

The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
 Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
 A Webber Training Teleclass

The race to stop the silent tsunami of antifungal drug resistance

Paul E. Verweij, MD

Centre of Expertise in Mycology Radboudumc/CWZ

Hosted by Paul Webber
 paul@webbertraining.com






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September 20, 2018

Disclosures



(potentiële) belangenverstrengeling	Zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
<ul style="list-style-type: none"> • Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk ... 	<ul style="list-style-type: none"> <li style="margin-right: 20px;">•  astellas <li style="margin-right: 20px;">•  f2g <li style="margin-right: 20px;">•  MERCK <li style="margin-right: 20px;">•  basilea PHARMACEUTICA <li style="margin-right: 20px;">•  Pfizer <li style="margin-right: 20px;">•  GILEAD

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Disclosure collaborations

UMCs





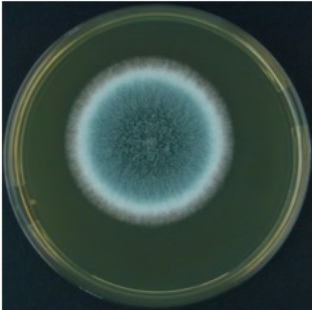
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Aspergillus fumigatus and its habitat



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Human aspergillus disease

Host

Is the host at risk?

Imaging

Consistent with fungal disease?

Mycology

Evidence for Aspergillus?

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Pathogenesis invasive aspergillosis

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Management of invasive aspergillosis



Antifungal therapy




Surgery




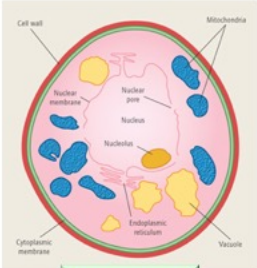
Reduce immune suppression

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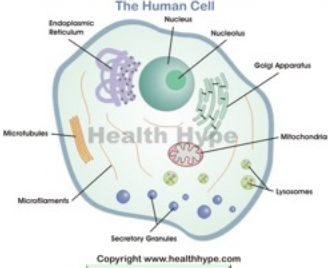
Antifungal therapy







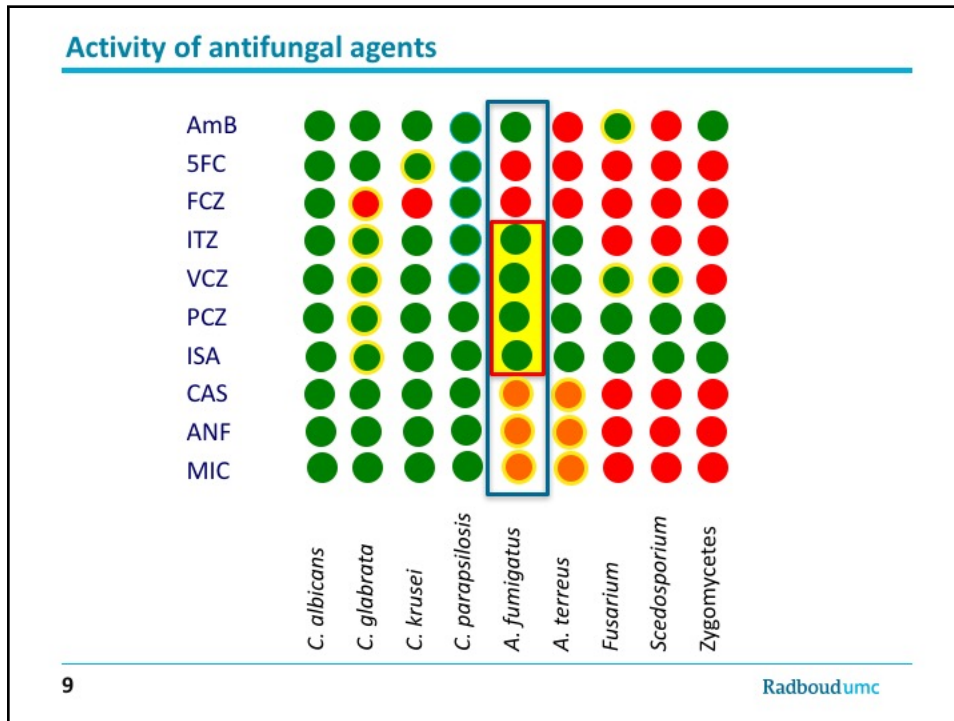
Fungal cell



Human cell

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Pre-azole era – before 2002

Amphotericin B deoxycholate

Invasive pulmonary aspergillosis – mortality 70%

CNS aspergillosis – mortality 99%

DEATH SENTENCE

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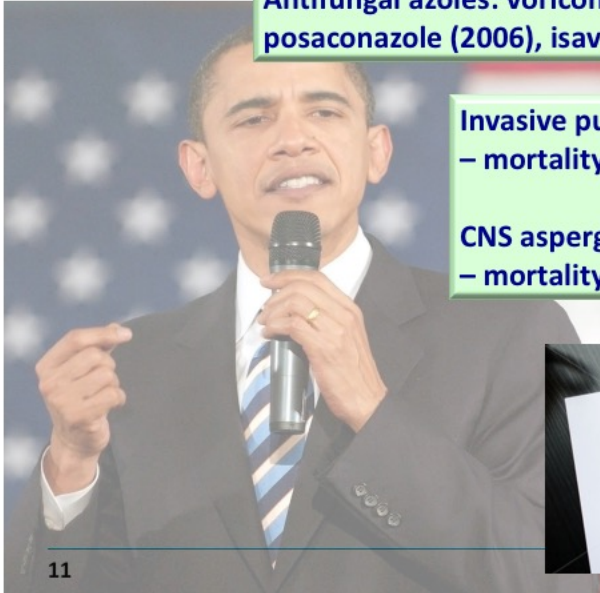
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Triazole era – after 2002: Change....."Yes we can"

Antifungal azoles: voriconazole (2002), posaconazole (2006), isavuconazole (2015)


Invasive pulmonary aspergillosis – mortality <30%

CNS aspergillosis – mortality 45% - 60% (VCZ)



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Case



15 year old child with X-linked CGD

Had previously survived an infection with *A. nidulans*

Was on ITZ prophylaxis for 6 years

12 N Engl J Med 2002;347:2173-4. Radboudumc


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Case

During ITZ prophylaxis a pulmonary infiltrate developed
 Sputum culture (April 4th 2002)

A. fumigatus

ITZ >16 mg/l
 VCZ 4 mg/l
 POS 1 mg/l



High dose VCZ (12 mg/kg/day) - survived

13 N Engl J Med 2002;347:2173-4. Radboudumc

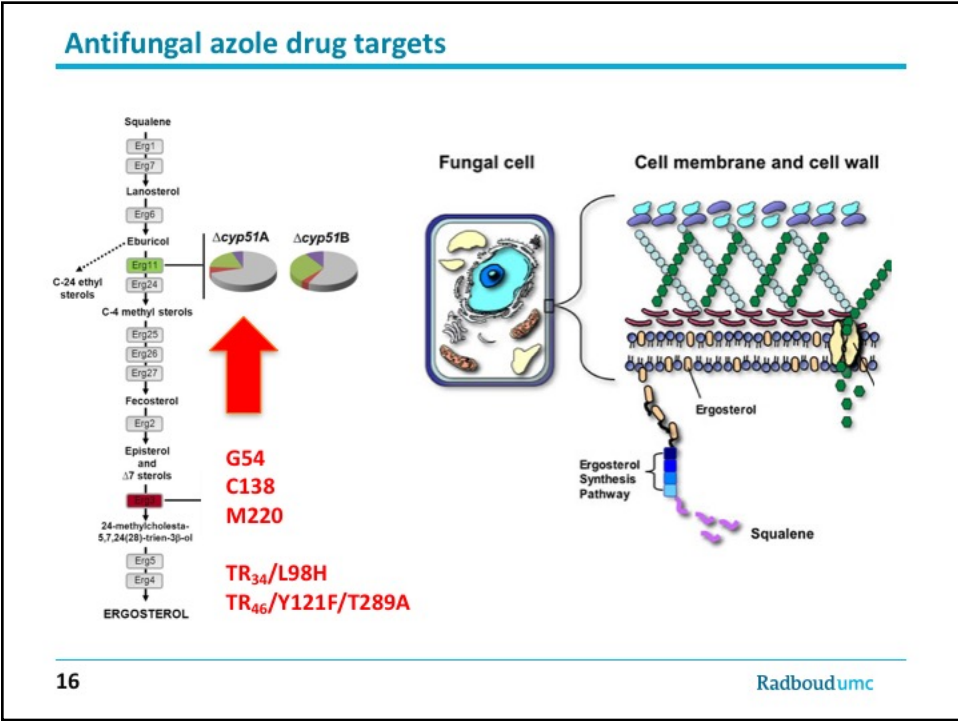
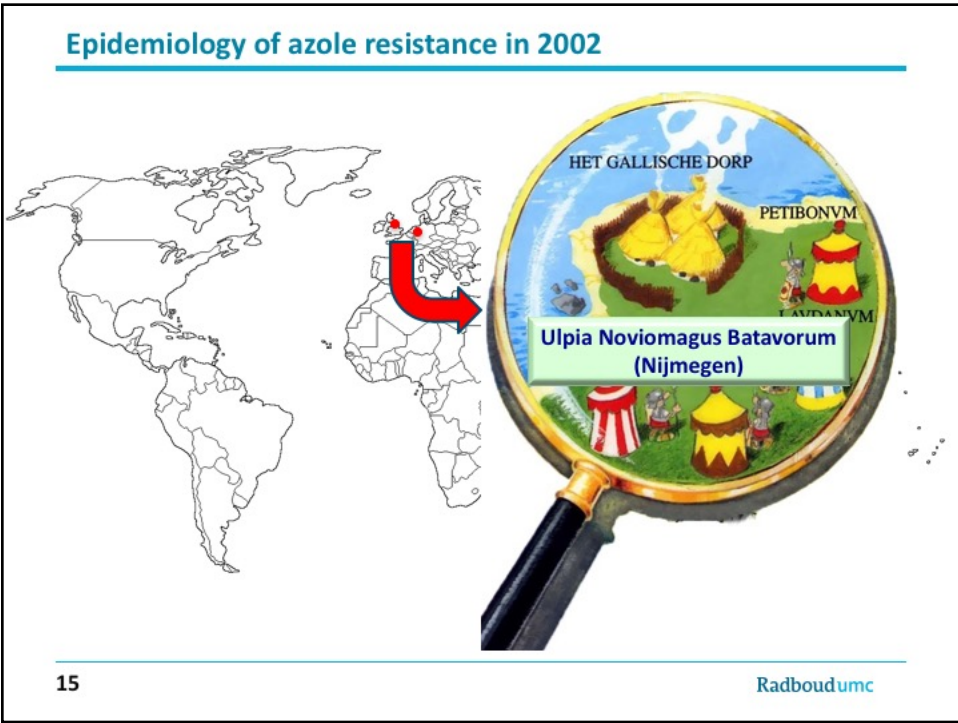
Azole R invasive aspergillosis

