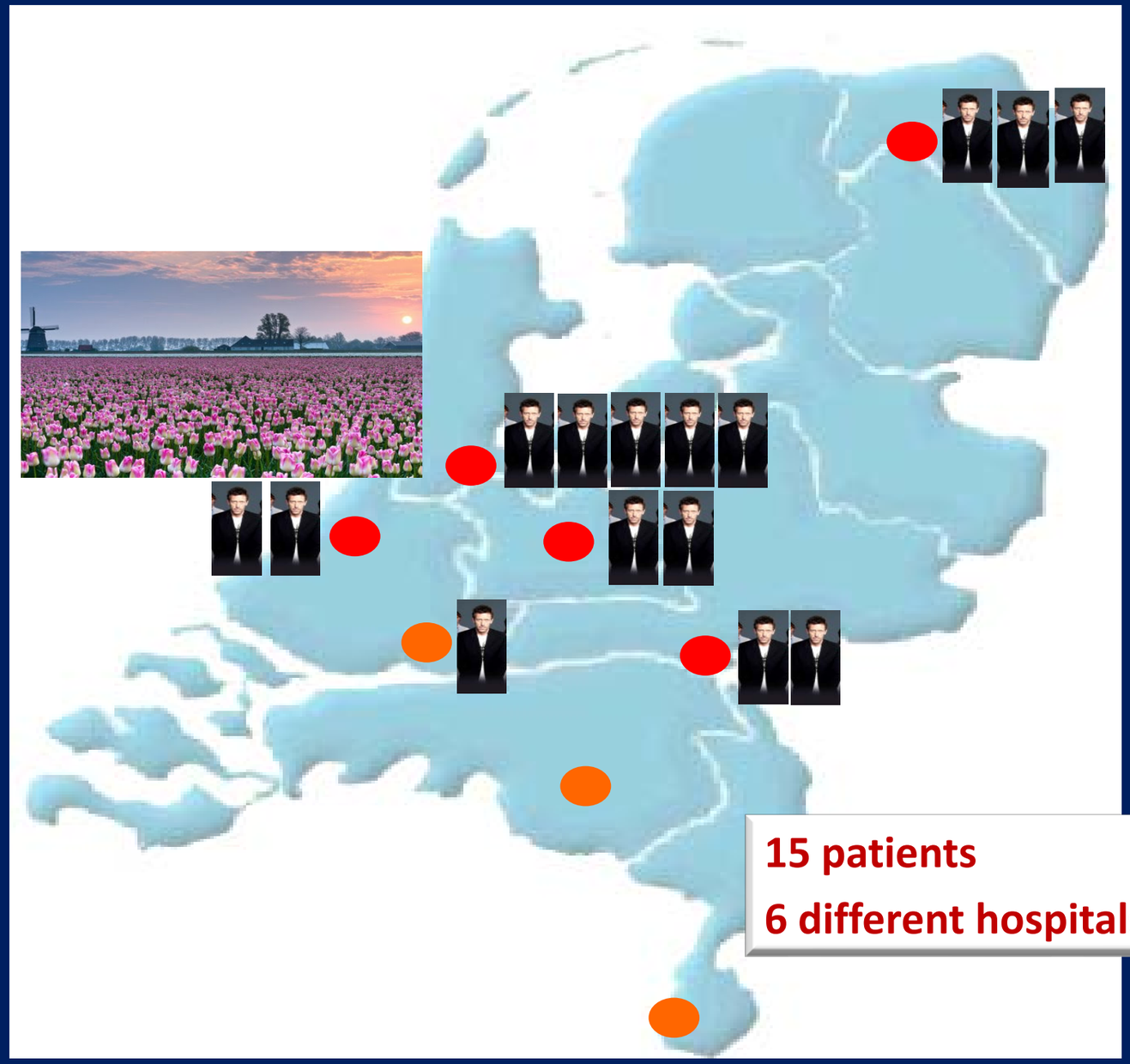
Plant protection

Appl Environm Microbiol 2009;75:4053-7

Azole resistance in *Aspergillus fumigatus*: a side-effect of environmental fungicide use?

