Aspergillus sp. et résistances : quel impact pour vos patients ?
Le point de vue du mycologue

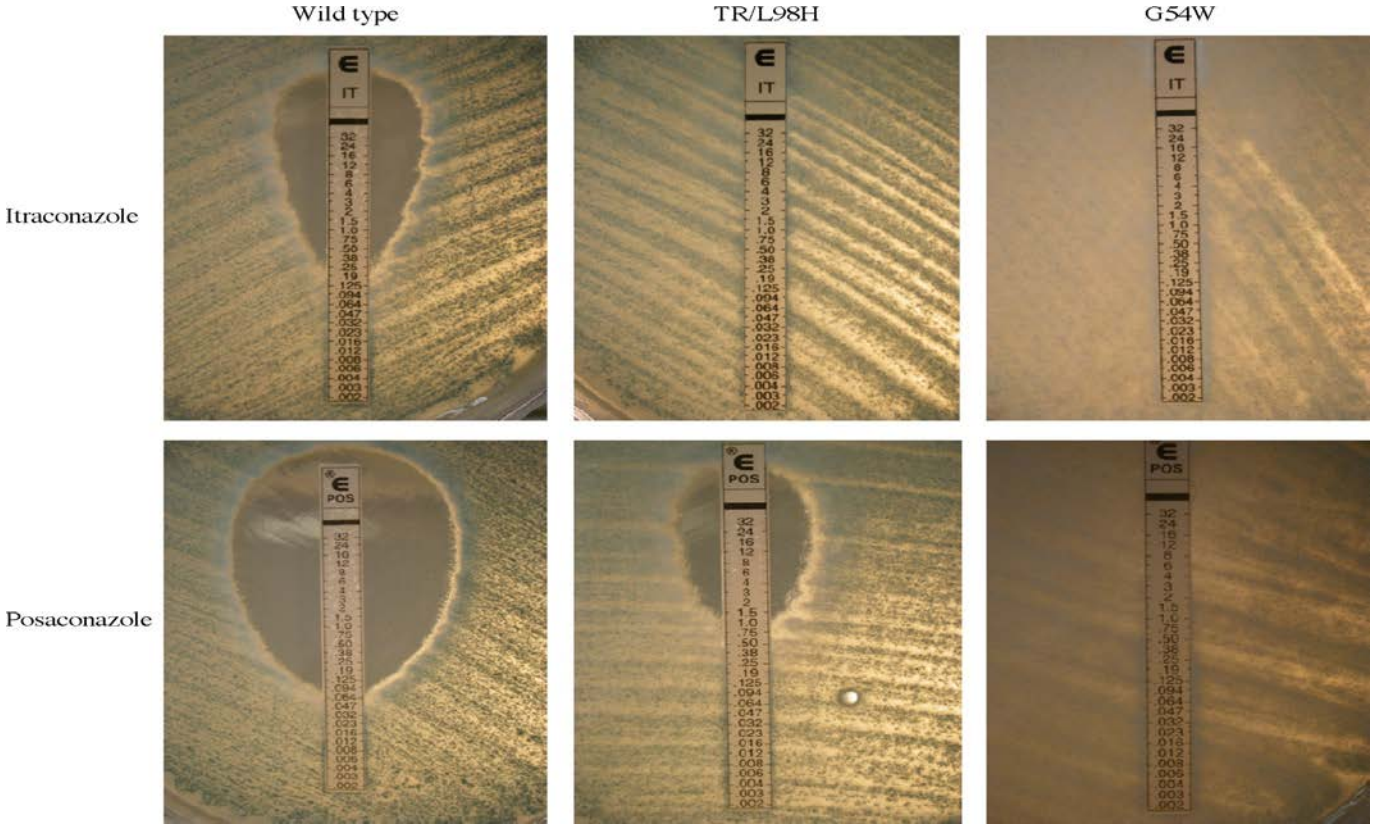
Paul E. Verweij, MD
Radboud university medical centre
June 2015

Radboudumc

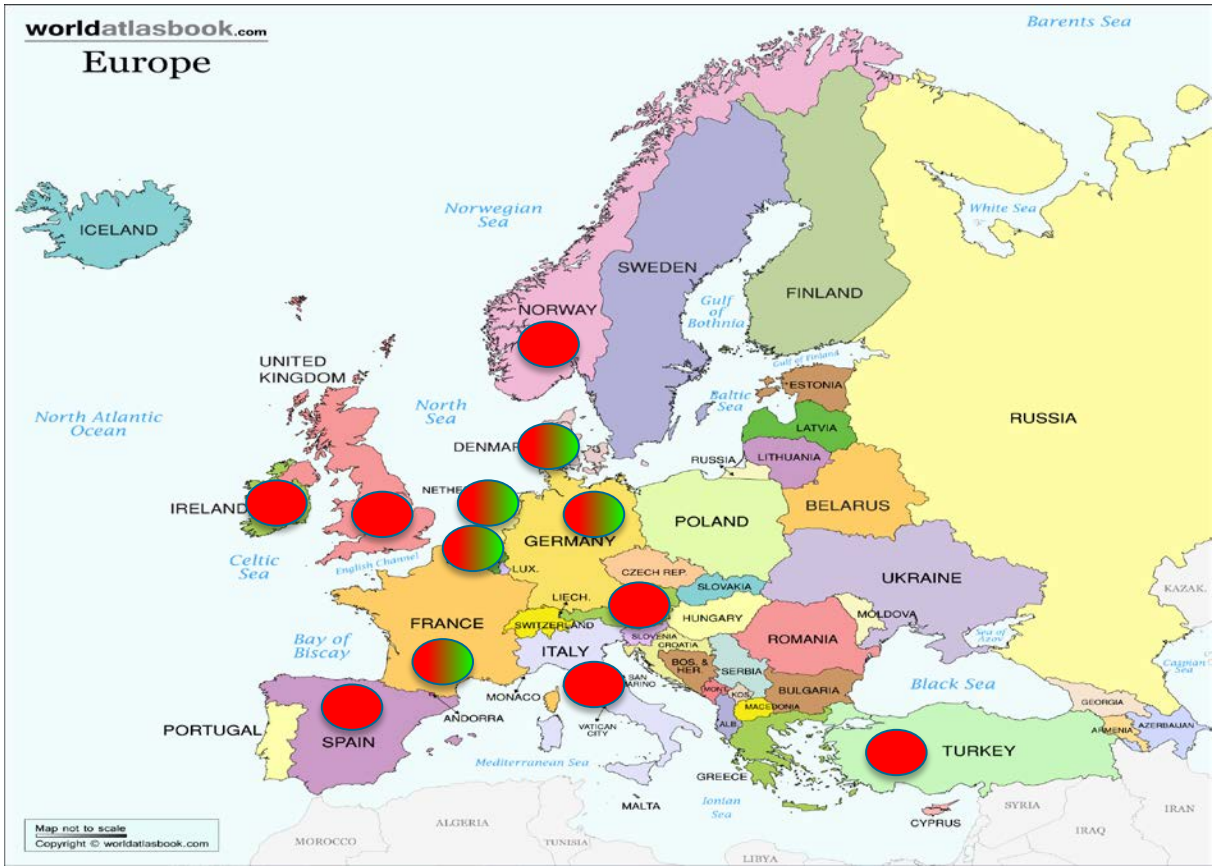
Disclosures

Research grants – advisory boards – speaker

Azole resistance in *Aspergillus fumigatus*



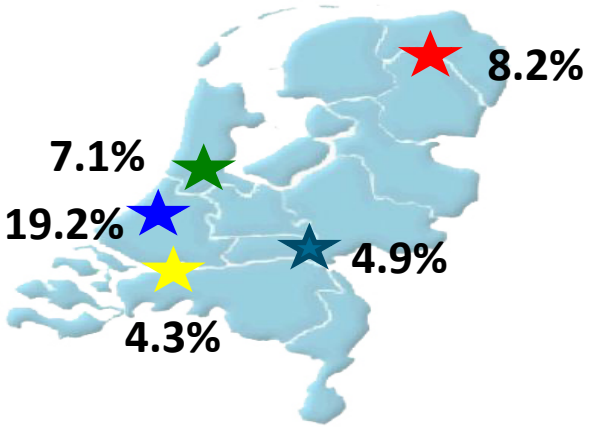
Azole resistance in *A. fumigatus* TR_{34}/L98H + TR_{46}/Y121F/T289A

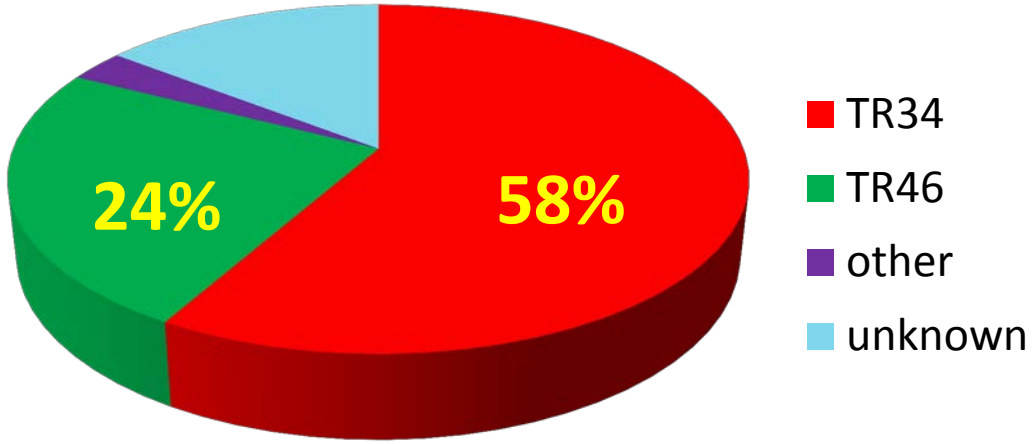


- Middle East
- Tanzania
- China
- India
- Australia

PLoS Pathog. 2013;9:e1003633

Azole resistance prevalence varies per institute





Overall 7.8%

Environmental: 82%

Azole resistance prevalence varies per department

Leiden University Medical Center:

2011 to 2013

ICU: **38 patients with *A. fumigatus* culture positive IA**
10 (26%) azole resistant

Van Paassen *et al., submitted*

Other departments: **24 (14%) azole-resistant *A. fumigatus* from 170 patients (p= 0.06).**

Utrecht University Medical Center:

2011 to 2013

105 *A. fumigatus* primary cultures from 105 patients at risk: hematology and ICU

The frequency of patients with azole-resistant isolates: 16.2%

hematology	**24.6%**
ICU	**4.5%**

Fuhren *et al., submitted*

La France

Med Mycol. **2010**;48:197-200.