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

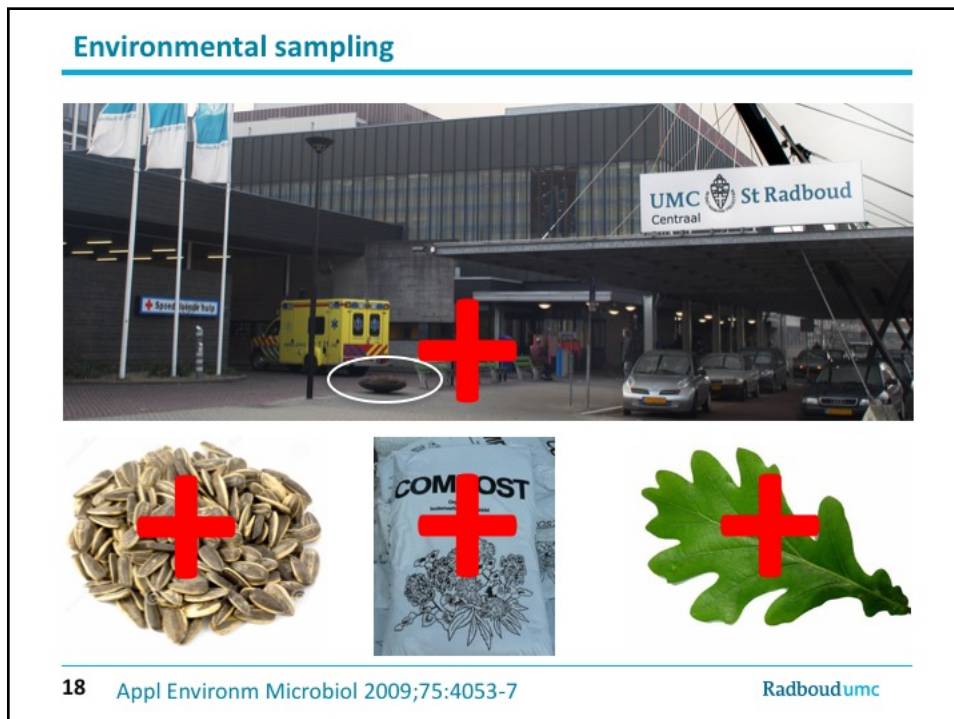
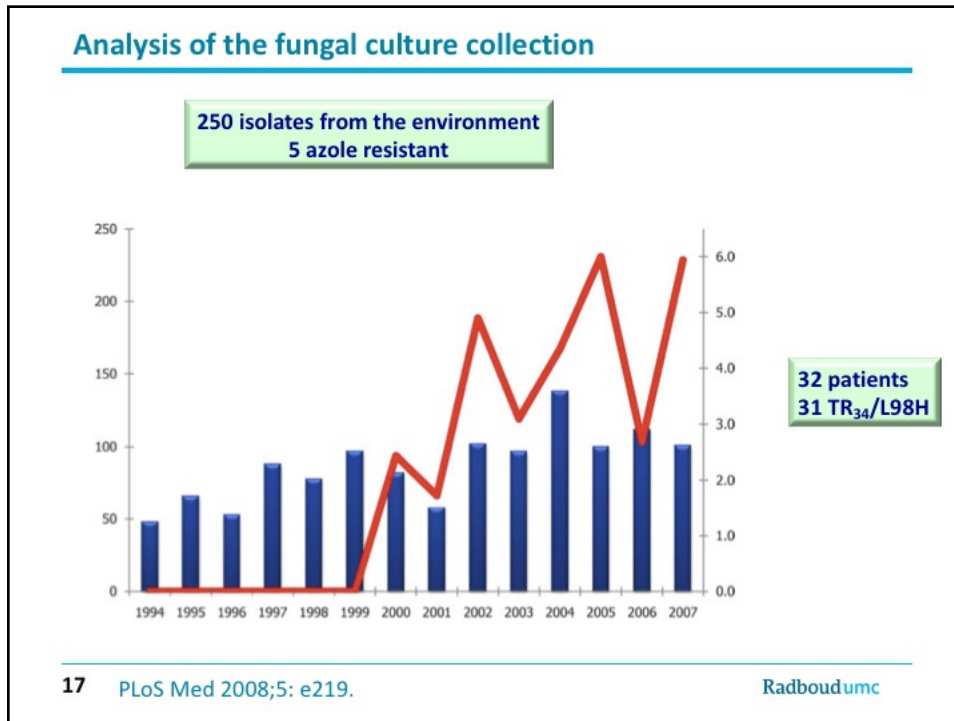
Sex	Yr of Age	Underlying Disease	Date of Isolation	Site of Isolation	Disease Classification ^a	Previous Azole Exposure	Treatment	Outcome
Male†	15	X-linked chronic granulomatous disease	April 4, 2002	Sputum	Breakthrough invasive pulmonary aspergillosis, proven	Prophylaxis with itraconazole (for 6 yr)	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

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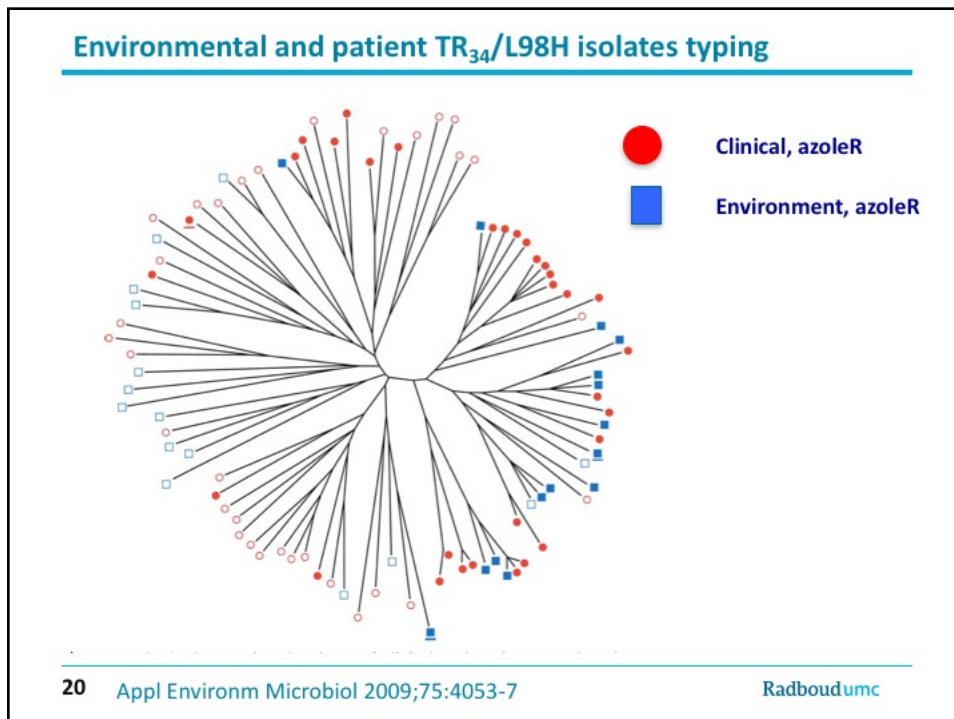
Environmental sampling

Category	Isolate no.	Source of isolate	Year of isolation	MIC (mg/liter) ^a						Cyp51A substitution ^b		
				ITZ	VCZ	POS	AMB	TER	CAS	TR	Codon 98	Other(s)
ITZ ^c	V17-24	Air sample, patient room	2002	>16	1	0.5	0.5	0.031	0.25	+	L98H	S297T, F495I
	V22-76	Air sample, patient room	2003	16	0.5	0.5	0.031	0.25	+	L98H		
	V37-56	Air sample, patient room	2005	>16	2	0.5	1	0.125	0.25	+	L98H	
	V61-56	Water filter sample	2007	>16	4	0.5	0.5	0.25	1	+	L98H	Q141H
	V61-57	Water filter sample	2007	>16	4	0.5	0.5	0.063	0.5	+	L98H	
	V61-50	Soil	2007	>16	4	0.5	0.5	0.25	>32	+	L98H	
	V61-79	Soil	2007	>16	8	0.5	1	0.016	0.5	+	L98H	
	V62-05	Soil	2007	>16	8	0.5	0.5	0.125	0.25	+	L98H	
	V62-09	Soil	2007	>16	4	0.5	1	0.063	1	+	L98H	
	V62-10	Soil	2007	>16	4	0.25	1	0.125	0.5	+	L98H	
	V62-14	Soil	2007	>16	4	0.25	1	0.063	1	-		
	V62-48	Seeds	2007	>16	4	0.5	0.5	0.25	1	+	L98H	
	V62-63	Compost	2007	>16	>16	0.5	1	0.0031	0.5	+	L98H	
V62-79	Soil	2007	>16	0.5	0.25	0.5	0.5	0.5	-			
ITZ ^c	V04-22	Air sample, patient room	2000	0.25	0.5	0.063	1	0.063	0.5	-		
	V22-74	Air sample, patient room	2003	0.25	0.5	0.031	1	0.063	0.5	-		
	V22-80	Air sample, patient room	2003	0.25	0.5	0.031	1	0.5	0.5	-		
	V57-35	Water filter sample	2007	0.25	0.5	0.031	1	0.063	0.5	-		
	V57-53	Water filter sample	2007	0.25	0.5	0.063	0.5	0.016	0.5	-		
	V62-04	Soil	2007	0.25	1	0.125	0.5	0.25	0.5	-		
	V62-06	Soil	2007	1	4	0.25	1	0.5	0.5	-	F46Y, M172V, E427K	
	V62-07	Soil	2007	0.5	0.5	0.125	1	0.063	1	-		
	V62-12	Soil	2007	0.5	4	0.25	1	0.031	1	-	F46Y, M172V, E427K	
	V62-13	Soil	2007	1	2	0.25	1	0.5	1	-		
	V62-23	Soil	2007	0.25	1	0.063	1	0.25	0.5	-		
	V63-01	Soil	2007	0.25	0.5	0.031	0.5	0.125	0.5	-		
	V63-03	Soil	2007	0.25	1	0.063	1	0.063	0.5	-		
	V63-04	Soil	2007	0.25	0.5	0.063	0.5	0.016	0.5	-		
	V63-05	Soil	2007	0.5	4	0.25	0.5	0.5	0.5	-		

^a VCZ, voriconazole; POS, posaconazole; AMB, amphotericin B; TER, terbinafine; CAS, caspofungin.