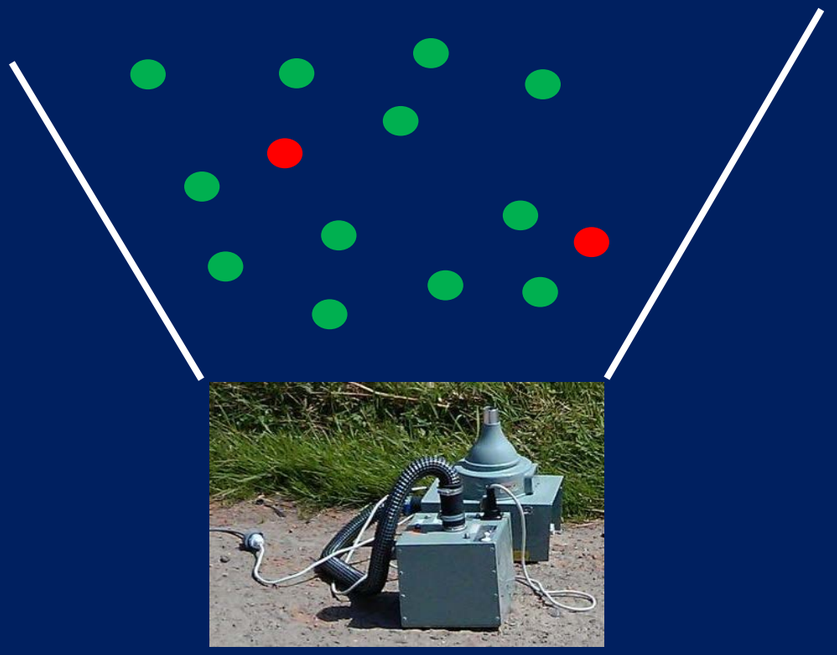
Paul E Verweij, Eveline Snelders, Gert H J Kema, Emilia Mellado, Willem J G Melchers **Lancet Infect Dis 2009; 9:789–95**

Spread of TR_{46}/Y121F/T289A in NL 2011



Clin Infect Dis. 2013;57(4):513-20

Air sampling for azole resistant *A. fumigatus* 14,000 L (2010-2011)



Clin Infect Dis. 2013;57(4):513-20

Netherlands 2011

Kitchen:

TR_{34}: +

TR_{46}: +

Back yard:

TR_{34}: +

TR_{46}: +

Living room:

TR_{34}: +

TR_{46}: +

Wards and hallways:

TR_{34}: +

TR_{46}: +

Hall:

TR_{34}: +

TR_{46}: +

Role of DMI's?

PLoS One 2012;7:e31801

- similar structure as medical azoles
- highest potential to select TR34/TR46 mutations

