Multi-resistant fungi from various human and animal sources

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National Institute for Public Health and the Environment
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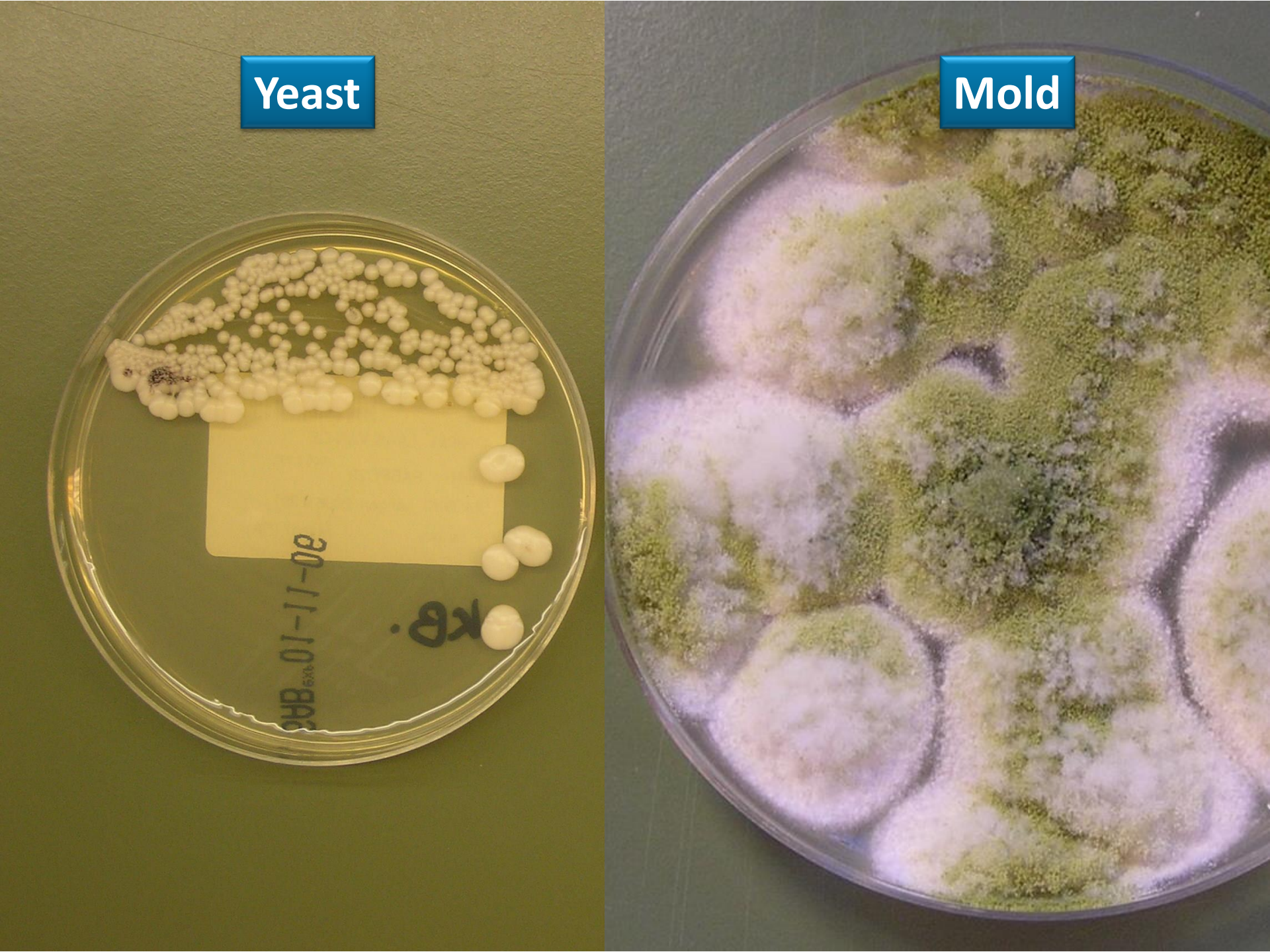
Radboudumc

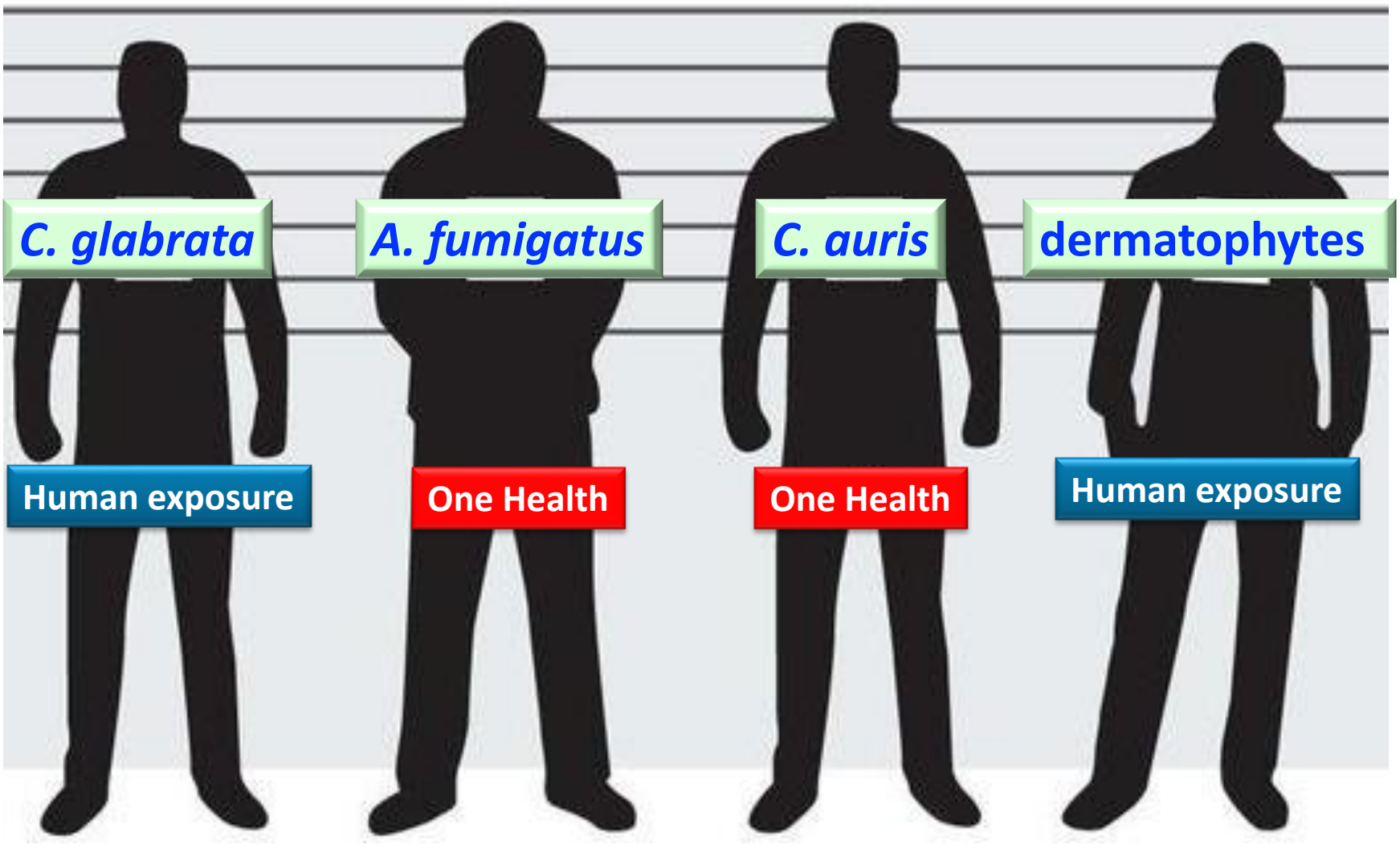
Disclosures


Fungi are everywhere!