J Antimicrob Chemother. **2011**;66:371-4.

Antimicrob Agents Chemother. **2012**;56:869-74.

J Antimicrob Chemother. **2012**;67:1870-3

Antimicrob Agents Chemother. **2012**;56:4948-50.

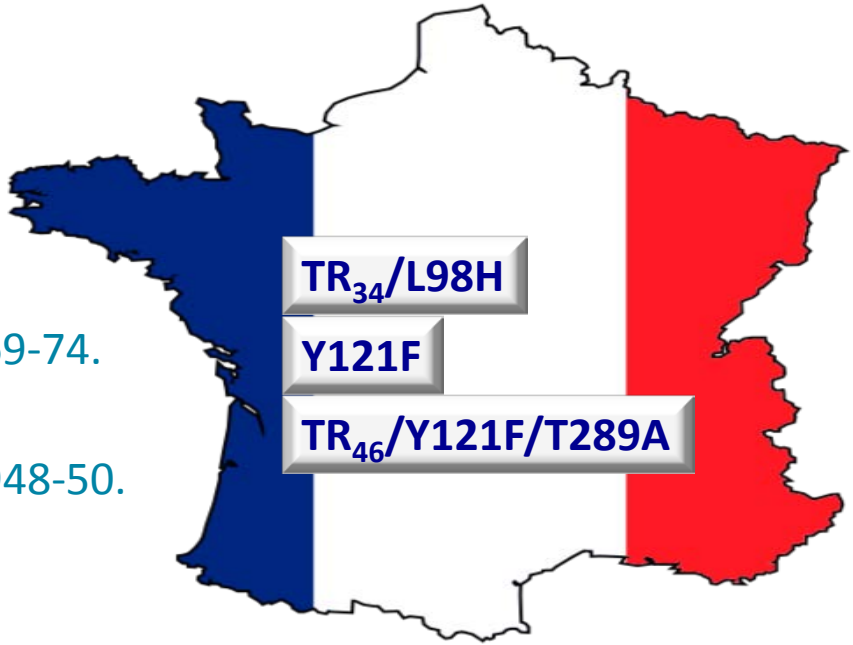
Poult Sci. **2014**;93:12-5.

J Clin Microbiol. **2014**;52:1724-6

J Antimicrob Chemother. **2014**;69:3244-7.

Antimicrob Agents Chemother. **2015** Apr 27.

Med Mycol. **2015** May 30

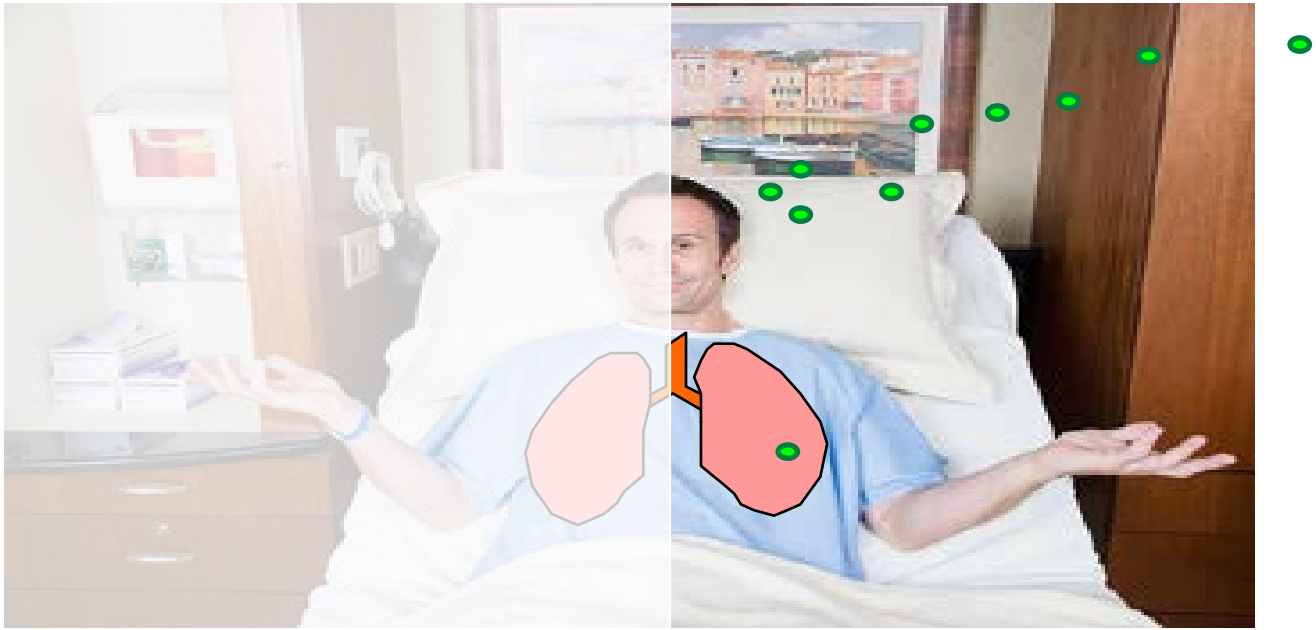


Mortality in culture-positive azole R invasive aspergillosis

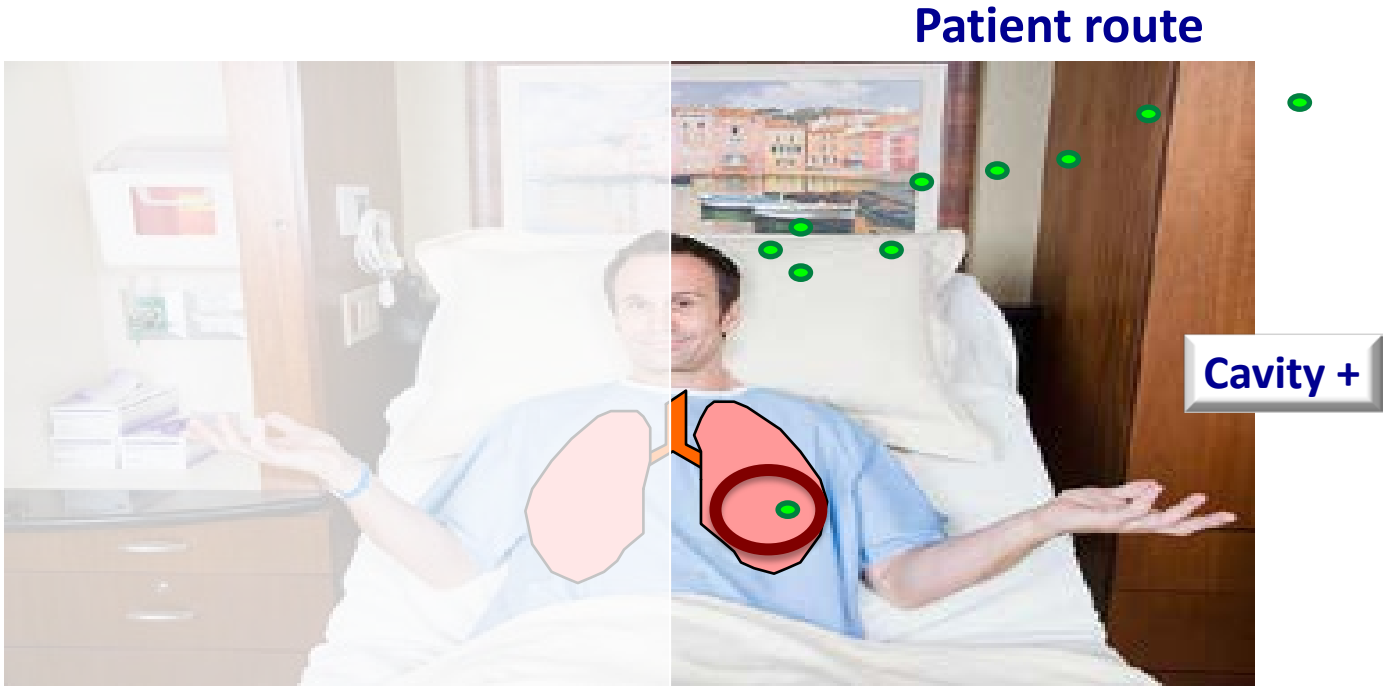
Country	Patient group	Resistance mechanism	Failure/mortality	Reference
Netherlands	Various	TR_{34}	7 of 8 **(88%)**	EID 2011;17:1846-54
Netherlands	Various	TR_{46}	6 of 8 **(50-75%)**	CID 2013;57:513-20
Netherlands	ICU	TR_{34} and TR_{46}	10 of 10 **(100%)**	van Paassen, *submitted*
Germany	HSCT	TR_{34}	7 of 8 **(88%)**	JAC 2015;70:1522-6