Bromuconazole
Epoxiconazole
Tebuconazole
Difenoconazole
Propiconazole

1970
amitrole

1973
carbendazim
fuberidazole
thiabendazole

1975
thiofanaat-methyl
Benomyl

1978
imazalil

1990
propiconazole

1992
fenchlorade-ethyl
cyproconazole
triflumizole
tebuconazole

1993
imazamethabenz-methyl
myclobutanil
nuarimole

1994
difenoconazole
epoxiconazole

1995
pyrimethanil

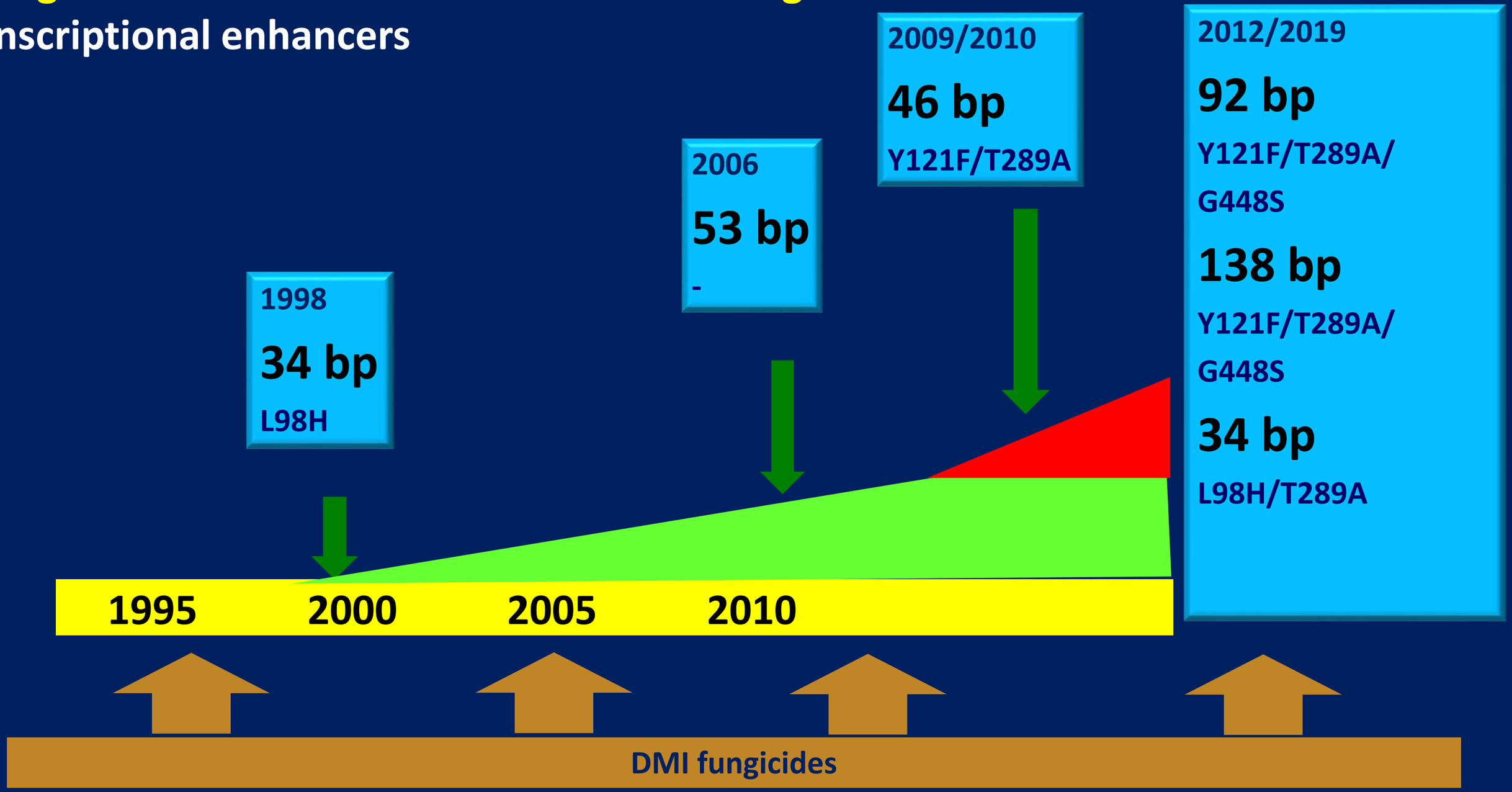
2000
cyprodinil

2005
fenamidone
metconazole
prothioconazole

First clinical TR_{34}/L98H isolate in 1998

1970 1980 1990 2000 2010

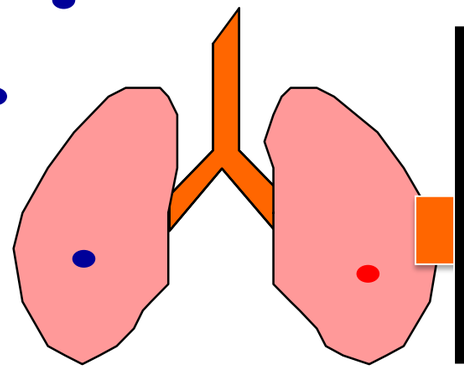
Emergence of resistance mechanisms involving transcriptional enhancers



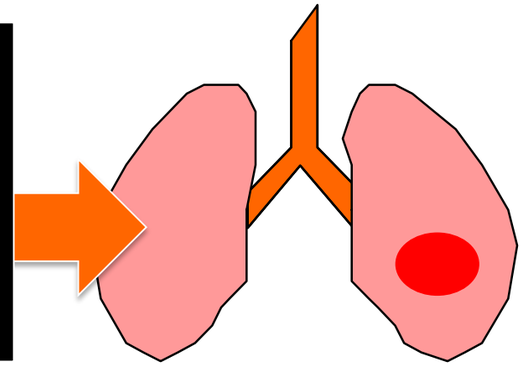
Different problems – different solutions?