19 Appl Environm Microbiol 2009;75:4053-7

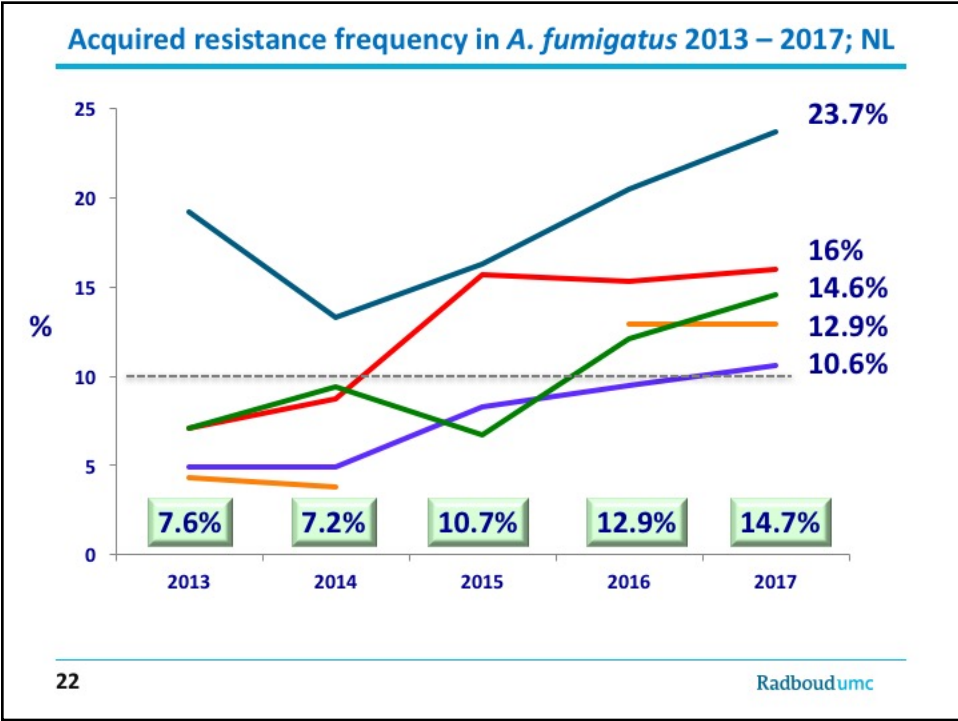
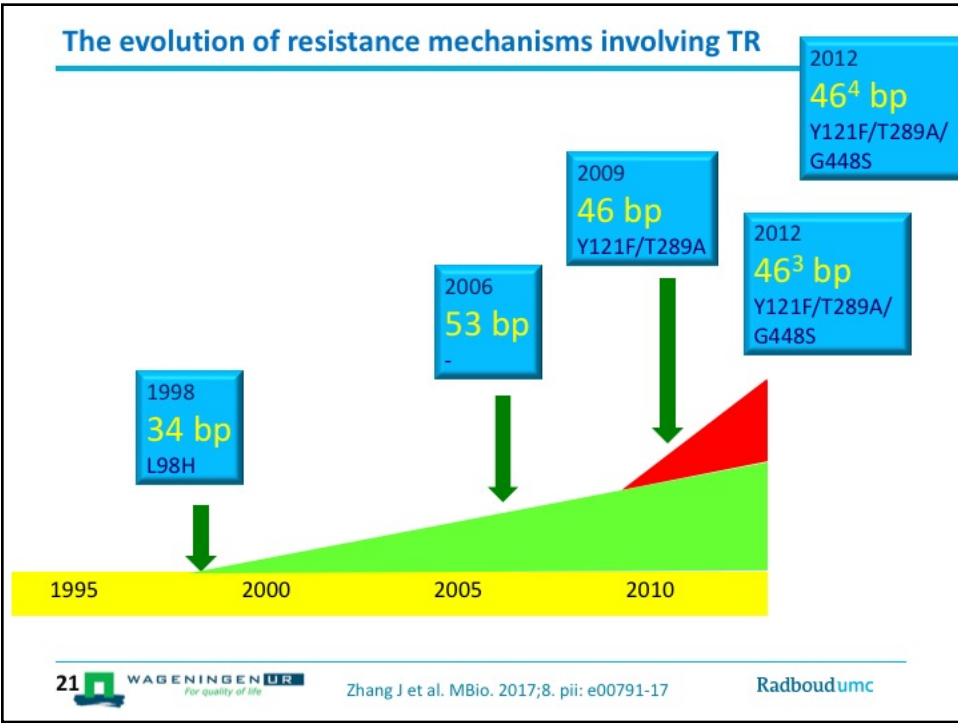
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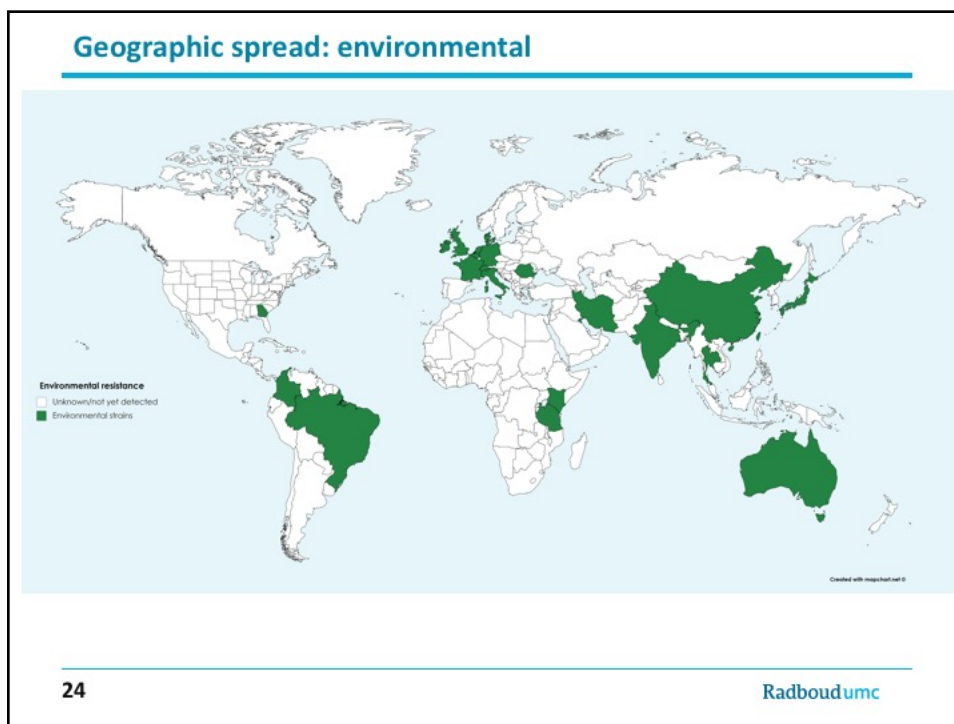
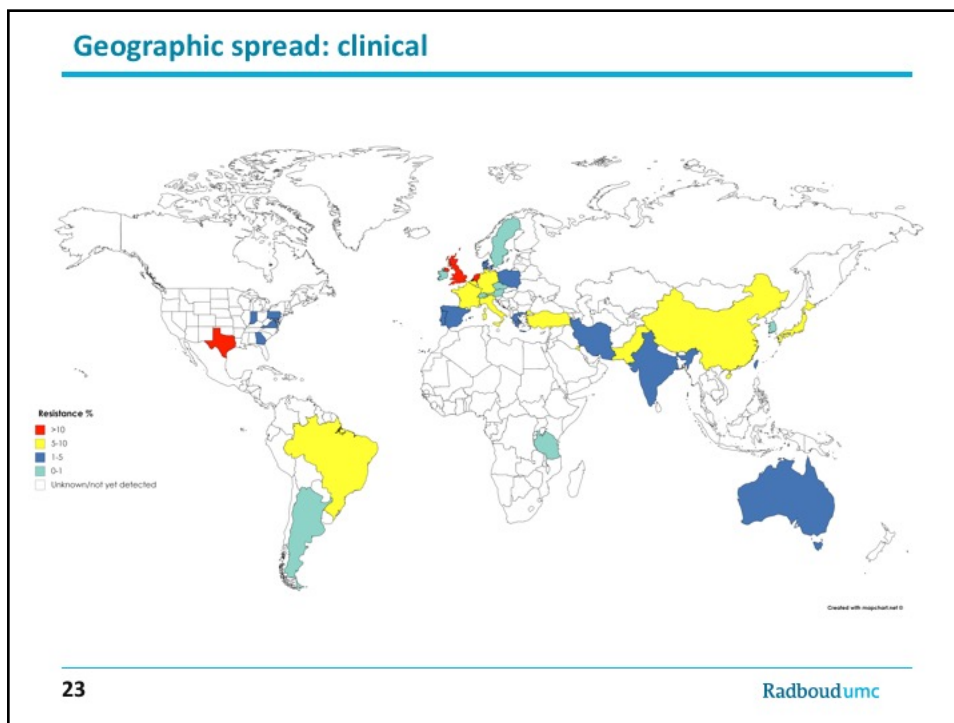
20 Appl Environm Microbiol 2009;75:4053-7

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Aspergillus fumigatus on the move...