Clinical implications……

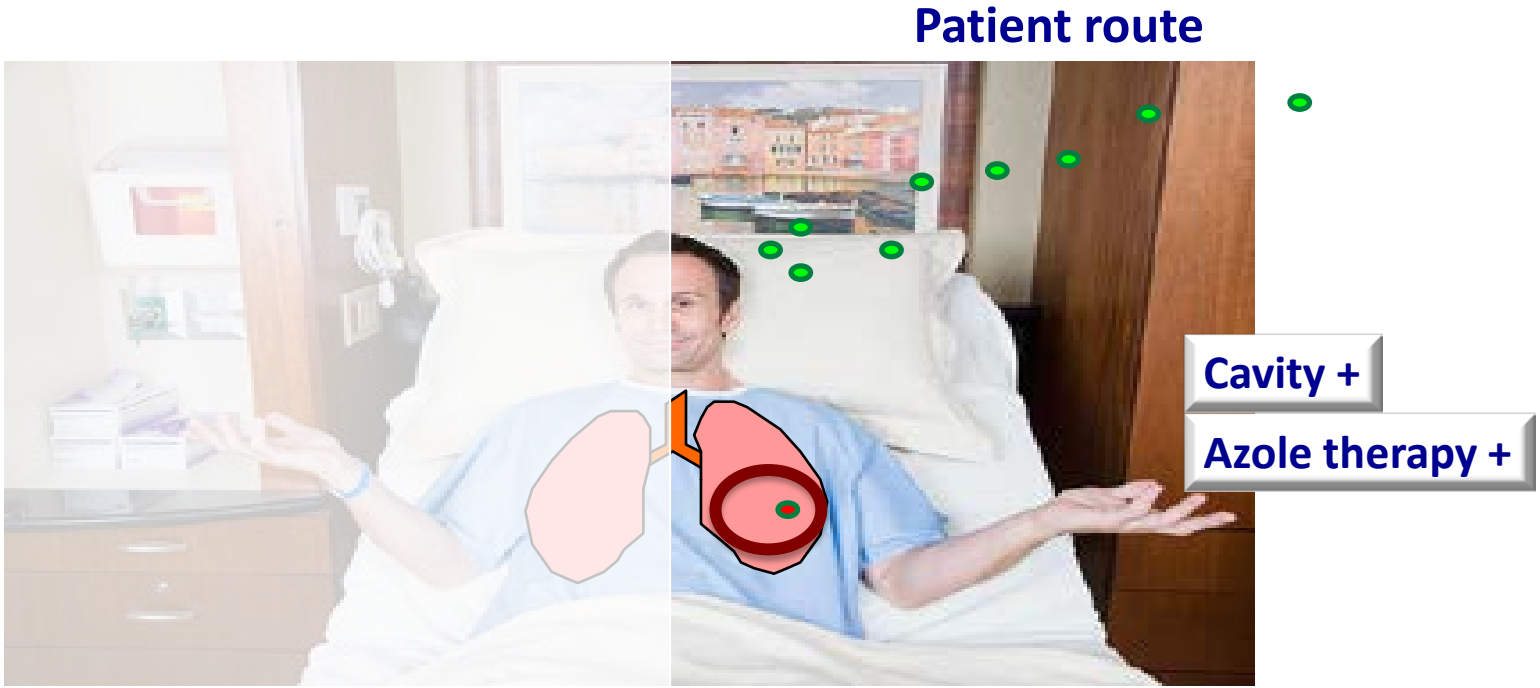
Patient route



Clinical implications……

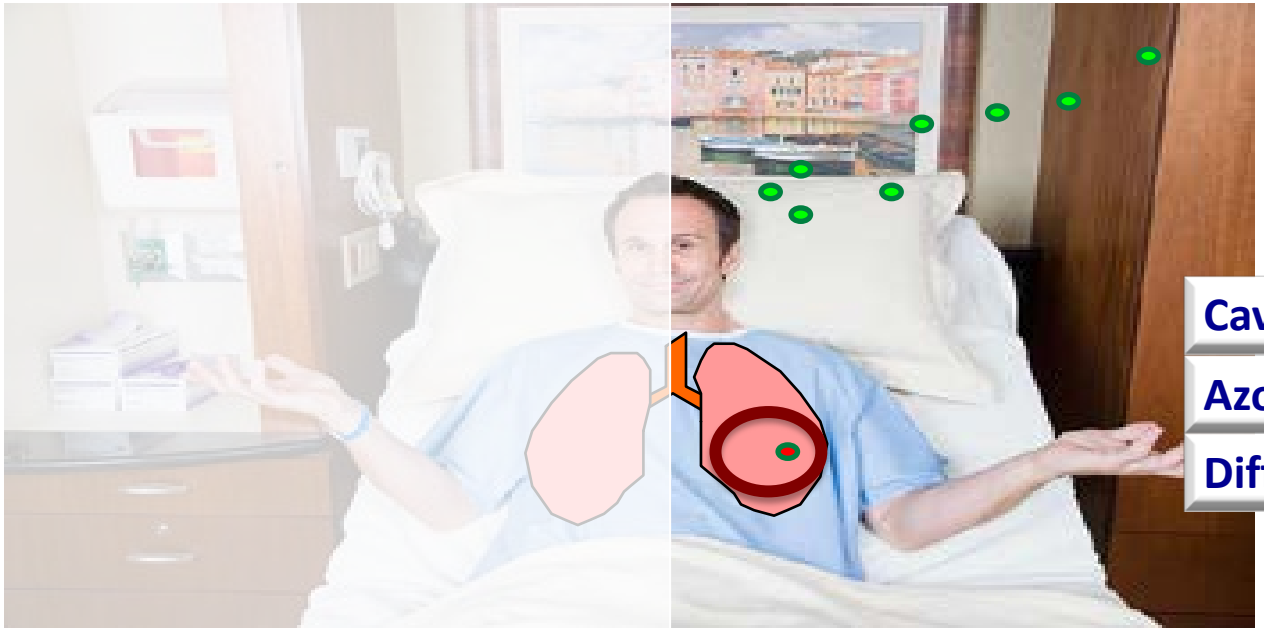


Clinical implications……



Clinical implications……

Patient route



Cavity +

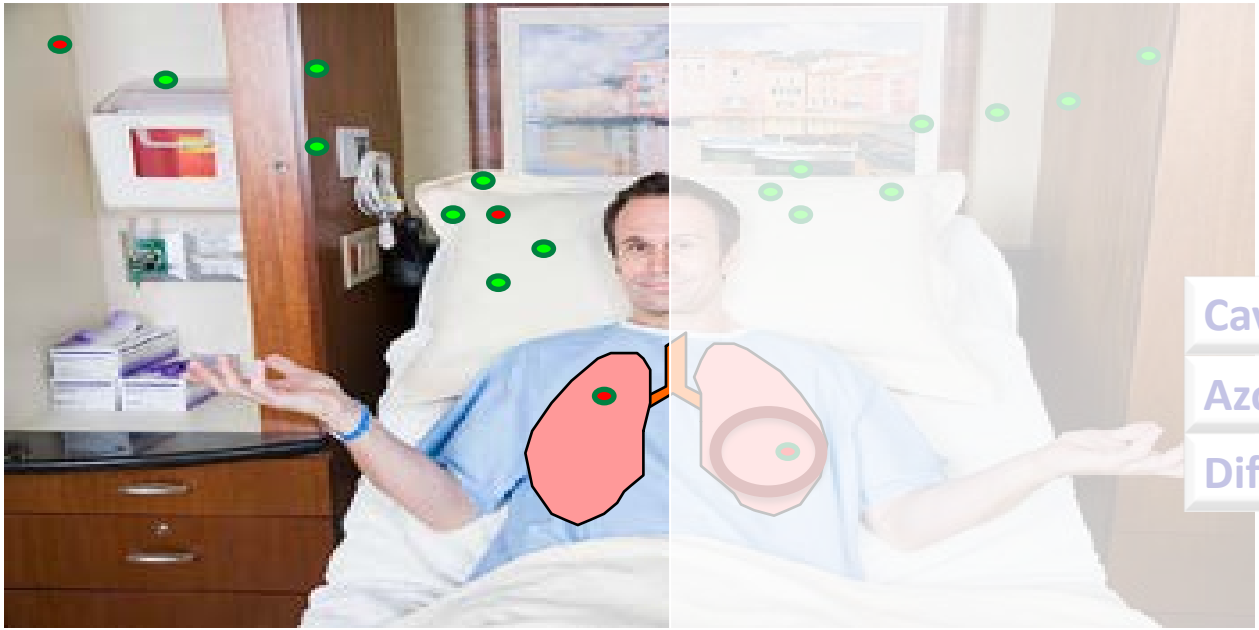
Azole therapy +

Different mutations

Clinical implications……

Environmental route

Patient route



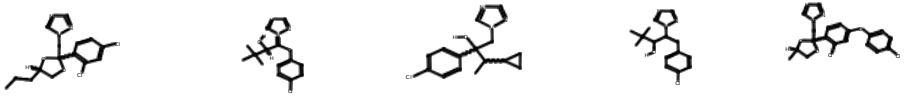
Cavity +

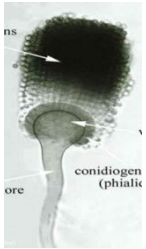
Azole therapy +

Different mutations

The environmental route

Propiconazole; tebuconazole; epoxiconazole; difenoconazole; bromuconazole



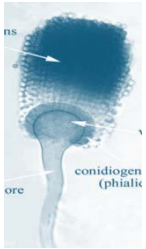


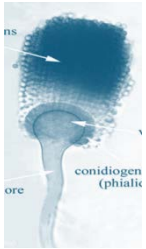
TR_{34}/L98H

TR_{53}

TR_{46}/Y121F/T289A

G54?