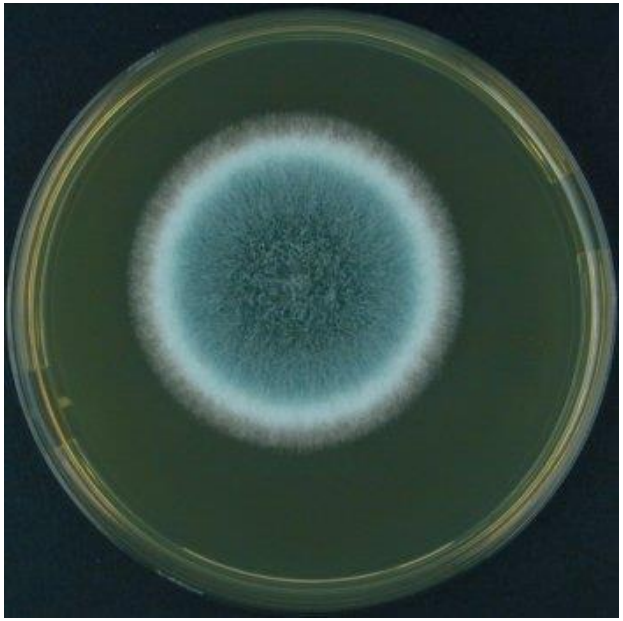
The fungal environment: 6 million species!?


Yeast
Mold

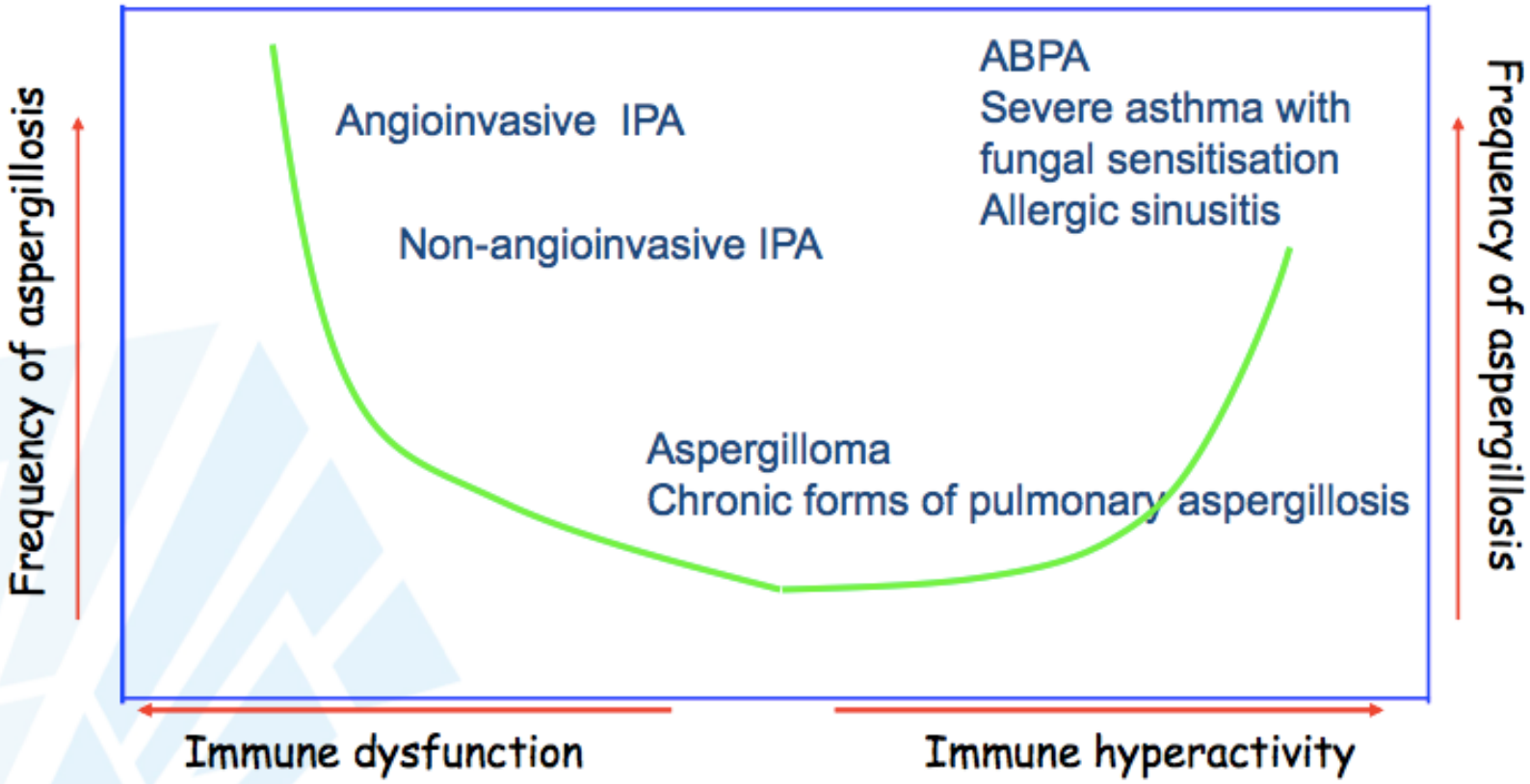
Acquired fungal resistance: the suspects