What are the clinical implications of azole resistance?

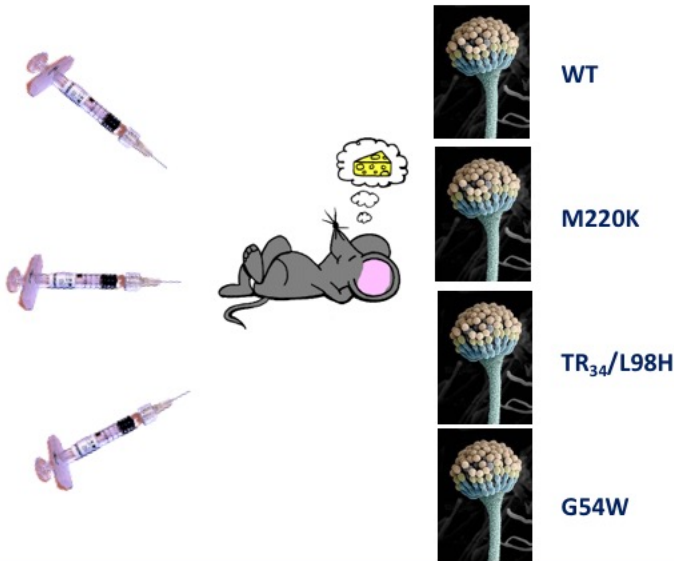


How is azole resistance selected in the environment?

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Clinical: does resistance result in treatment failure?



26 AAC 2010; 54:860-5; AAC 2010; 54:8745-64

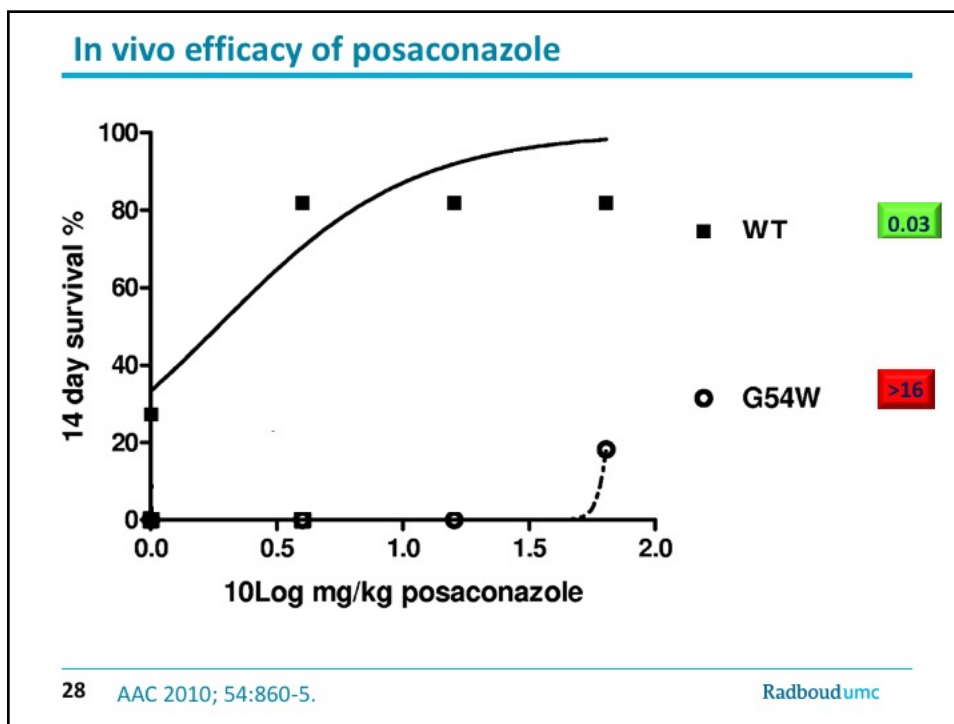
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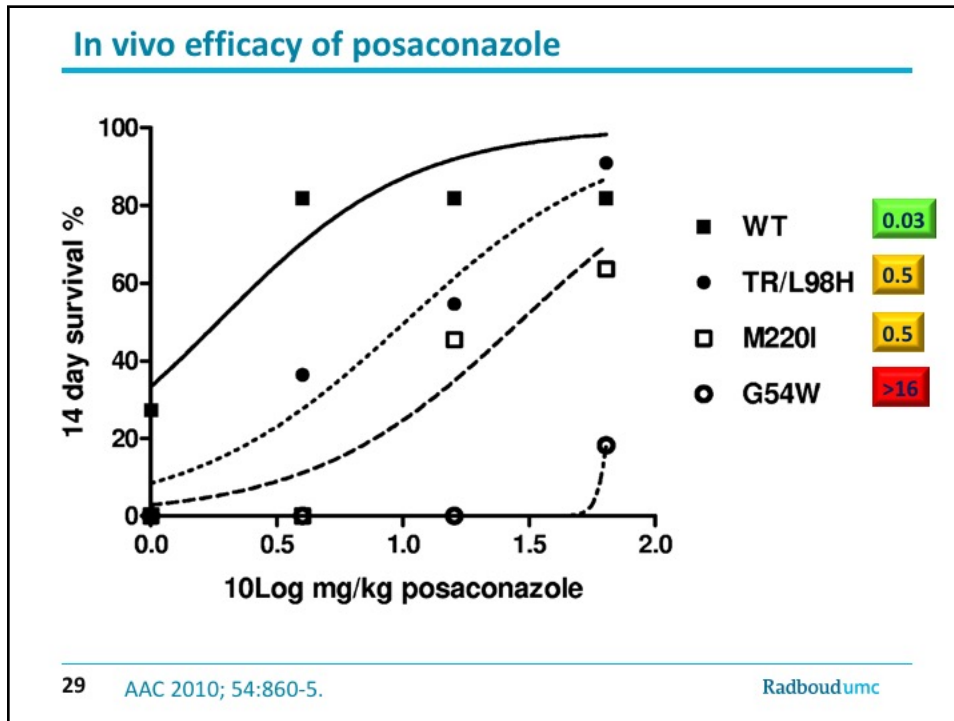
Clinical: does resistance result in treatment failure?

	ITZ	VCZ	POS
WT	0.125	0.25	0.03
TR ₃₄ /L98H	>16	2	0.5
G54W	>16	0.125	>16
M220I	>16	0.25	0.5

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Does azole resistance contribute to treatment failure?

What was the status of the underlying condition?

Was there sufficient voriconazole exposure?

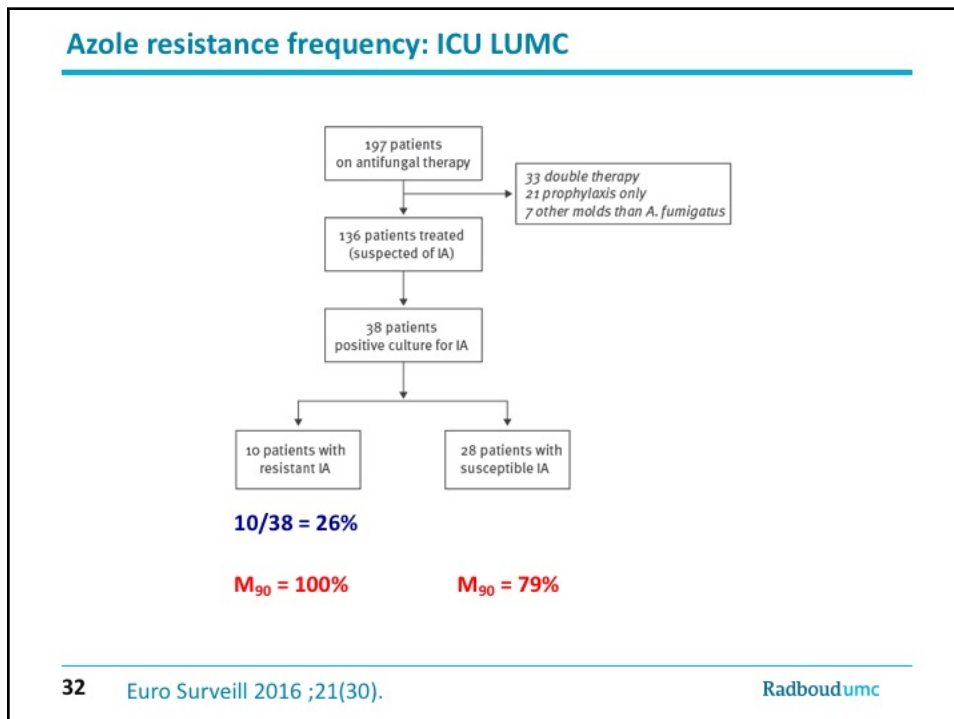
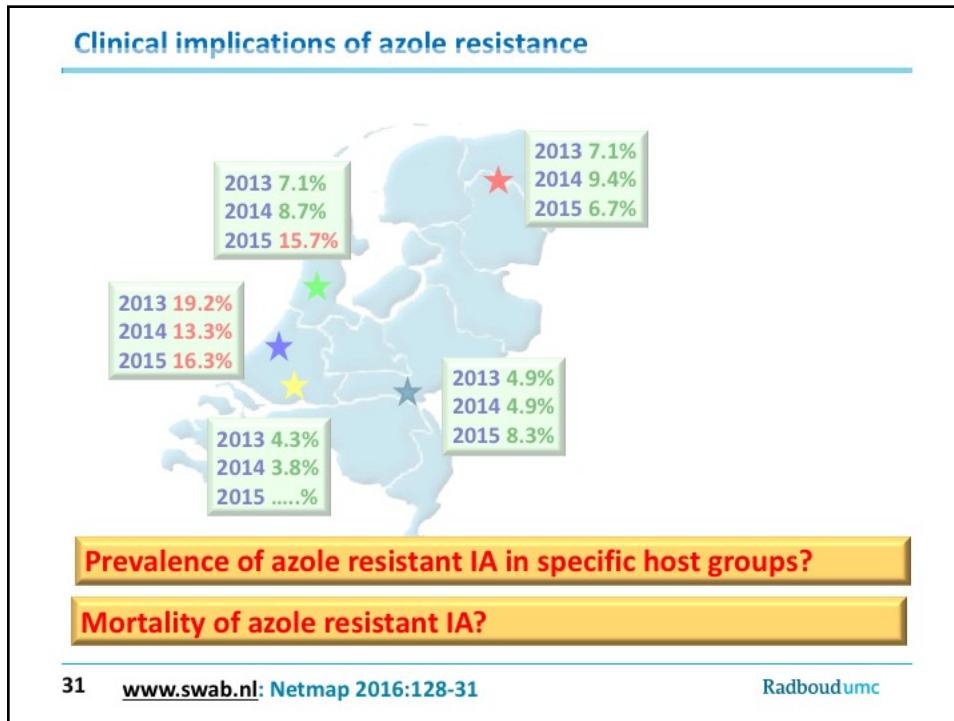
High mortality of CNS aspergillosis

Was the timing of therapy appropriate?