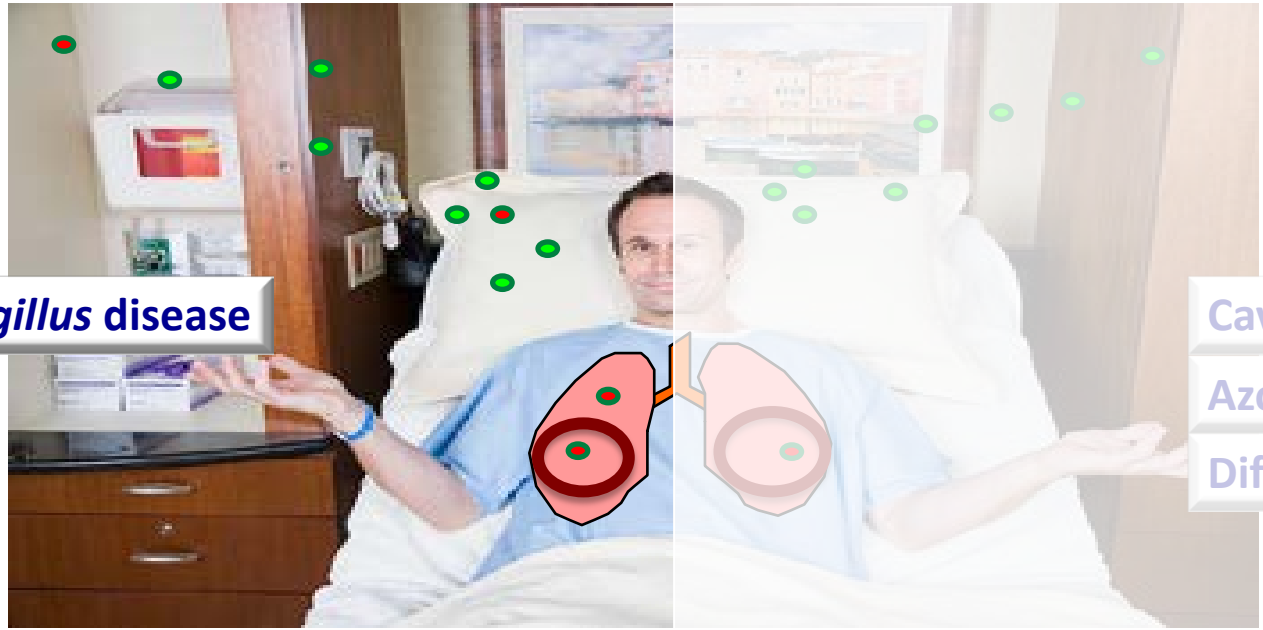


Medical azoles

Clinical implications……

Environmental route

Patient route



Any *Aspergillus* disease

Cavity +

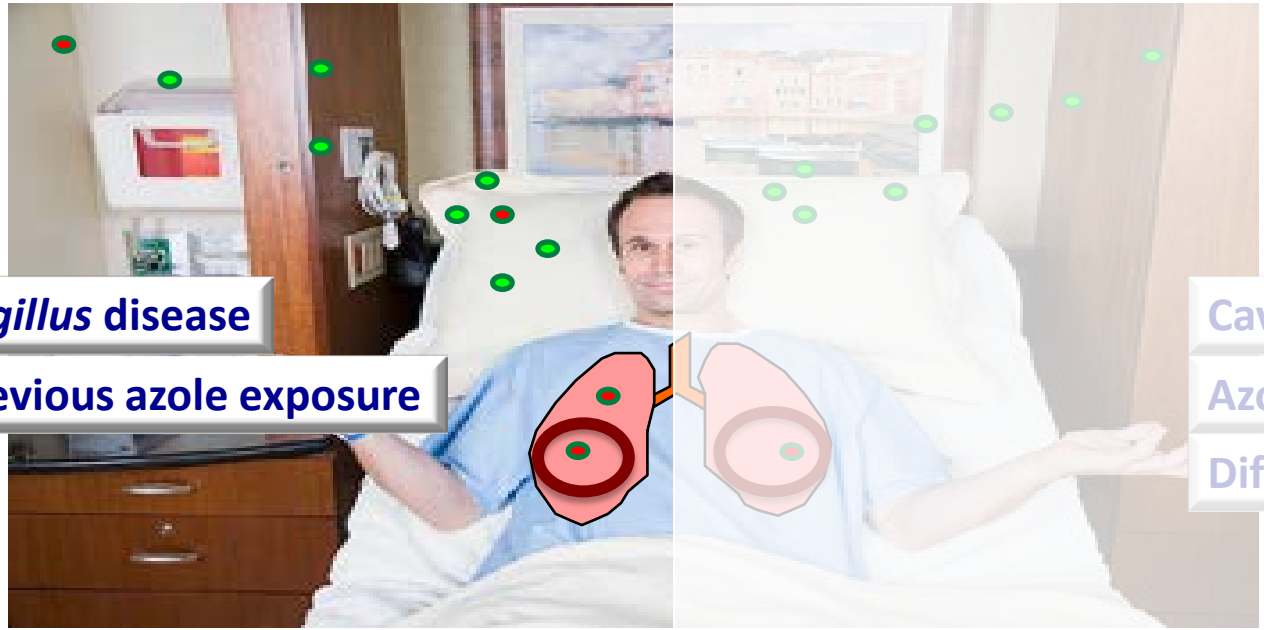
Azole therapy +

Different mutations

Clinical implications……

Environmental route

Patient route



Any *Aspergillus* disease

64% no previous azole exposure

Cavity +

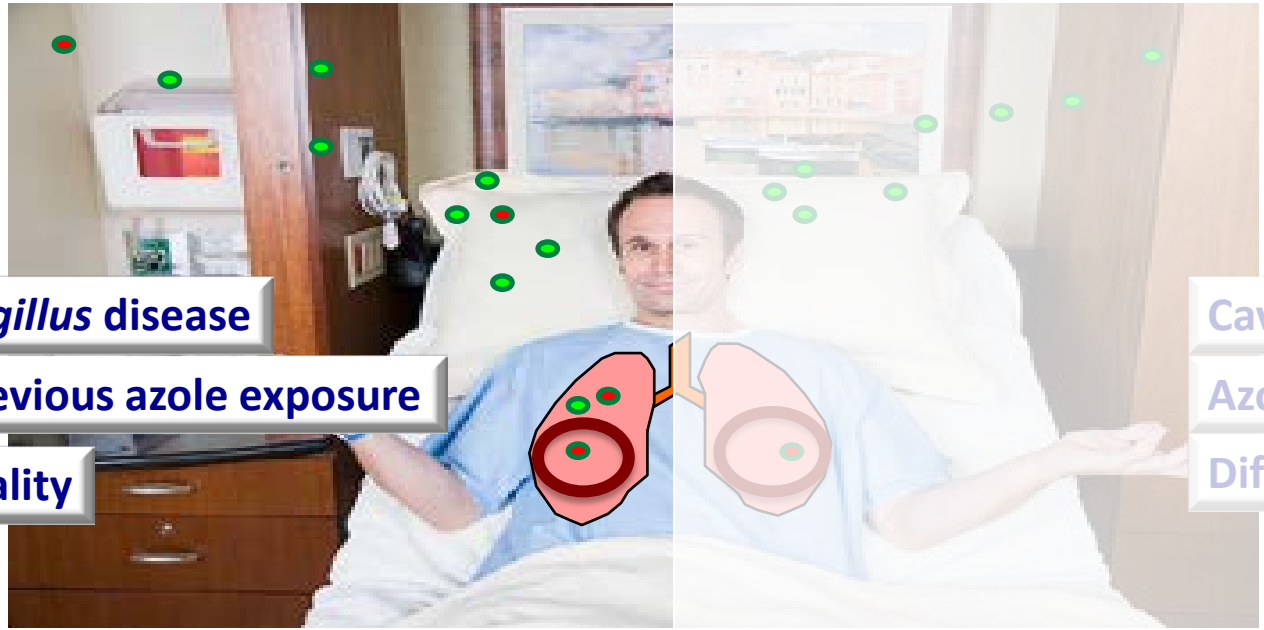
Azole therapy +

Different mutations

Clinical implications……

Environmental route

Patient route



Any *Aspergillus* disease

64% no previous azole exposure

High mortality

Cavity +

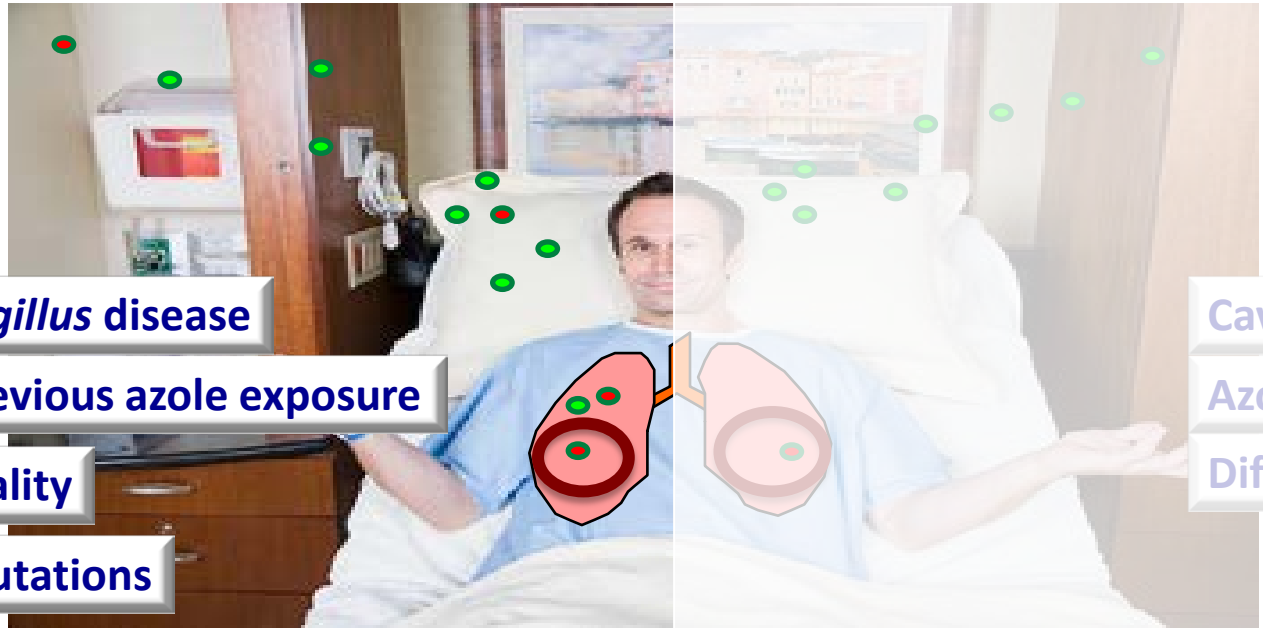
Azole therapy +

Different mutations

Clinical implications……

Environmental route

Patient route



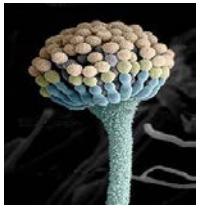
- Any *Aspergillus* disease
- 64% no previous azole exposure
- High mortality
- Specific mutations