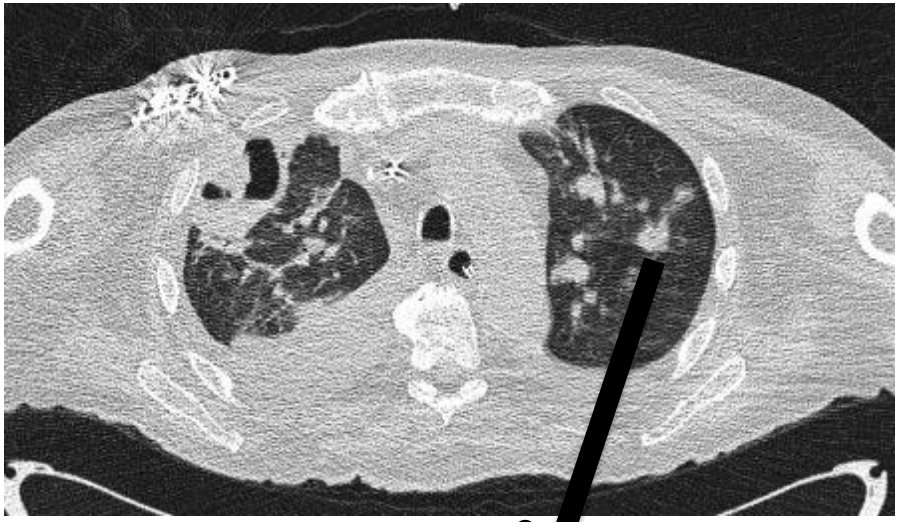
Aspergillus and its habitat

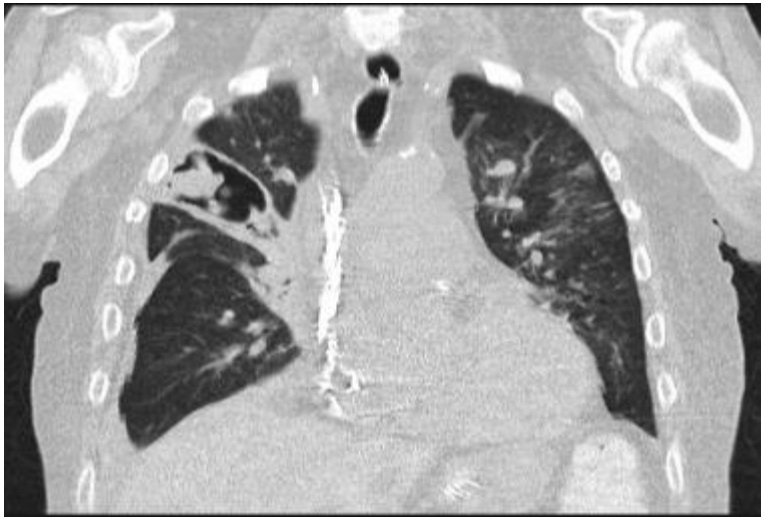


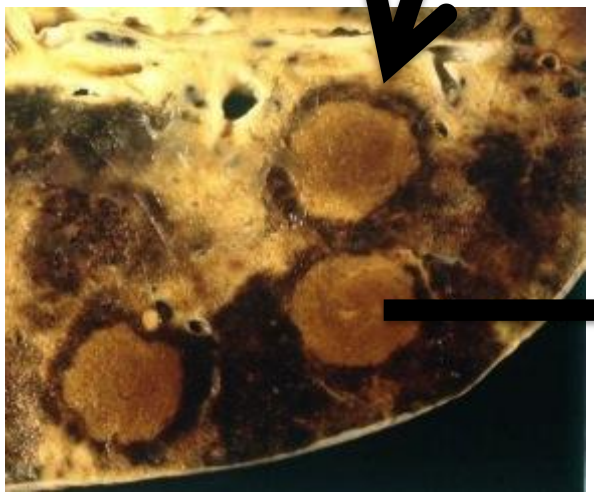
The spectrum of *Aspergillus* diseases

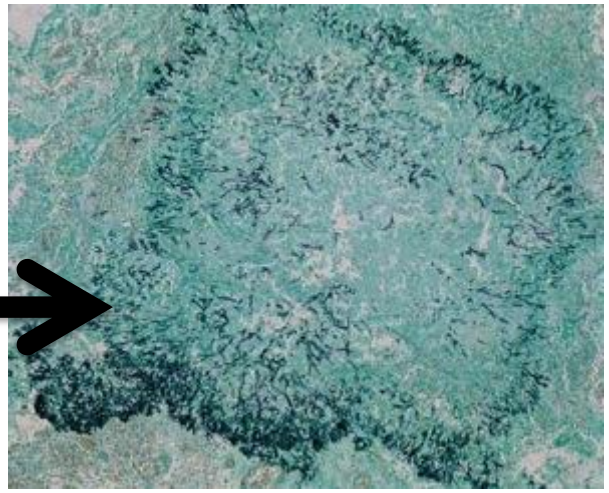


Pathogenesis invasive aspergillosis

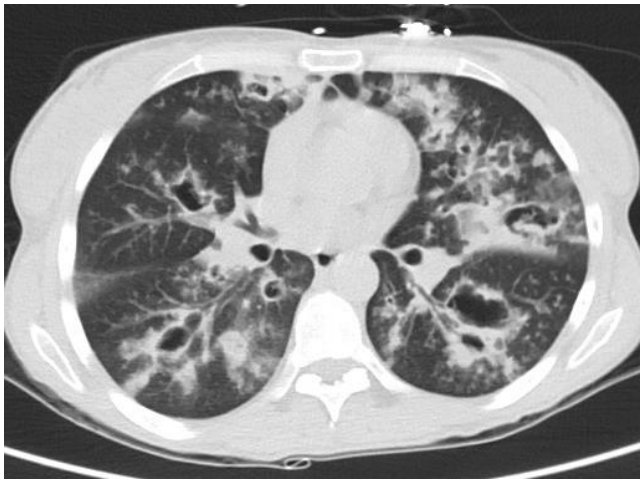








Change? Influenza-associated aspergillosis



Am J Respir Crit Care Med. 2017;196:524-527

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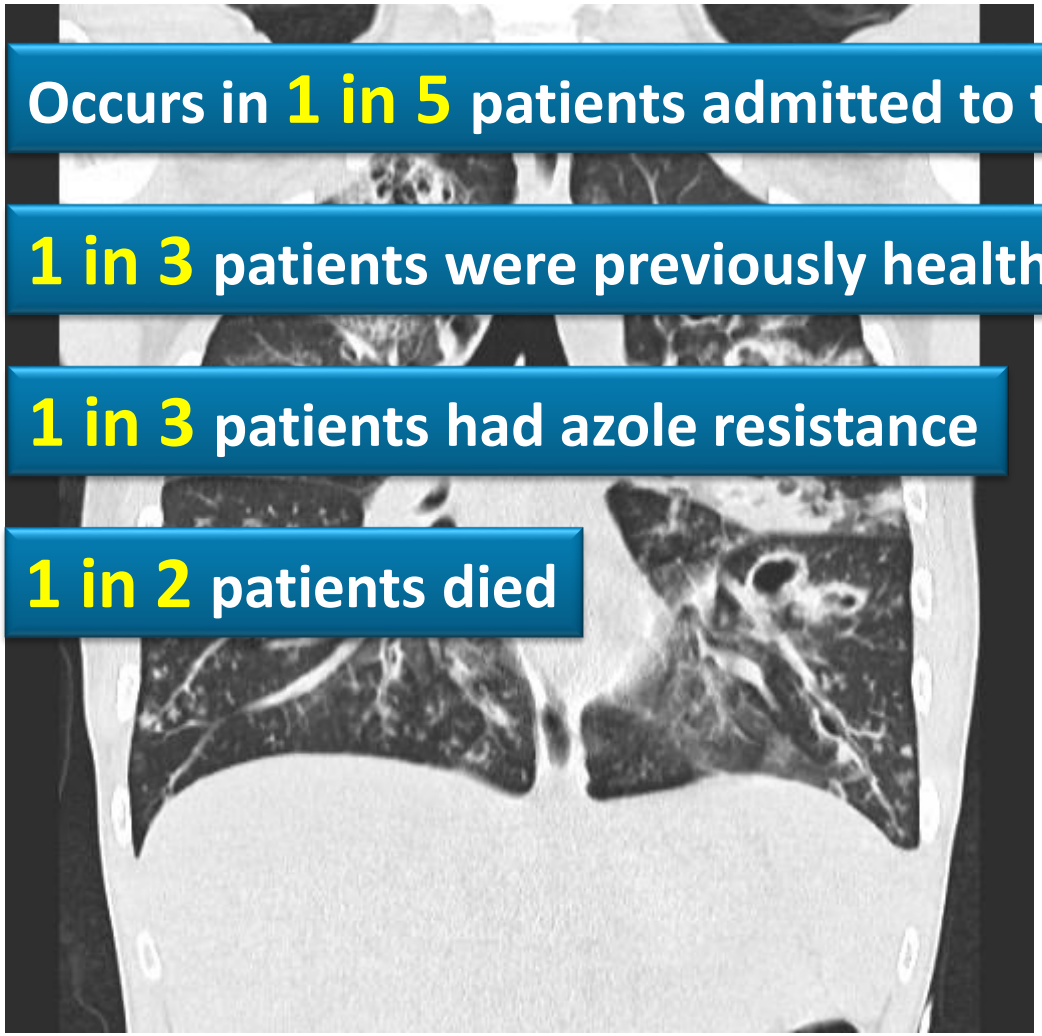
An very unfavorable combination……