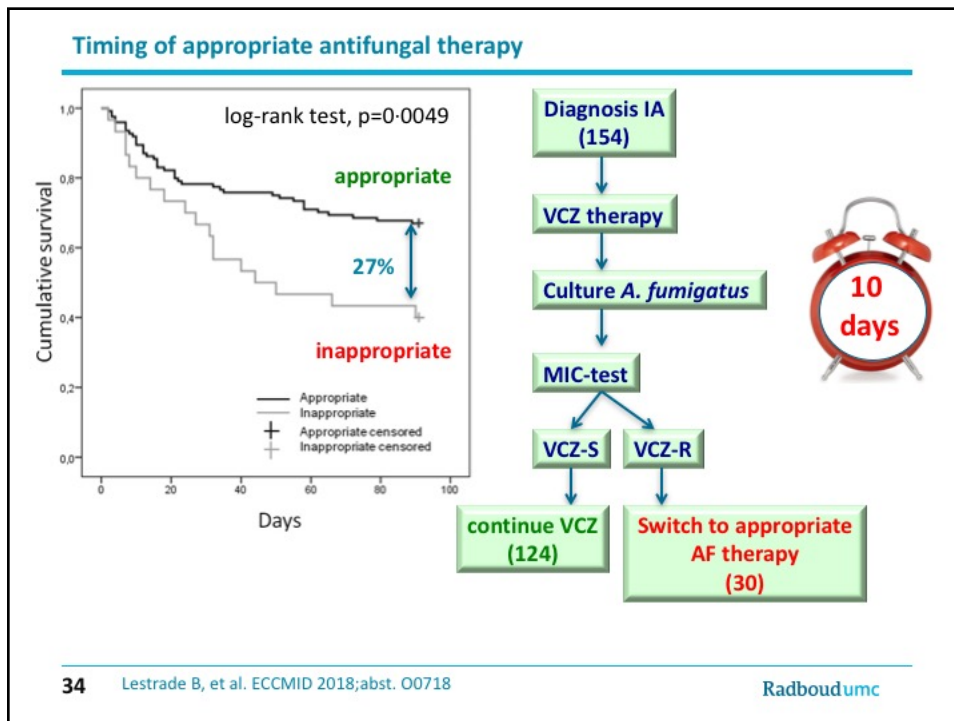
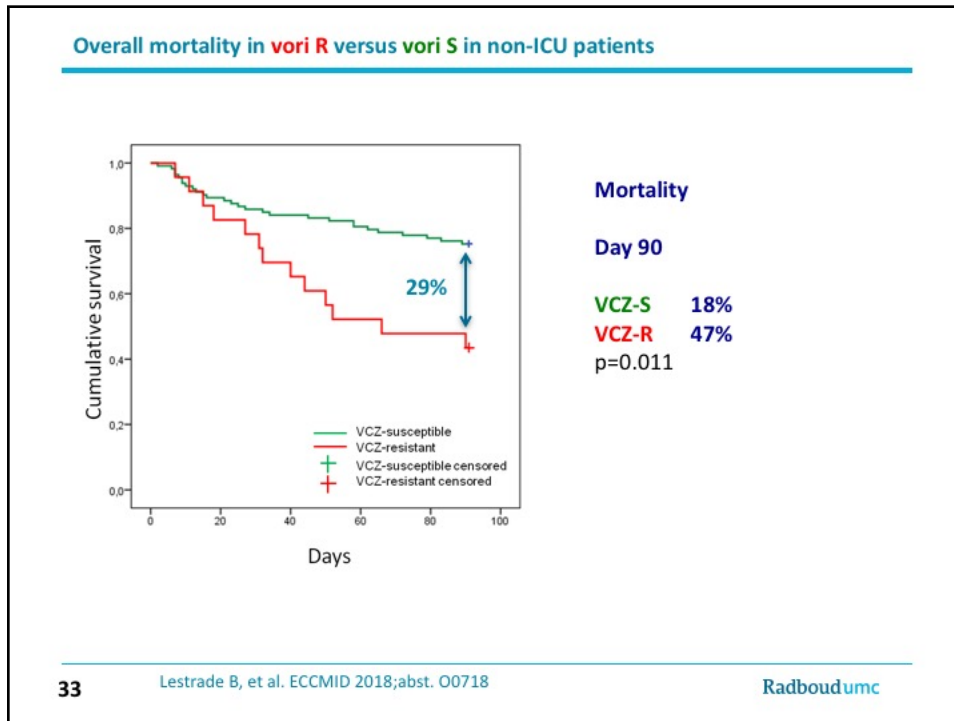
Did the azoleR isolate cause the disease?

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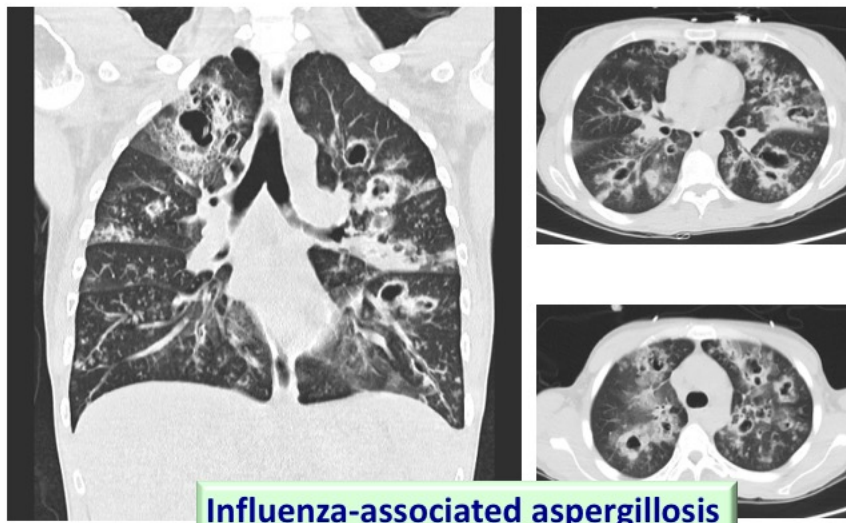


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On the move.....38 year old female admitted to the ICU



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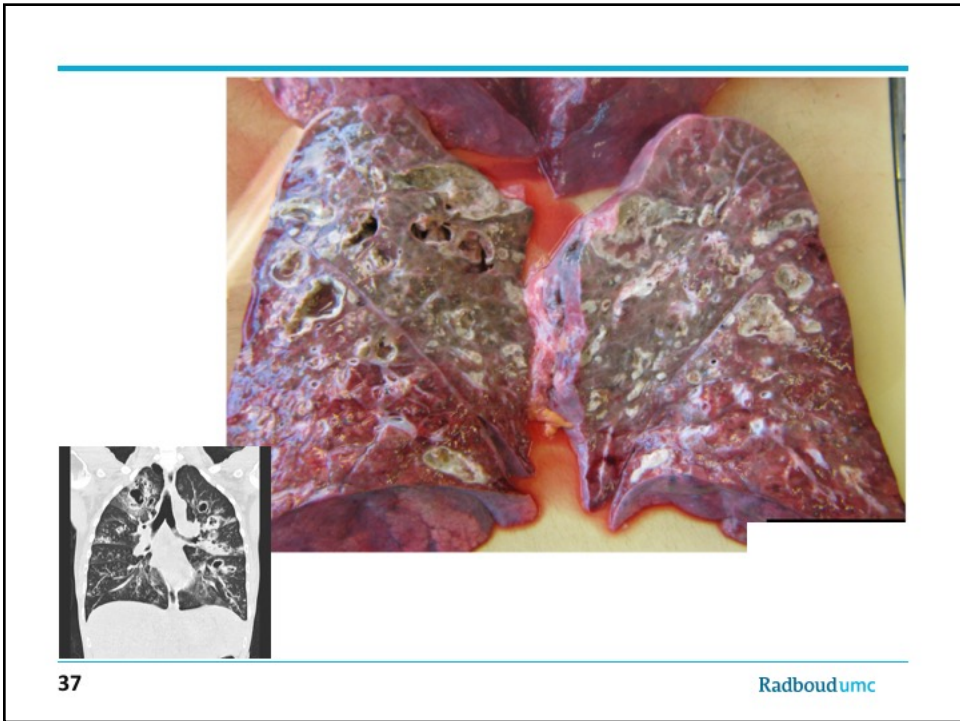
Aspergillus tracheobronchitis.....inside the bronchi



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Azole resistance

In vitro susceptibility

16 patients – 5 azole R (31%)