- Cavity +
- Azole therapy +
- Different mutations

How to treat azole R aspergillosis?

WT

M220K



TR_{34}/L98H

G54W

AAC 2010; 54:860-5

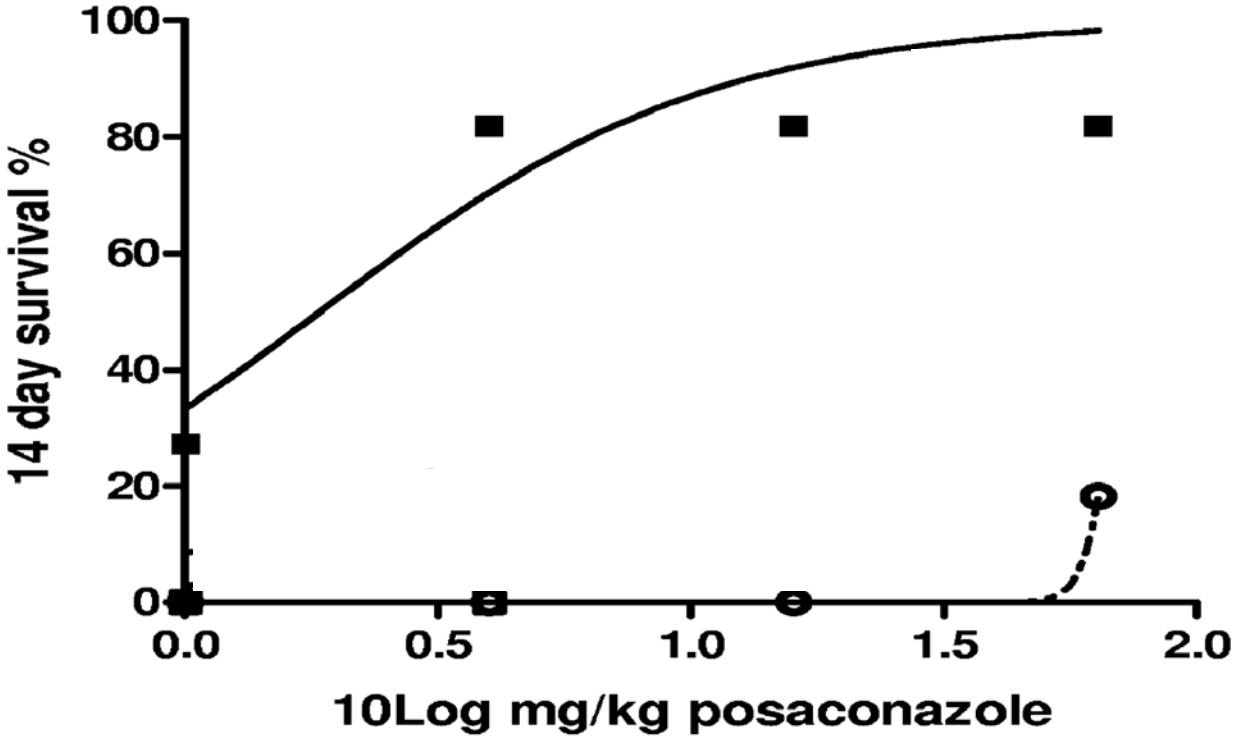
Radboudumc

Can we still use the azoles?

	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

AAC 2010; 54:860-5

In vivo efficacy of posaconazole

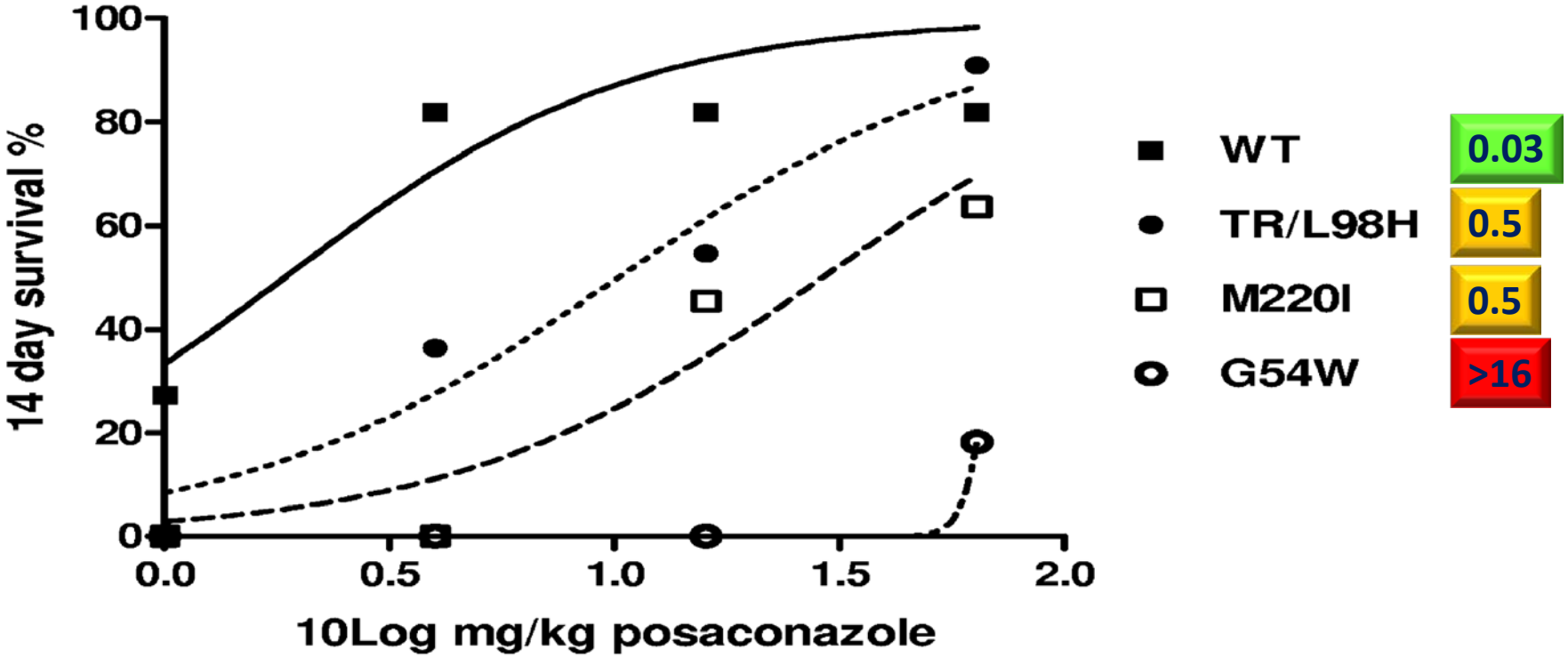


0.03

>16

AAC 2010; 54:860-5.

What about isolates with attenuated susceptibility?



AAC 2010; 54:860-5.