Influenza

Aspergillosis

Influenza-associated aspergillosis

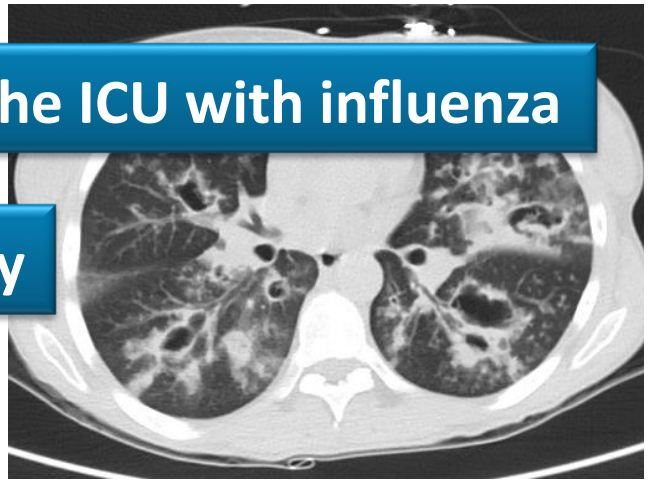


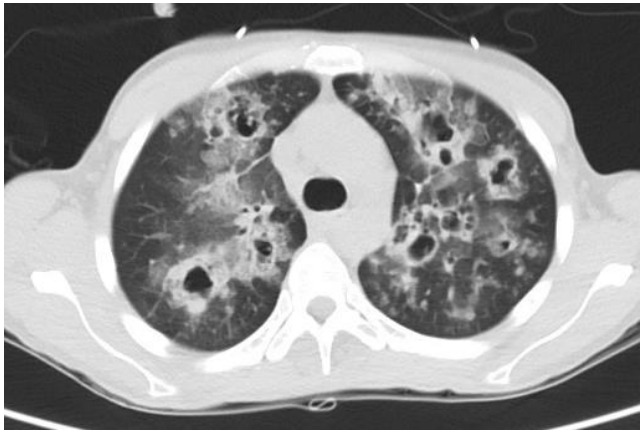
Occurs in **1 in 5** patients admitted to the ICU with influenza

1 in 3 patients were previously healthy

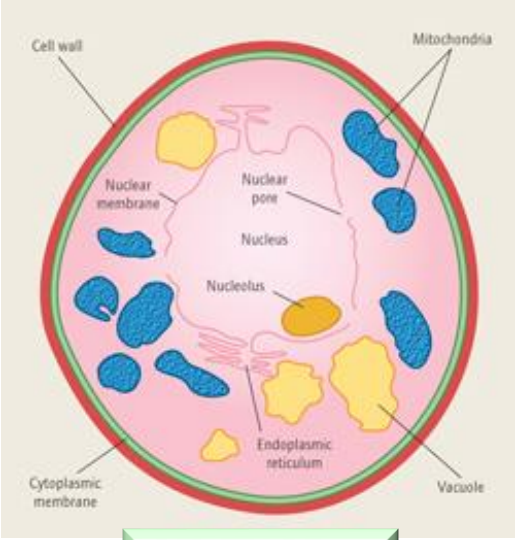
1 in 3 patients had azole resistance

1 in 2 patients died

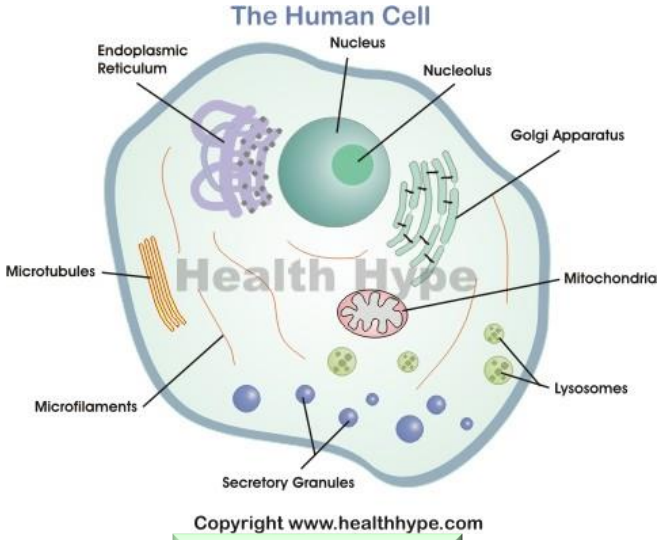




Fungi are eukaryotes just like humans…..