Environmental route

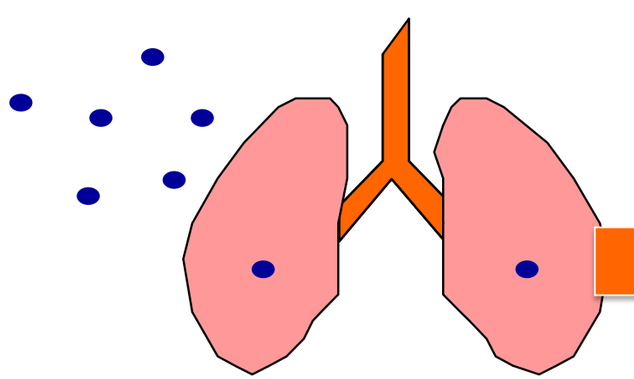
Exposure of *A. fumigatus* in the environment to azole fungicides with activity against aspergilli



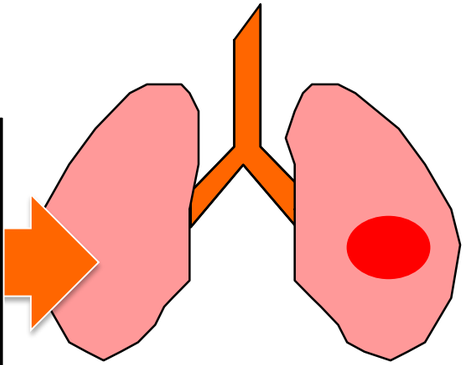
Characteristics
- Majority of patients are azole naïve
- Patients with invasive aspergillosis and chronic aspergillus diseases
- Only a few resistance mechanisms described
- Resistance mechanisms consist of Cyp51A-substitution with transcriptional enhancer



Patient route



Characteristics
- Long term azole therapy
- Mainly chronic cavitary pulmonary aspergillosis
- Point mutations in the Cyp51A-gene or unknown resistance mechanisms
- Multiple resistance mechanisms may be found in different colonies from a single specimen



Verweij et al. 2015 Drug Resist Updat; 21-22: 30-40

Aspergillus fumigatus and azole resistance……

What are the clinical implications of azole resistance?

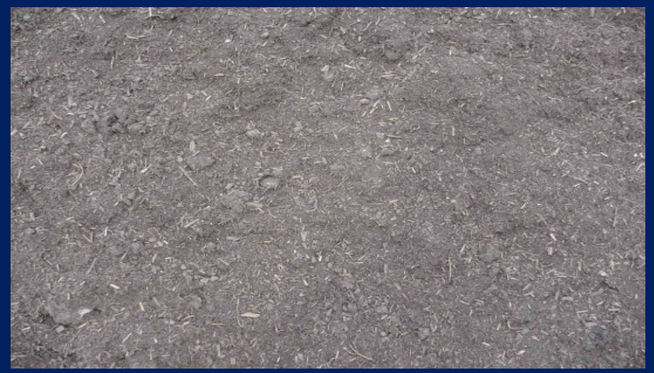
How is azole resistance selected in the environment?

Where?