Radboudumc

Summary of *in vivo* models of IA

Voriconazole

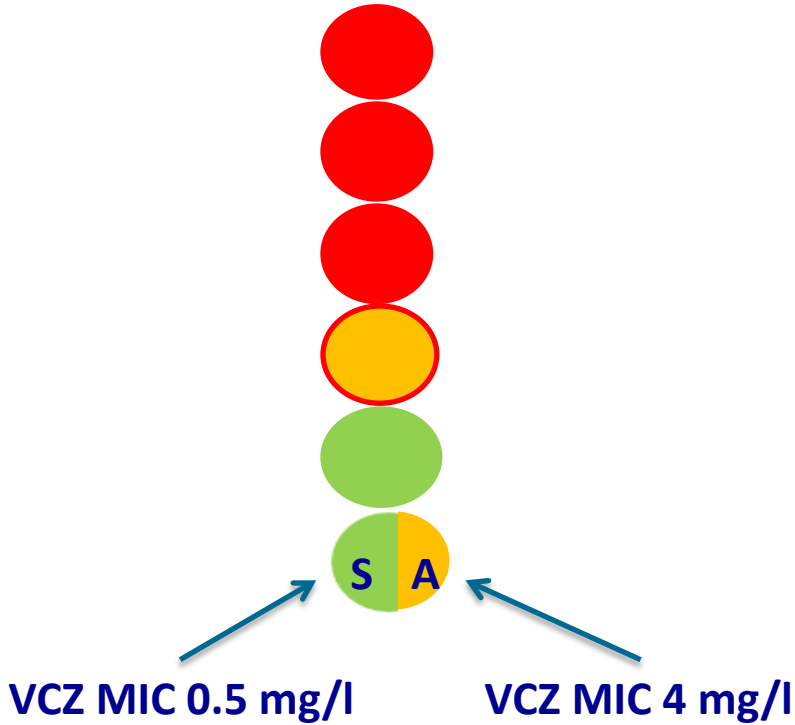
Posaconazole

Isavuconazole

Anidulafungin

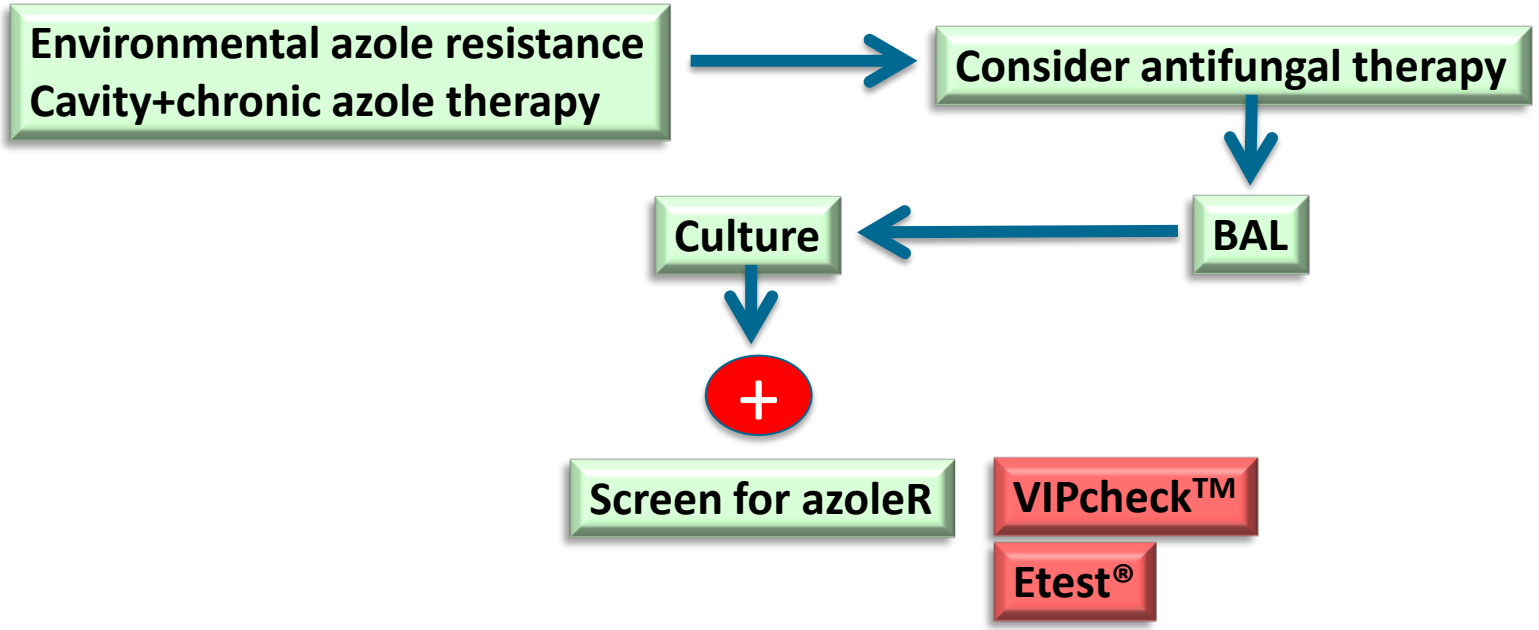
Liposomal amphotericin B

Voriconazole + Anidulafungin

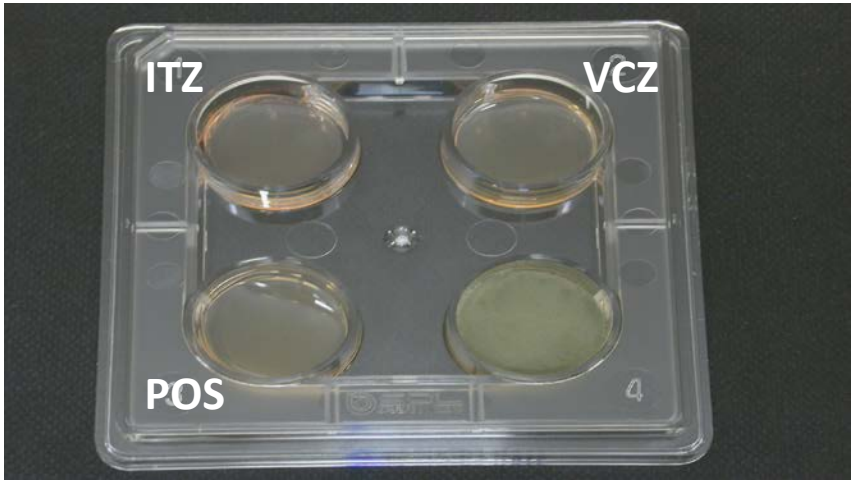


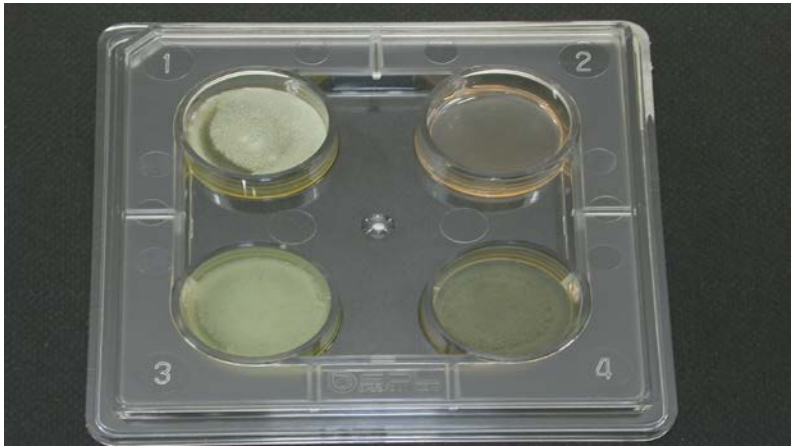
MIC >16 mg/l ???