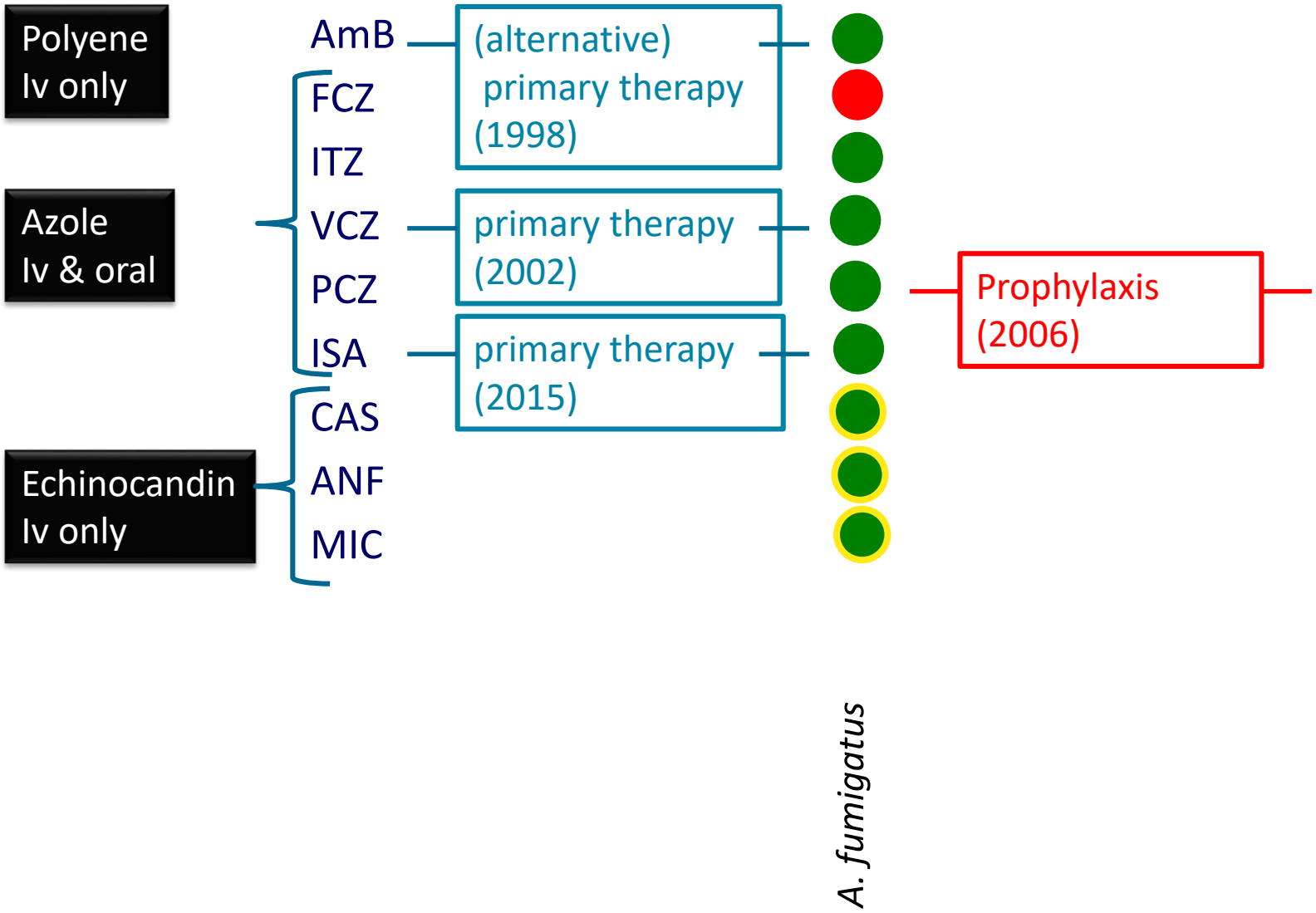


Fungal cell

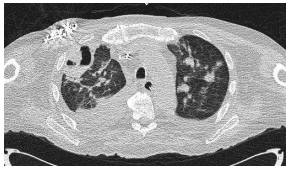


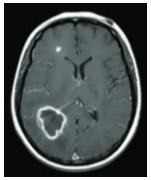
Human cell

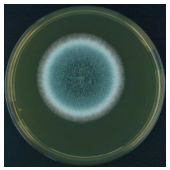
Azoles are the main drug class for management of IA

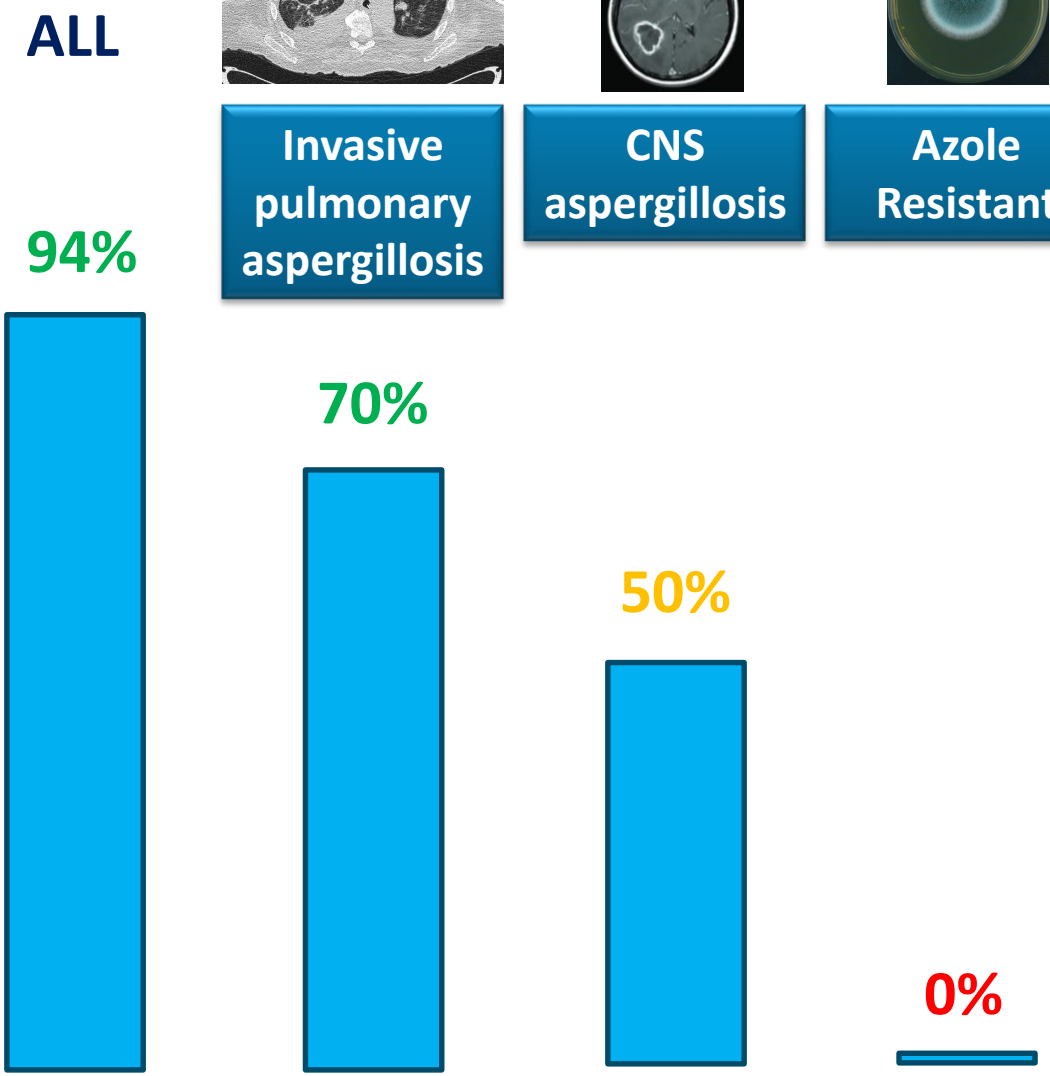


Impact of resistance

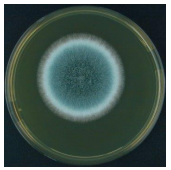








Why?



Azole Resistant

Lack of sensitive diagnostic tools for early resistance detection

Lack of alternative drugs with similar efficacy

0%

Azole resistance

Clinical implications?

Mortality of voriconazole R IA > voriconazole S IA?