application of fungicides

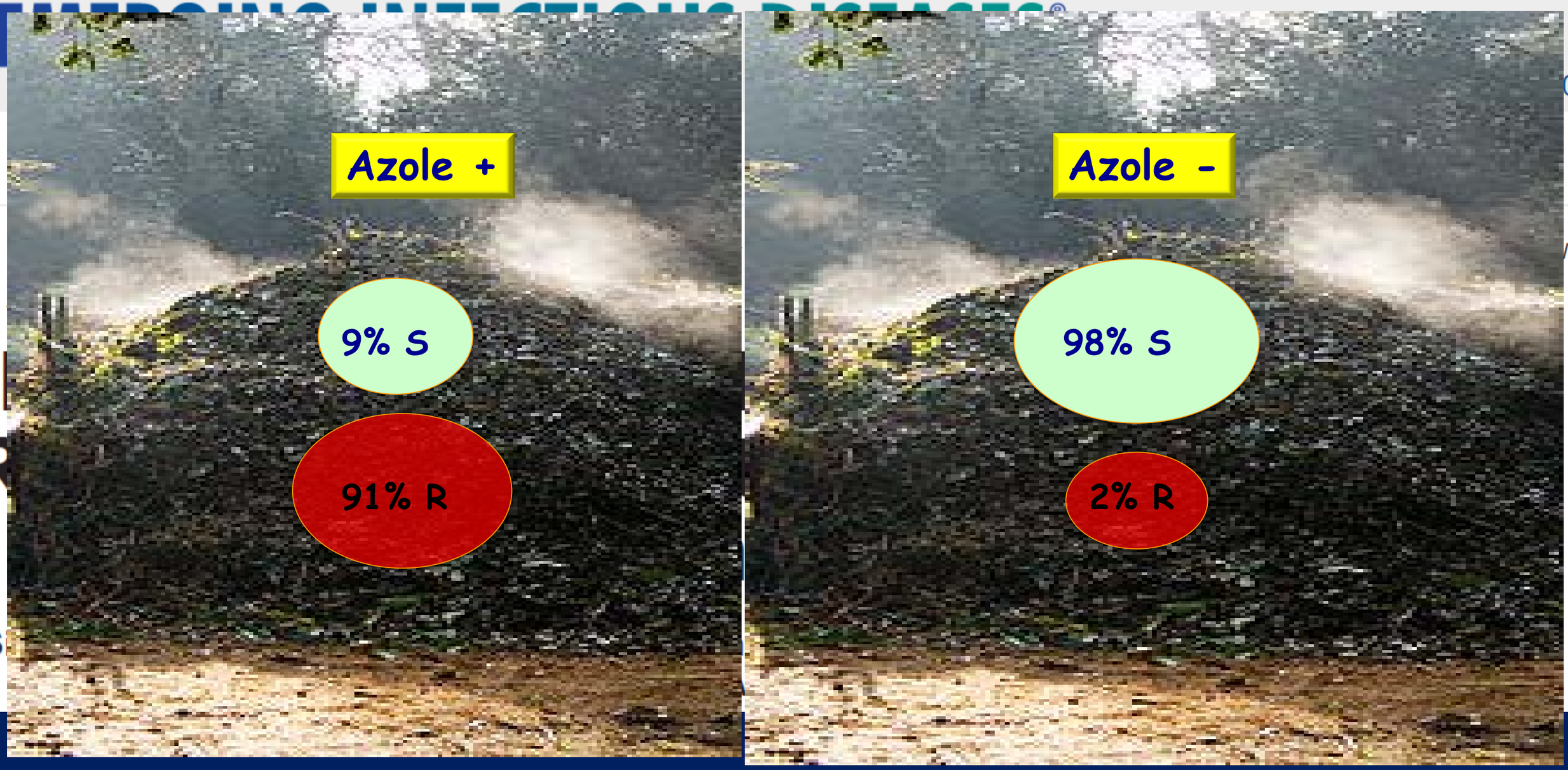
collection of organic waste

composting

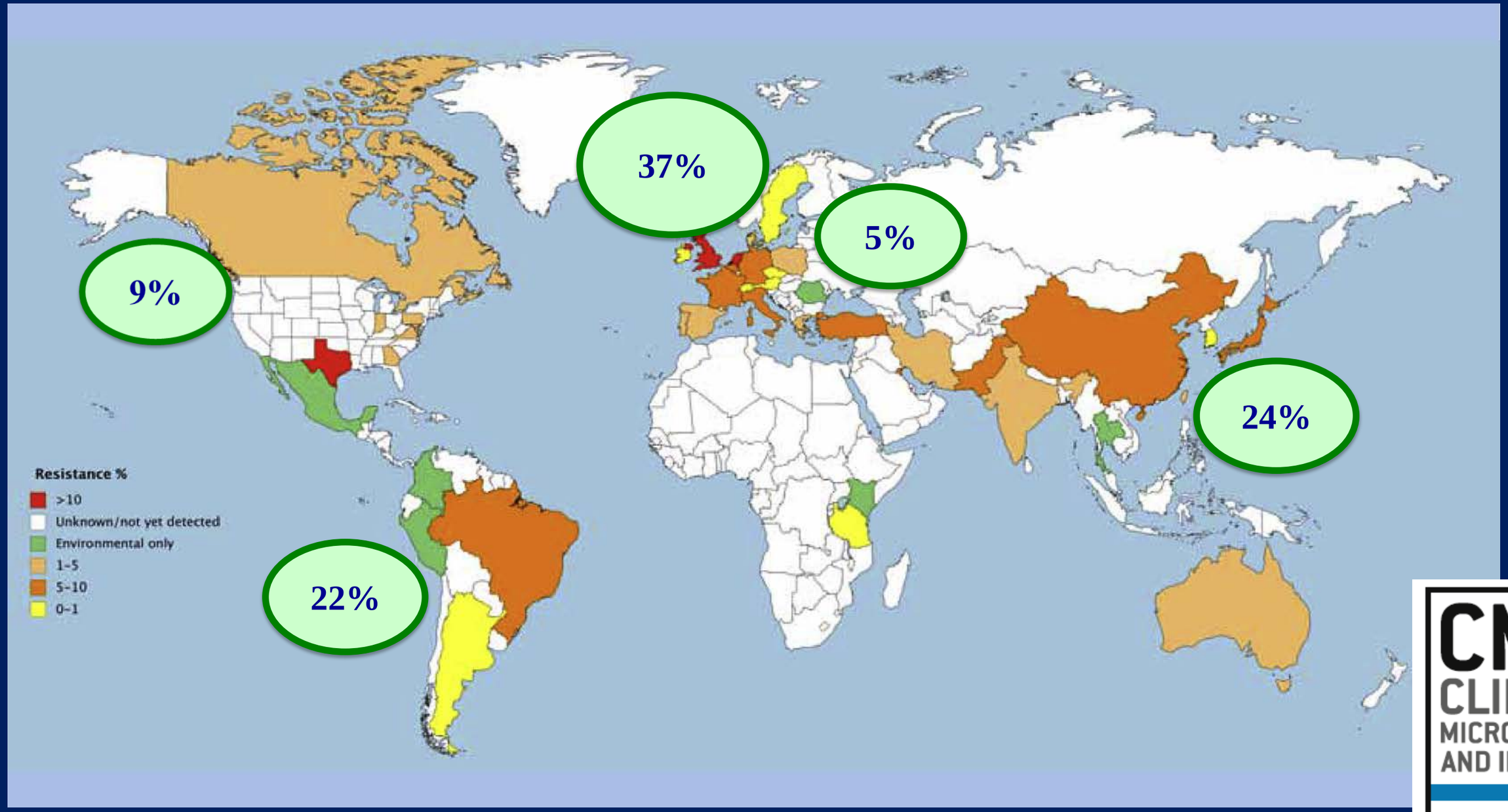


mature compost

Understanding resistance selection



Azole resistance and % market share fungicides



Curr Fungal Infect Rep (2012) 6:178–191

Clinical Microbiology and Infection 25 (2019) 799–806

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European Centre for Disease Prevention and Control

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ECDC Portal > English > Media Centre > News

ECDC examines current evidence for the possible environmental origin of azole resistance in Aspergillus species

28 Feb 2013

In its risk assessment, ECDC examines current evidence for the environmental origin of resistance to medical triazoles in *Aspergillus* spp. and makes recommendations for further steps to assess the risks and consequences of the environmental usage of azole derivatives. The report was prepared with the support of European and US experts.

Aspergillosisrefers to a group of diseases which can result from *Aspergillus* infection and includes allergic bronchopulmonary aspergillosis, chronic pulmonary aspergillosis, aspergilloma and the most severe form, invasive aspergillosis.

ECDC es... from ch... aspergillosis, annually complicates the management of other diseases including leukaemia, transplantation, chronic obstructive pulmonary disease (COPD) and medical intensive care.

Triazole therapy has become the established treatment for human *Aspergillus* diseases. However, triazole resistance in *Aspergillus* spp. isolates... options. ... health costs.