How the laboratory helps the clinician: diagnostic tools

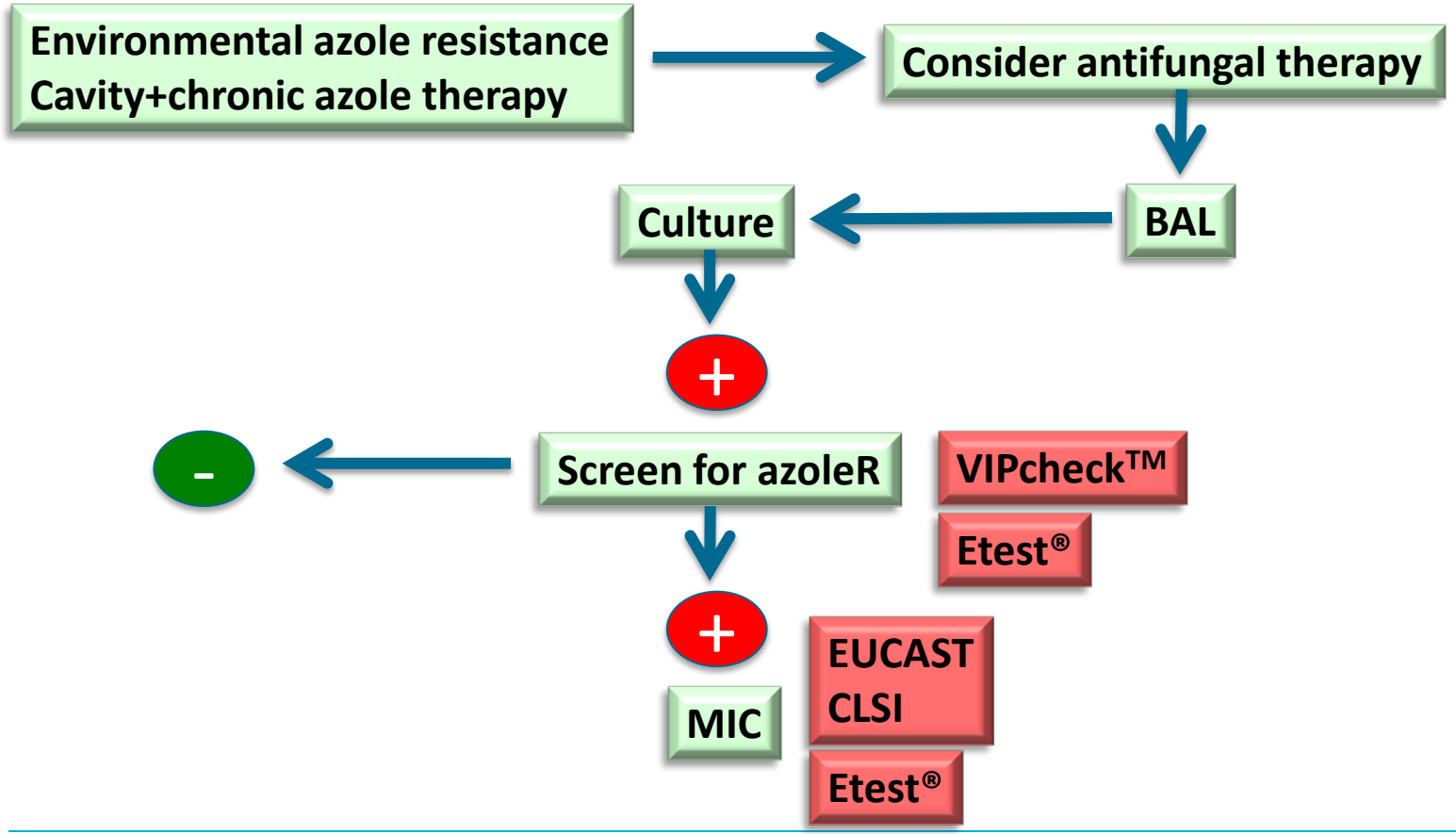


Screening for azole resistance: VIPcheck™

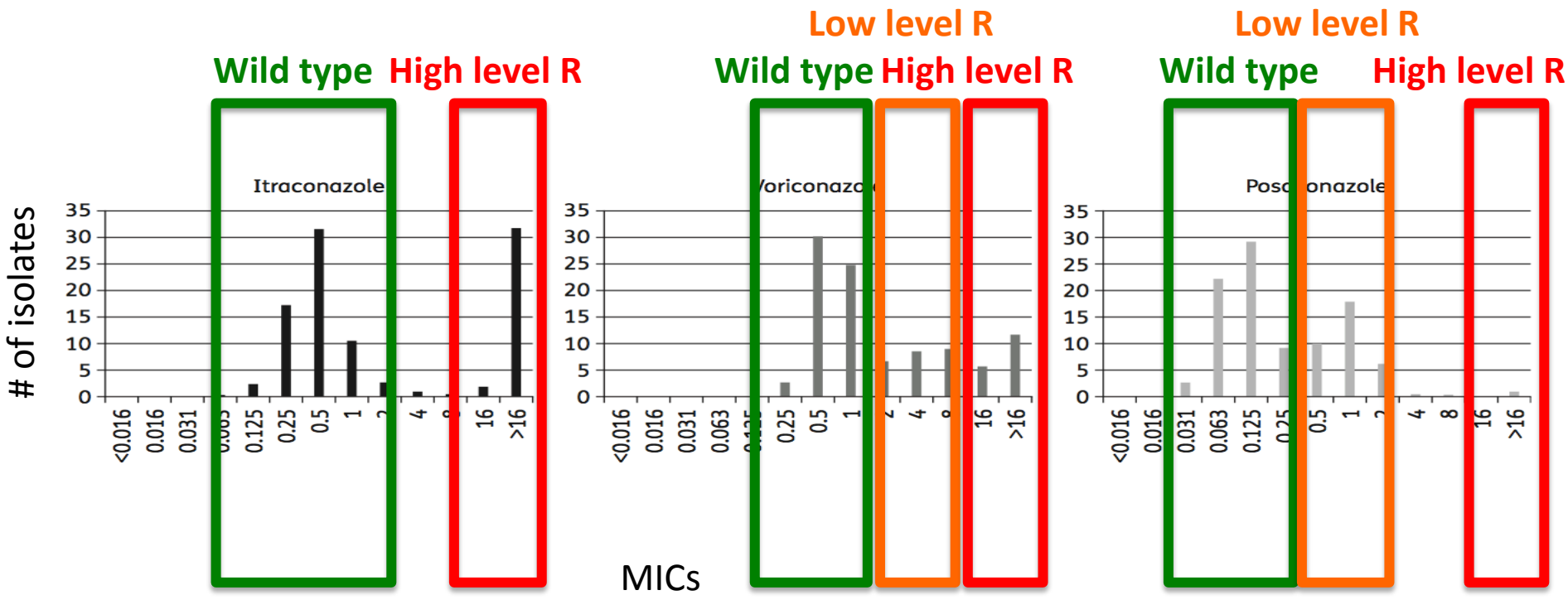




How the laboratory helps the clinician: diagnostic tools

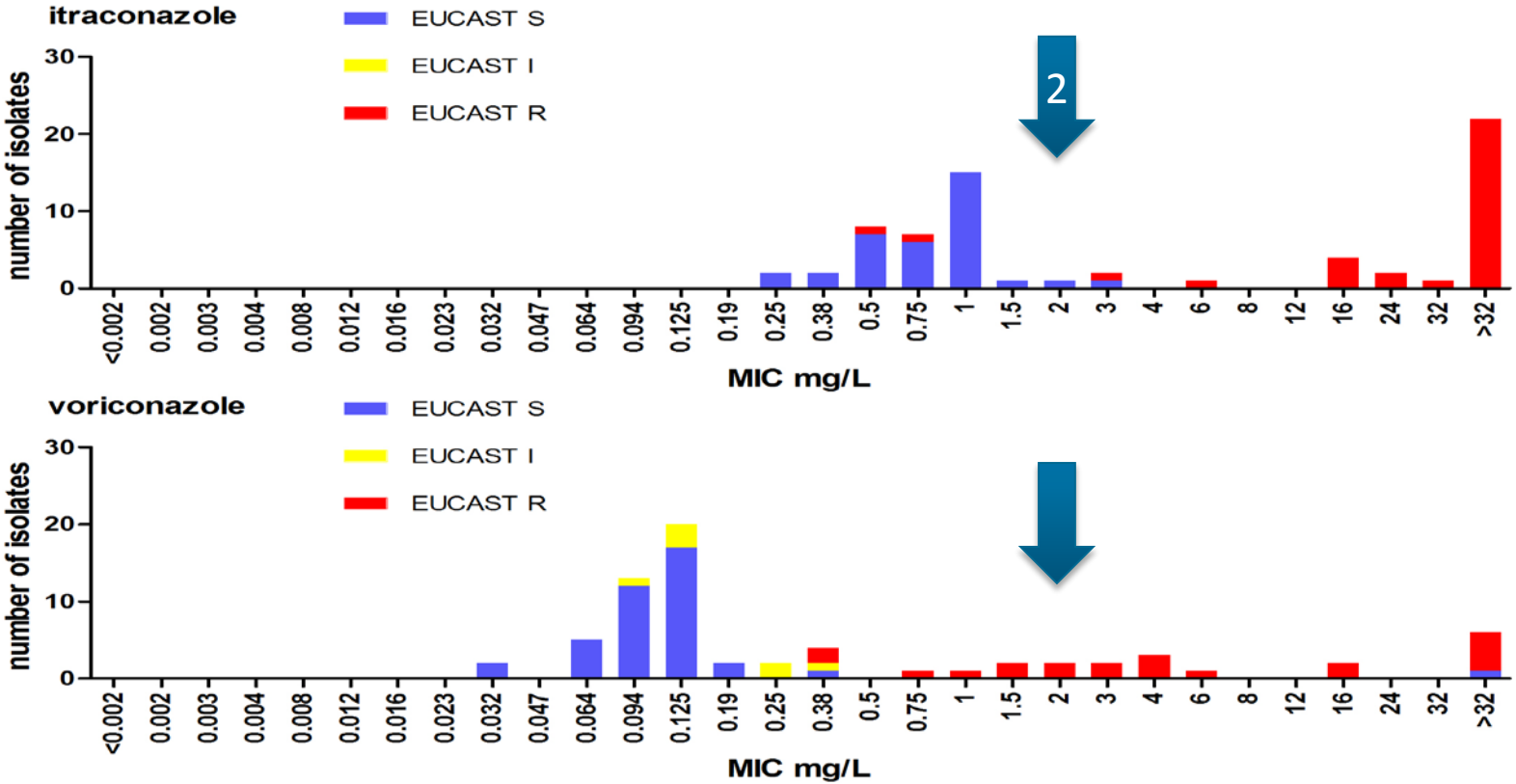


EUCAST: MIC distributions for 952 clinical *A. fumigatus* isolates

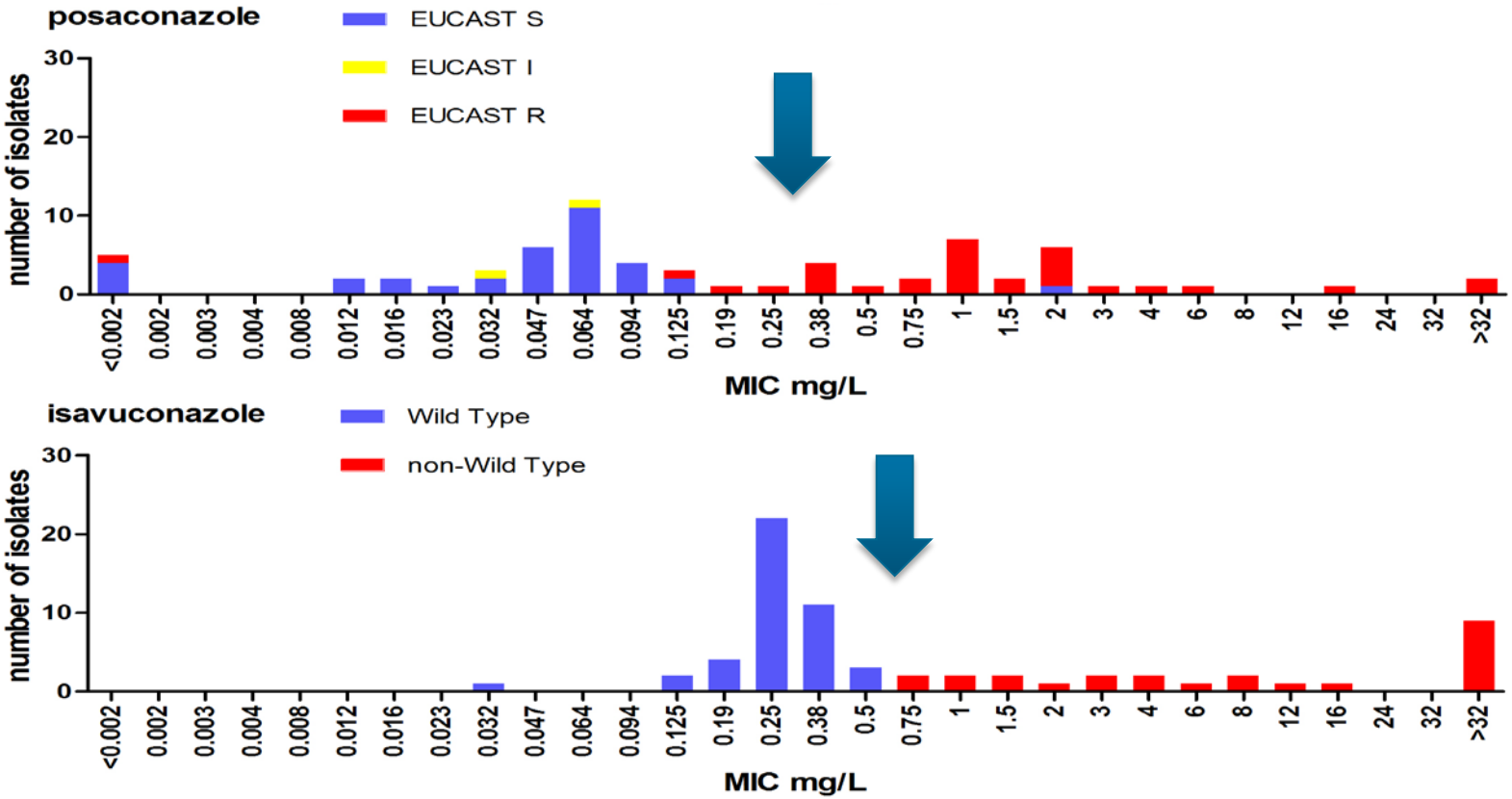


J Antimicrob Chemother 2015;70:178–81

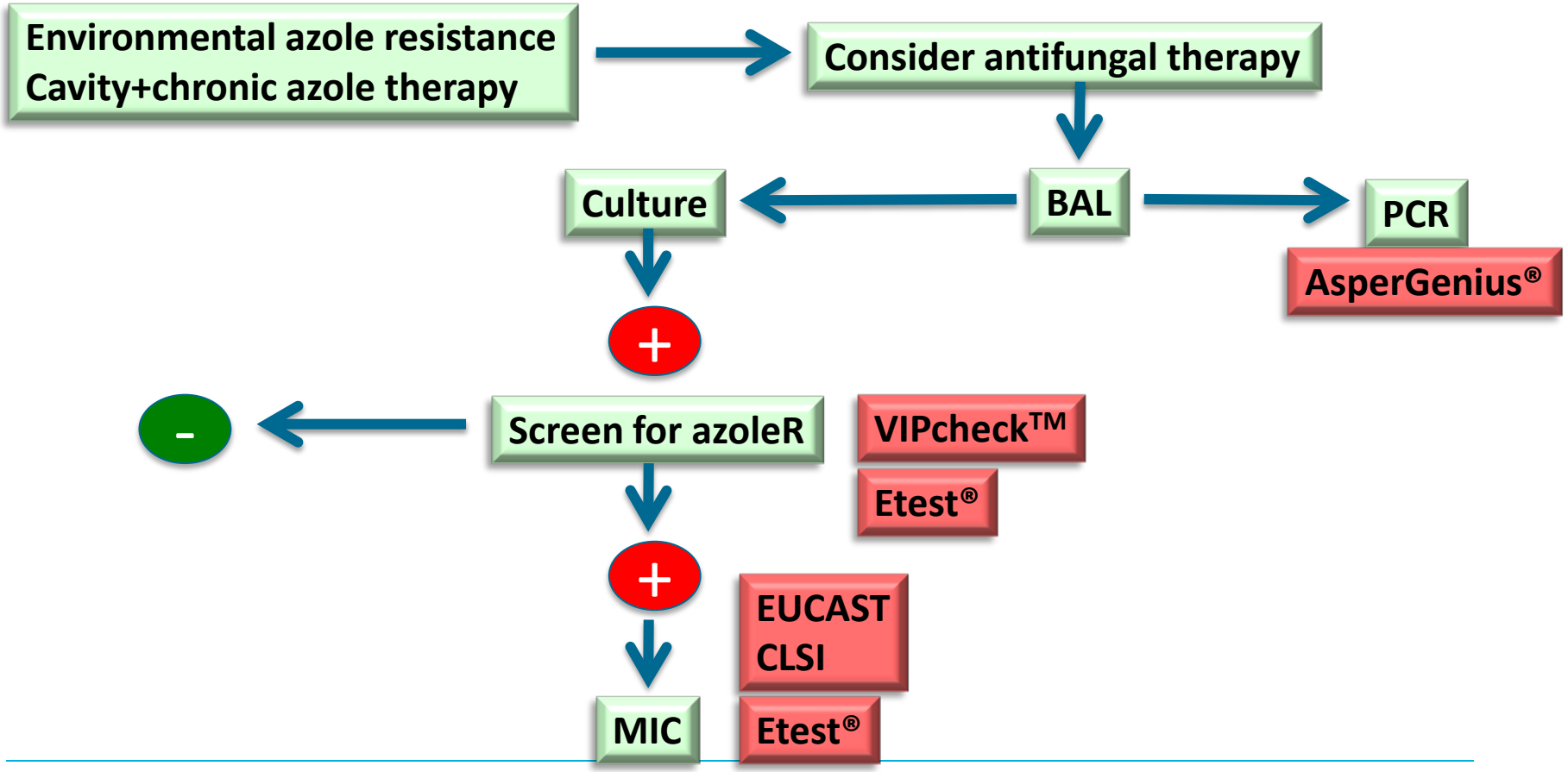
EUCAST compared with Etest®



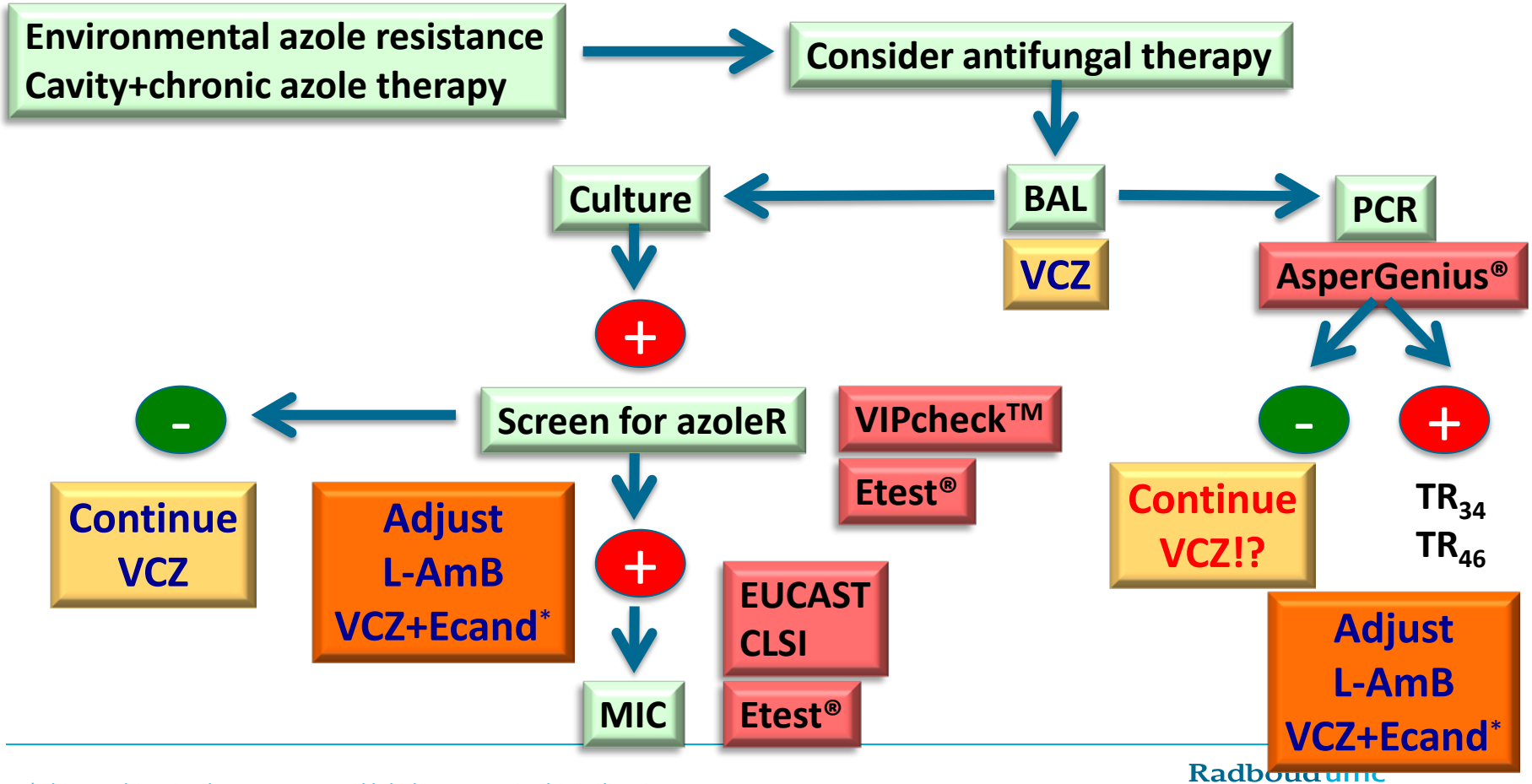
EUCAST compared with Etest®



How the laboratory helps the clinician: diagnostic tools



How the laboratory helps the clinician: treatment decisions



*This combination has no approved label in France in this indication

Conclusions

Know your local epidemiology to the ward-level!

Timely diagnosis of azole resistance is difficult!

Screen for azole resistance in multiple colonies in culture positive patients

Molecular detection of resistance is promising but has limitations

In hospital wards with high resistance rates consider alternative primary therapy: L-AmB or VCZ+AFG*

**This combination has no approved label in France in this indication*