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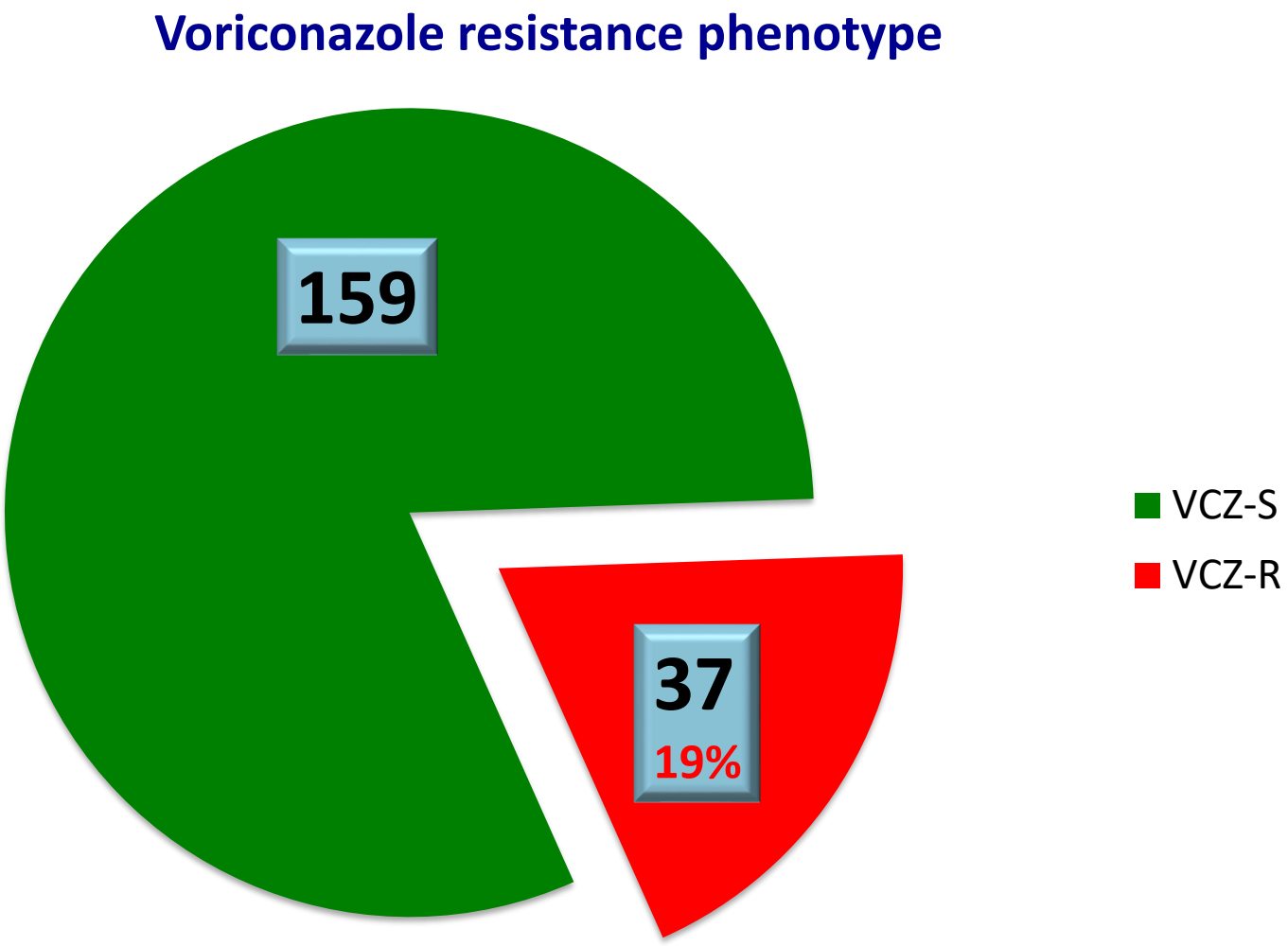
2011 - 2015