... is ... proven.

The report concludes on the importance of improved surveillance and diagnosis of resistance in *Aspergillus* diseases, as well as the development of further environmental and laboratory studies to confirm the environmental hypothesis.

Risk assessment on the impact of environmental usage of triazoles on the development and spread of resistance to medical triazoles in Aspergillus species

STAY...

- In...
- Influenza ... updates
- Influenza RSS feeds - S... ...ic advances
- RSS feeds for EC...
- RSS feeds f... ...ancies
- RSS feeds ... ...ons
- Seasonal i... - News
- Influ... ...ews
- Influenza pa... ...dness RSS
- ...eds - News
- Influenza ... ...lth
- develop...
- Seasonal influenza RSS feeds - Publications

EUROSURVEILLANCE

- More about Eurosurveillance

Environmental Resistance is One Health

Stewardship is needed both in hospitals and in the environment

Increase surveillance and resistance detection in hospitals

Early Detection, Better Protection

✓ Detect disease in your field long before you see it in your crops.

The Spornado is a simple passive spore catcher priced to work within your fungicide budget. The sampler is placed in the field trapping airborne spores through wind currents on a specialized filter. These filters are then collected for molecular analysis for fungal pathogens that cause crop disease.

✓ 20/20 Seed Labs will test all of the samples and provide quick results.

Having this detection system in place, you can now monitor and gather the information to guide and help you narrow the timing gap for when fungicide spraying is critical.

We're taking the guess work out of when to spray.