Patient ID/age	Underlying disease	Phenotype first culture (specimen)	Azole resistant isolate	MIC (mg/l)(interpretation)*						Resistance mutation	Initial antifungal therapy*	Subsequent treatment regimens*	Outcome*
				AmB	ITZ	VCZ	PDS	ISA	AFG				
2-1 / 34	None	Azole-resistant (BAL)	First culture	0.5 (S)	>8 (R)	2 (I)	0.5 (R)	>8 (R)	0.016	TR ₁₉₇ /L98H	Voriconazole (+7)	Li-AmB (+22)	Died (+27)
4-2 / 52	None	Mixed (sputum)	First culture	0.25 (S)	2 (I)	>8 (R)	0.5 (R)	>8 (R)	0.031	TR ₁₉₇ /Y121F/T289A	Voriconazole (0)	L-AmB (+4)	Died (+13)
5-5 / 38	None	Wild type (sputum)	At autopsy	0.5 (S)	8 (R)	2 (I)	0.5 (R)	8 (R)	0.031	TR ₁₉₇ /L98H	Voriconazole (-5)	VCZ+AFG (0); VCZ-Li-AmB (+5)	Died (+16)
2-3 / 44	Asthma, sinusitis	Mixed (sputum)	First culture	1 (S)	>8 (R)	4 (R)	0.5 (R)	>8 (R)	0.016	TR ₁₉₇ /L98H	Voriconazole (+11)	Li-AmB (+16); CAS (+26); Li-AmB (+30)	Survived
5-1 / 71	Lung cancer, COPD	Azole-resistant (sputum)	First culture	0.5 (S)	>8 (R)	4 (R)	0.5 (R)	>8 (R)	0.016	TR ₁₉₇ /L98H	Voriconazole (+5)	VCZ+AFG (+9); Li-AmB (+11); VCZ+AFG (+14)	Survived

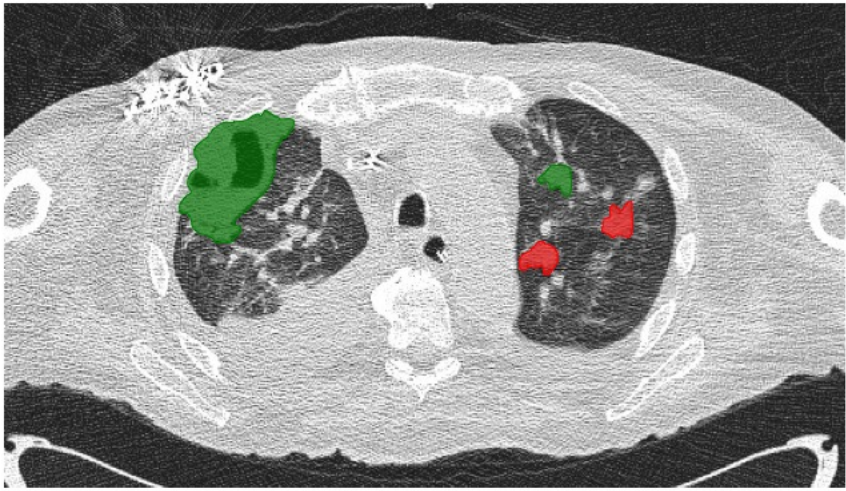


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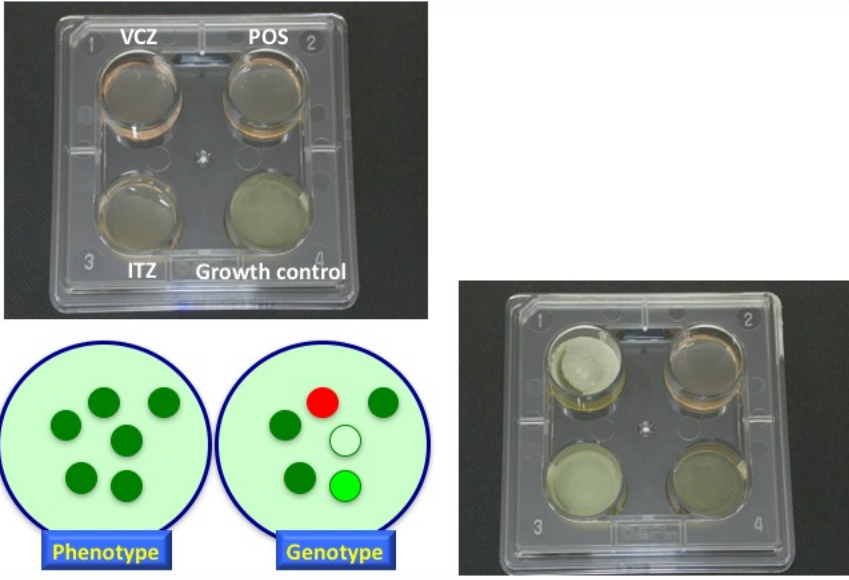
Pathogenesis of mixed infection



● Azole susceptible ● Azole resistant

39 Am J Resp Crit Care Med 2016;193:927-9 Radboudumc

Environmental route: Screening for azole resistance - VIPcheck™



VCZ POS
ITZ Growth control

Phenotype Genotype

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Post-azole era – after 2015?

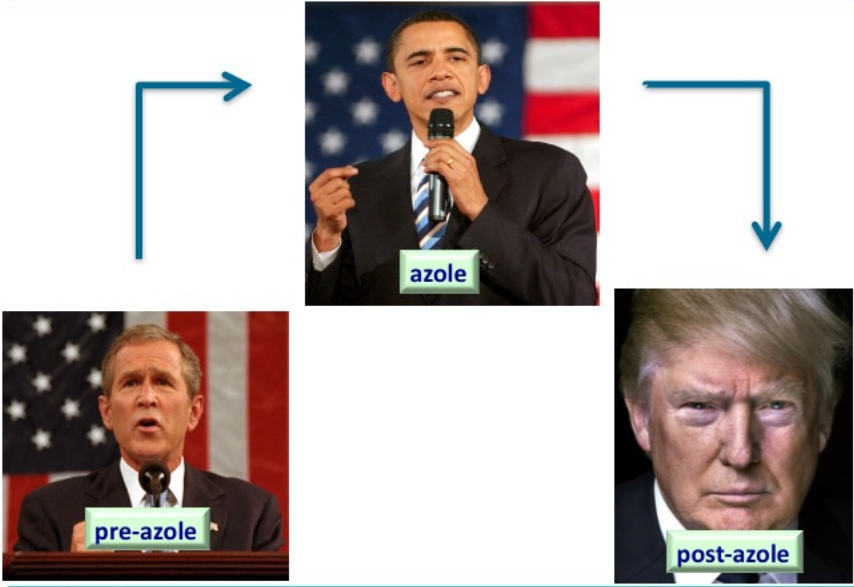
Liposomal AmB, combinations

Invasive azoleR pulmonary aspergillosis – mortality 80%

CNS azoleR aspergillosis – mortality >85%



A. fumigatus on the move.....

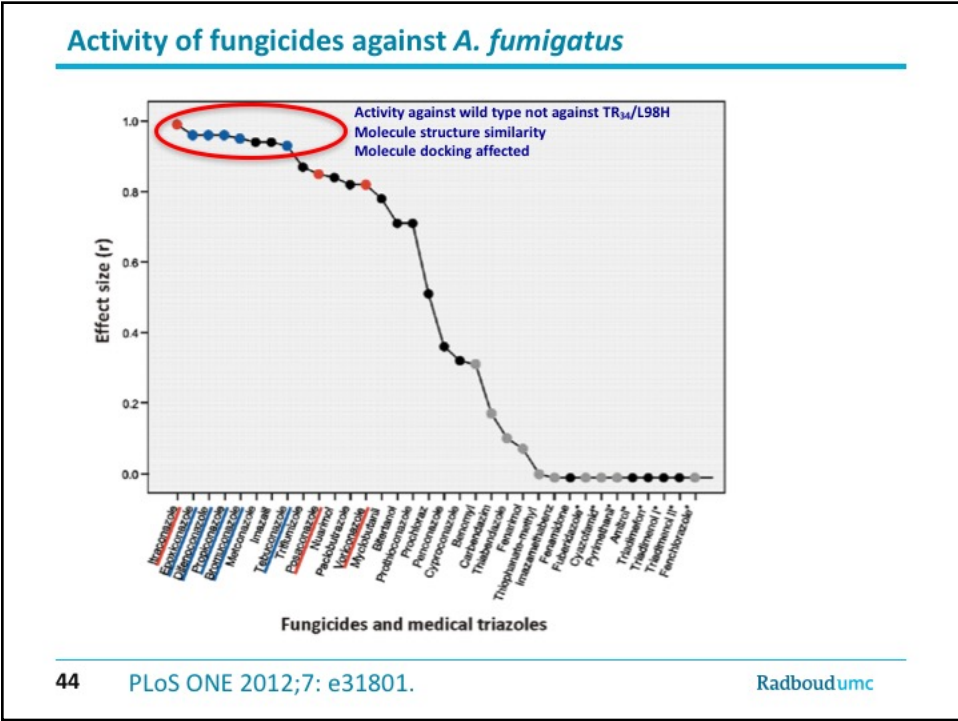
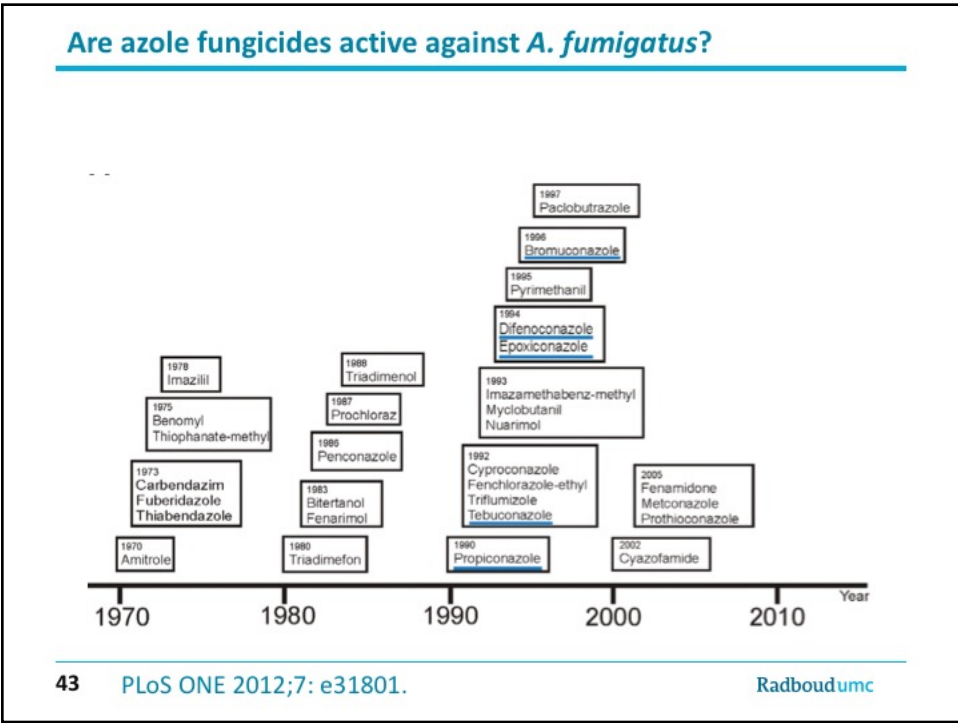