All patients with *A. fumigatus* in culture

All isolates screened with VIPcheck™

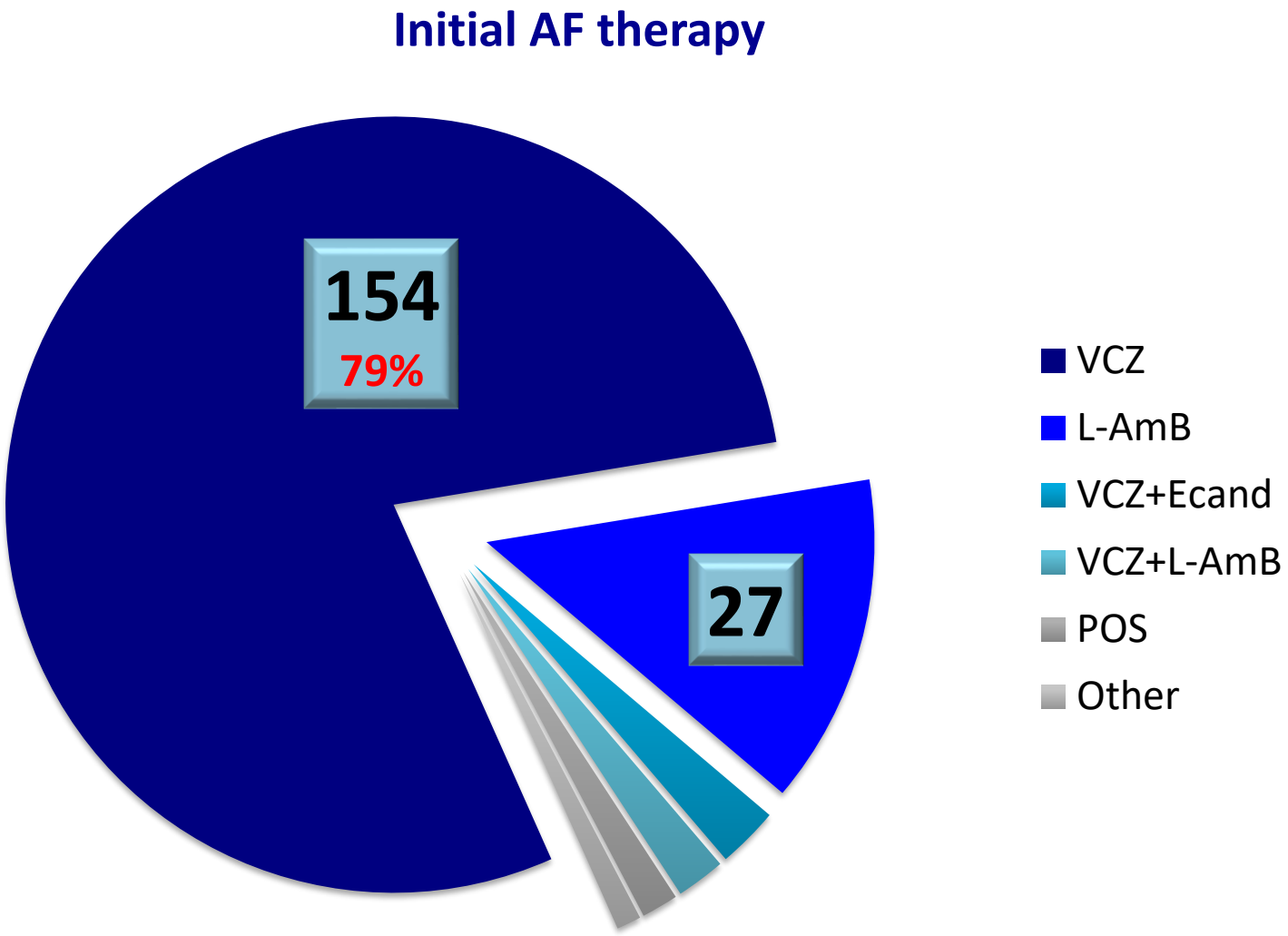
Compare mortality in R versus S

196 patients with invasive aspergillosis



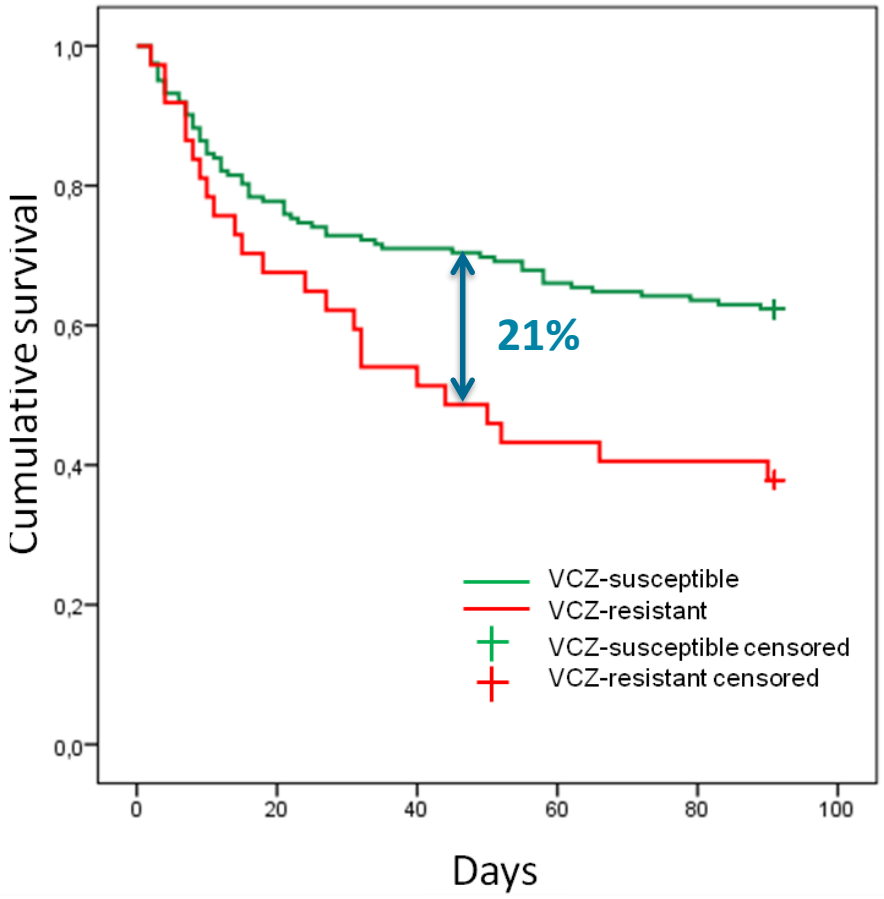
P. Lestrade et al. Clin Infect Dis 2019;68:1463–1471.

196 patients with invasive aspergillosis



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

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.

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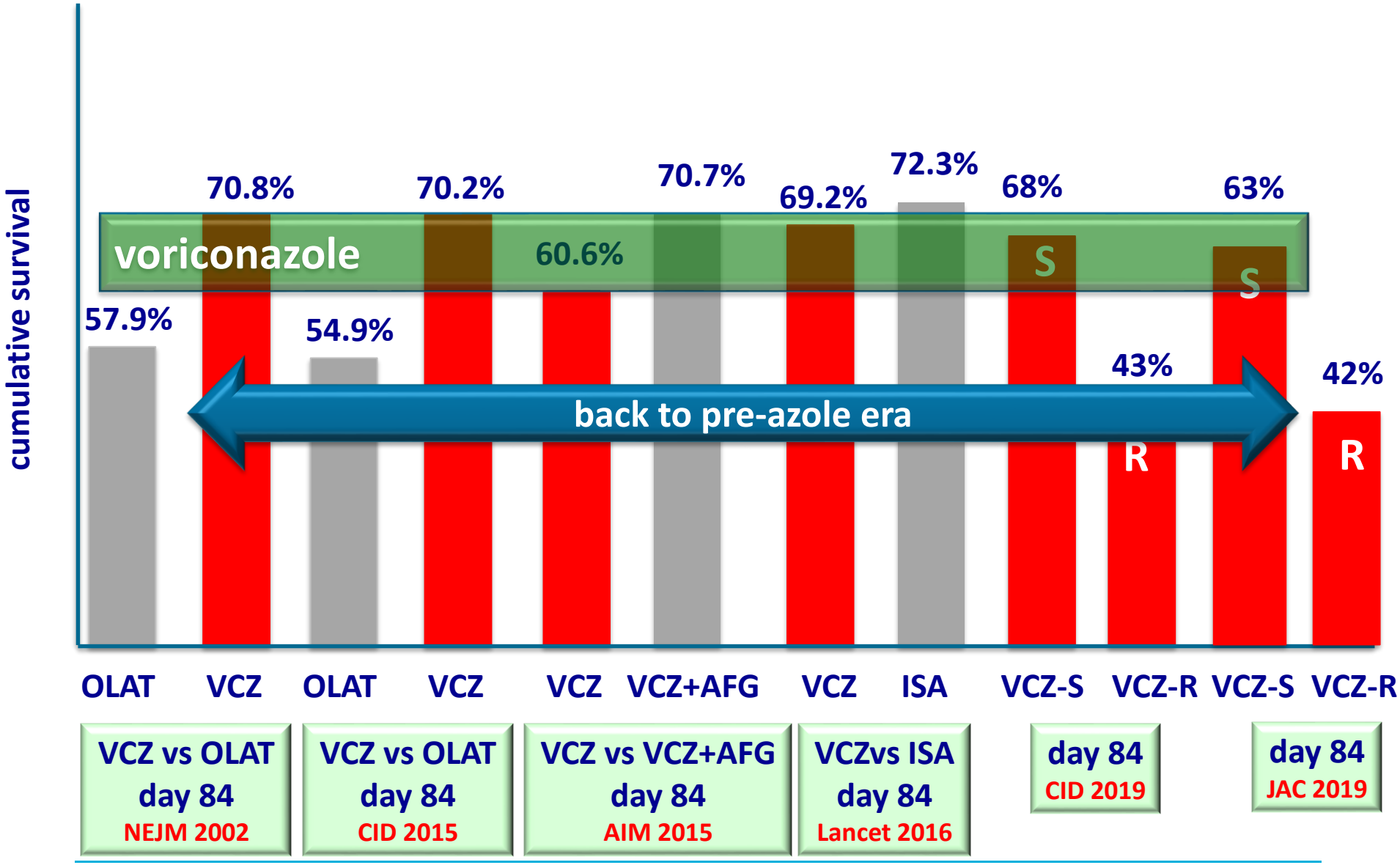
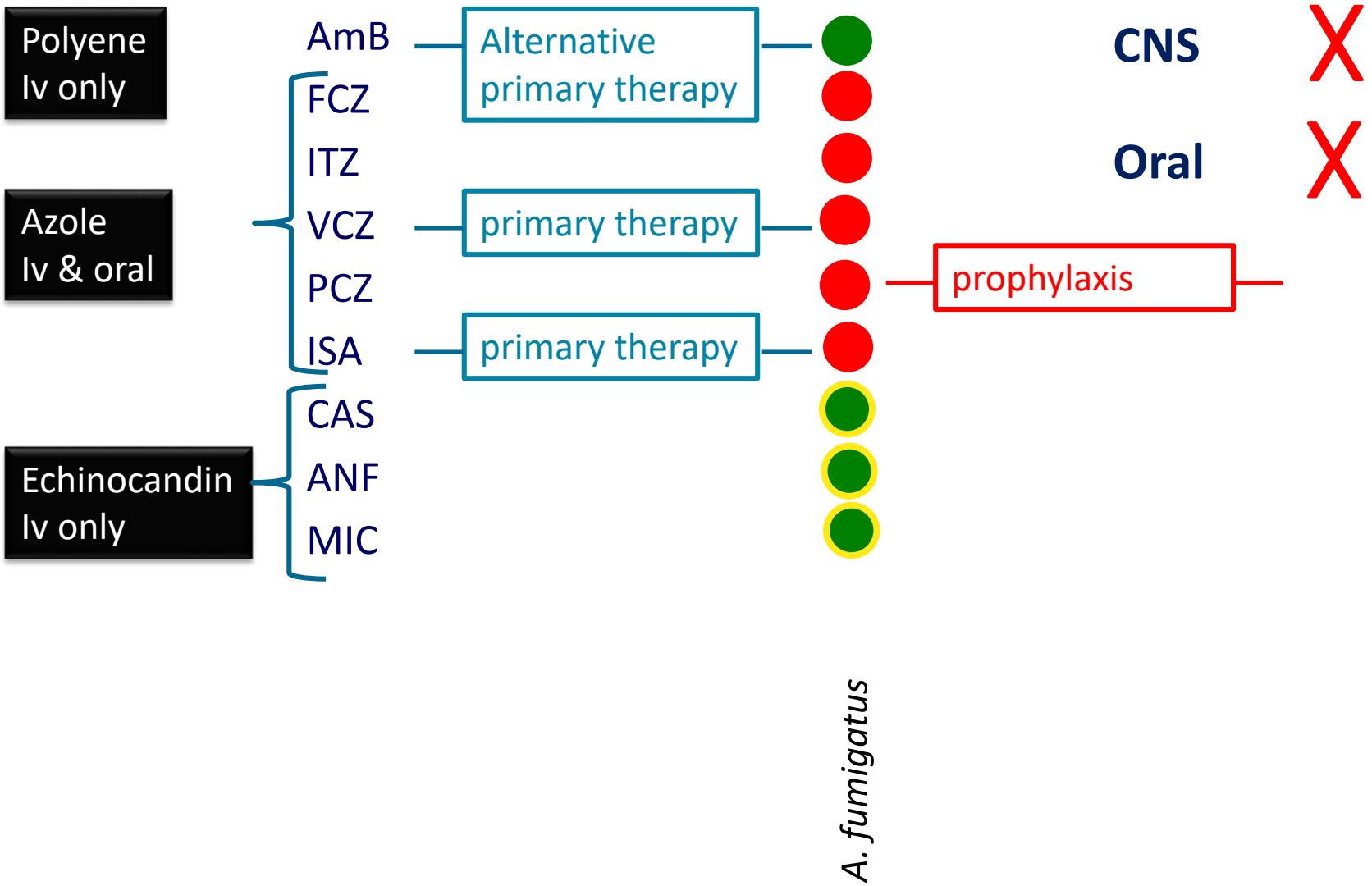
Putting azole-resistant associated 12-week mortality of IA in perspective