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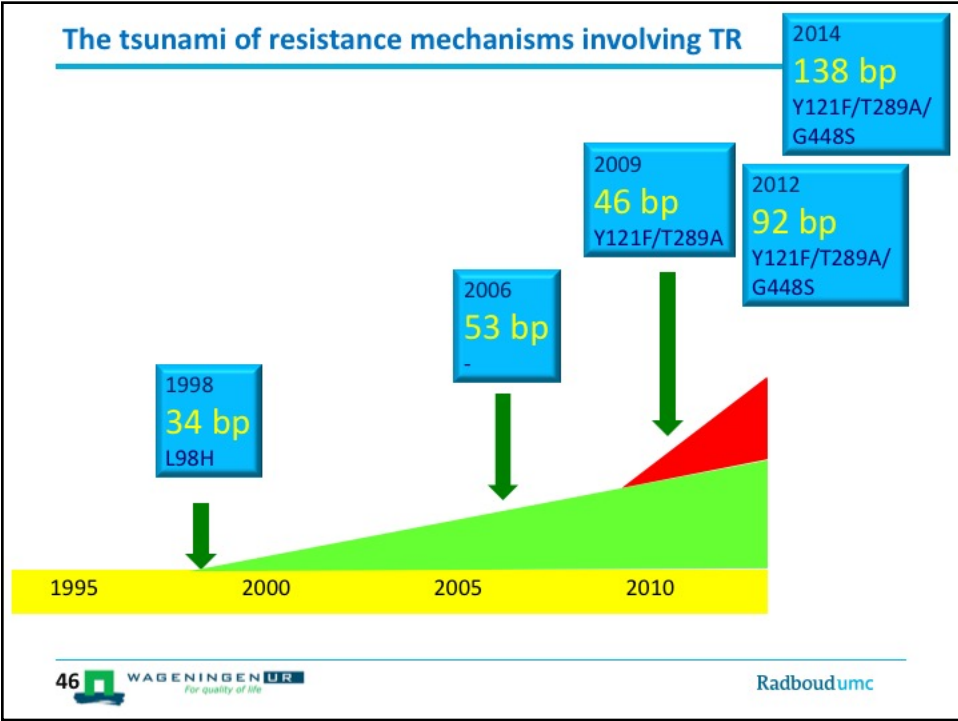
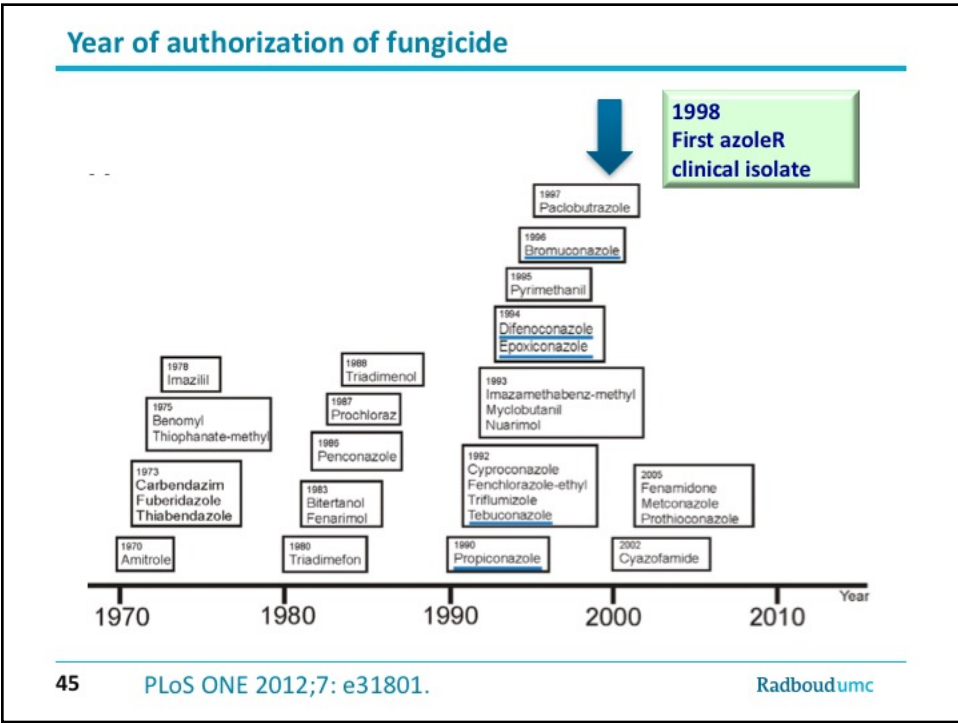
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Environmental azole exposure?

Plant protection



130,000 kg vs 400 kg

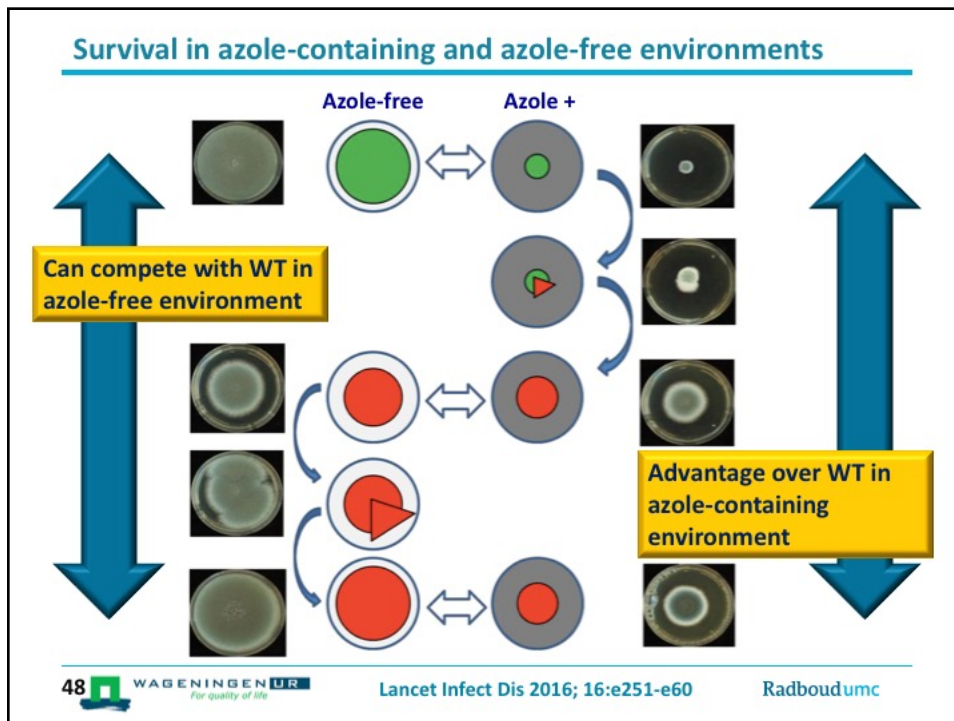
Material protection








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Survival in azole-containing and azole-free environments

Azole-resistant phenotype
 $TR_{34}/L98H$
 $TR_{46}/Y121F/T289A$

Fitness
 Survives in competition with WT

49 **WAGENINGEN UR** For quality of life
 Lancet Infect Dis 2016; 16:e251-e60
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In-host adaptation and triazole resistance

Starting azole therapy

Switching azole therapy


Stopping azole therapy

50 **WAGENINGEN UR** For quality of life
 Lancet Infect Dis 2016; 16:e251-e60
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Sampling of compost heaps in the Netherlands

A





Droevendaal, Wageningen
51° 58' 0" N,
5° 40' 0" E


B



Hillegom
52° 17' 30" N,
4° 34' 46" E





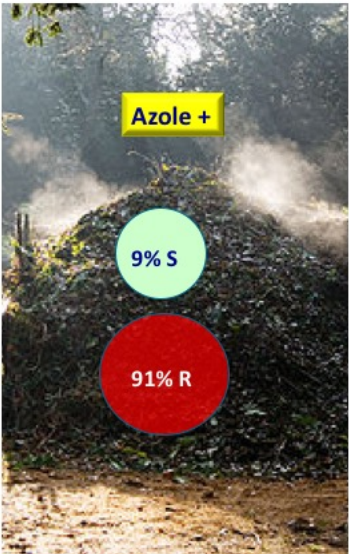
51  WAGENINGEN UR
For quality of life

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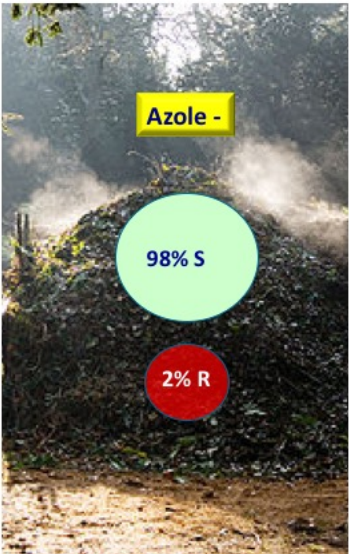
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Understanding resistance selection

Azole +



Azole -

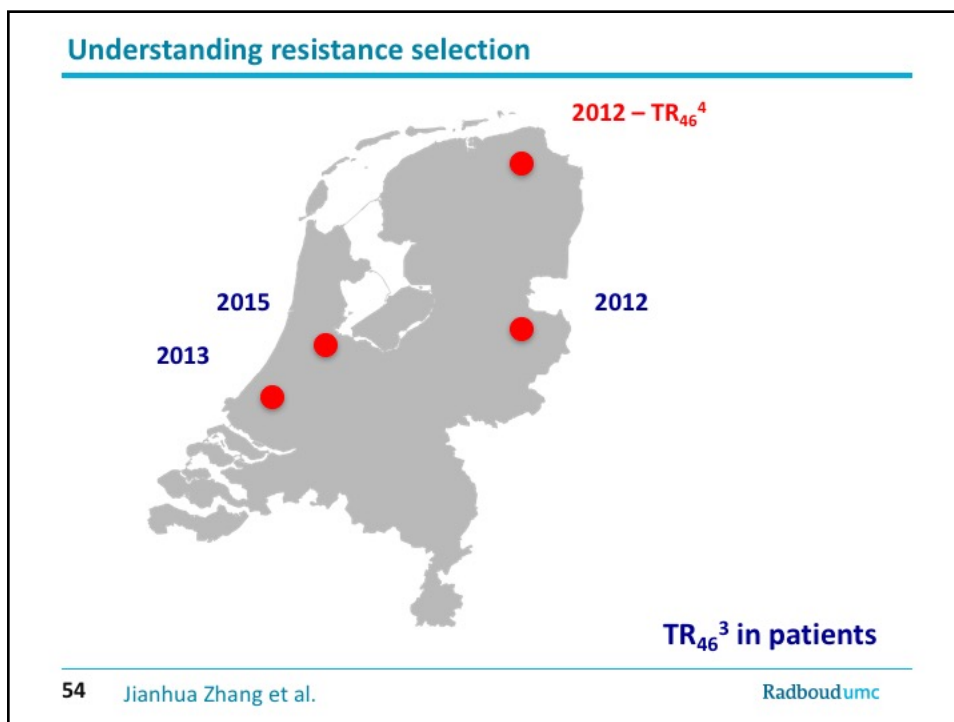
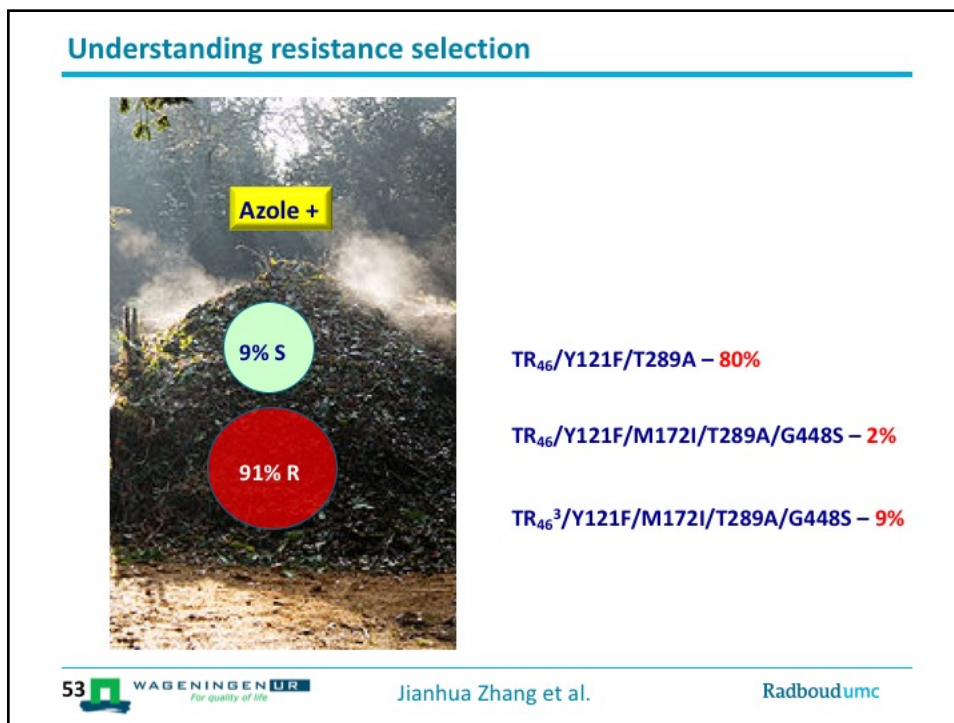


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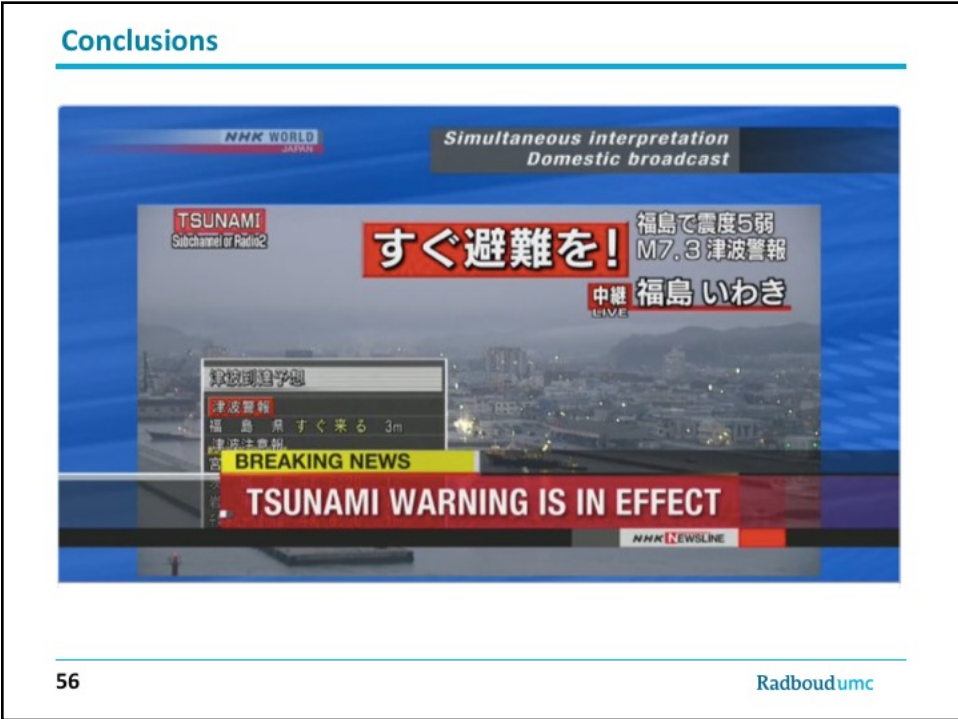
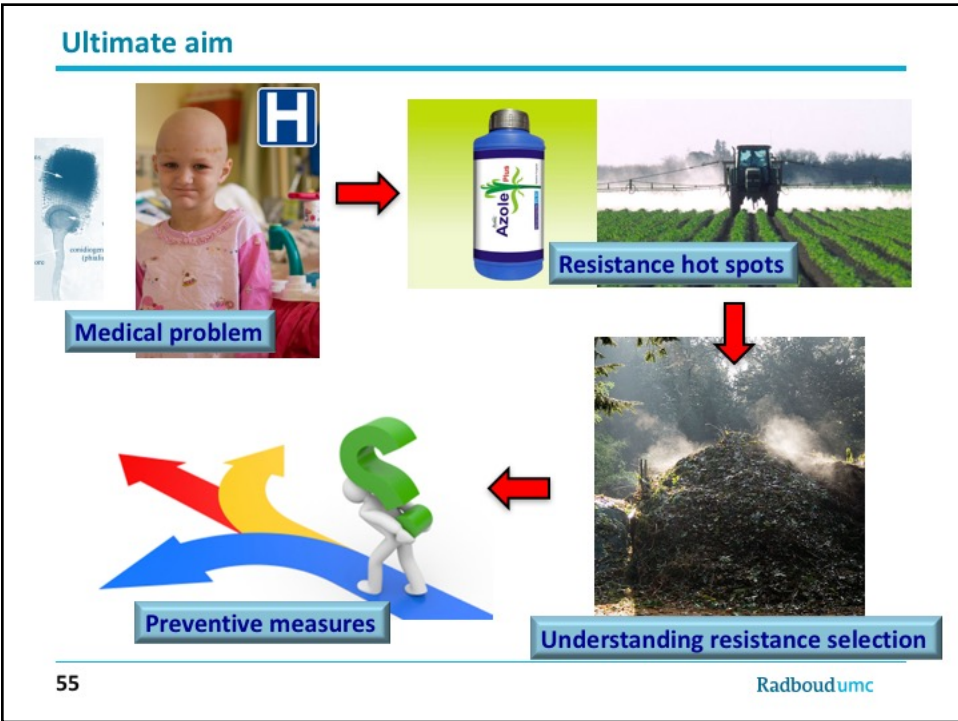
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The Race to Stop the Silent Tsunami of Antifungal Drug Resistance
Dr. Paul E. Verweij, Centre of Expertise in Mycology, Radboud University Medical Center
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Conclusions: evacuation is not an option....



Understanding resistance selection is critical to retain the azole class for both medical and non-medical applications

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September 27, 2018	<u>CHLORHEXIDINE USE AND BACTERIAL RESISTANCE</u> Speaker: Prof. Jean Yves Maillard , Cardiff University, Wales <i>(FREE European Teleclass - Broadcast live from the 2018 IPS conference)</i>
September 30, 2018	<u>Cottrell Lecture ... SURVEILLANCE BY OBJECTIVES: USING MEASUREMENT IN THE PREVENTION OF HEALTHCARE ASSOCIATED INFECTIONS</u> Speaker: Prof. Jennie Wilson , University of West London <i>(FREE European Teleclass - Broadcast live from the 2018 IPS conference)</i>
October 2, 2018	<u>Ayliffe Lecture ...THE IMPACT OF DISINFECTANTS ON ANTIMICROBIAL RESISTANCE - AN AYLIFFE PREDICTION</u> Speaker: Prof. Shaheen Mehtar , Stellenbosch University, Cape Town, South Africa <i>(FREE CBIC Teleclass)</i>
October 11, 2018	<u>INFECTION CONTROL CHAMPIONS ARE MADE, NOT BORN</u> Speaker: To be announced <i>(South Pacific Teleclass)</i>
October 17, 2018	<u>BIOFILMS IN THE HOSPITAL ENVIRONMENT - INFECTION CONTROL IMPLICATIONS</u> Speaker: Prof. Karen Vickery , Macquarie University, Australia <u>INFECTION PREVENTION CORE PRACTICES: RESETTING THE BAR FOR SAFE PATIENT CARE</u> Speaker: Prof. Ruth Carrico , University of Louisville
October 18, 2018	

Hosted by Paul Webber paul@webbertraining.com
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