Activity of antifungal agents: azole resistance



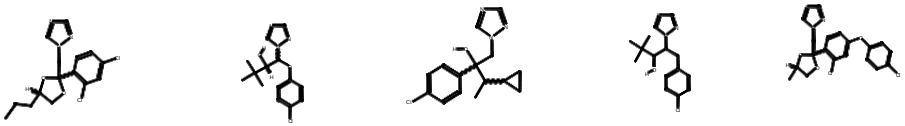
How are patients with resistant IA infected?

Disease	Route of resistance	Comments
CF	E > P	
ABPA	?	
Aspergilloma	P >> E	azole therapy, cavity, multiple R-mutations, fitness cost
CPA	P >> E	azole therapy, cavity, multiple R-mutations, fitness cost
IA - pulmonary	E	2/3 no azole therapy, TR_{34} > TR_{46}, mixed infections
IAA	E	TR_{34} > TR_{46}, mixed infections, tracheobronchitis
CNS-IA	E	TR_{34}&TR_{46}, sanctuary site

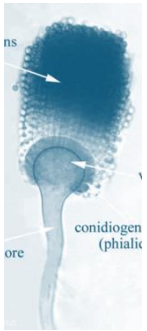
P = patient route E = environmental route

How are patients with resistant IA infected?

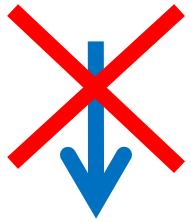
Propiconazole; tebuconazole; epoxiconazole; difenoconazole; bromuconazole



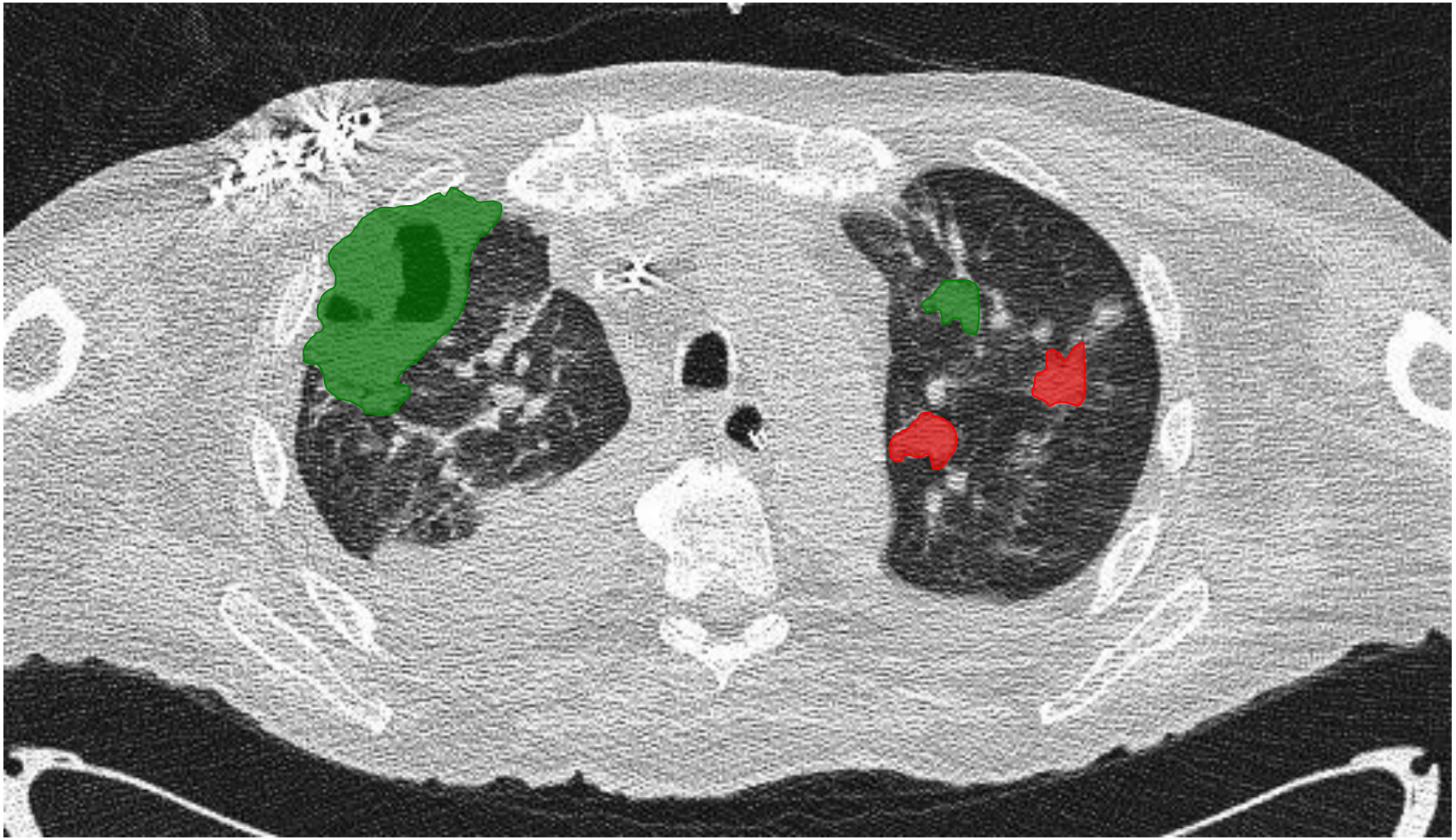
TR_{34}/L98H
TR_{53}
TR_{46}/Y121F/T289A



Medical triazoles



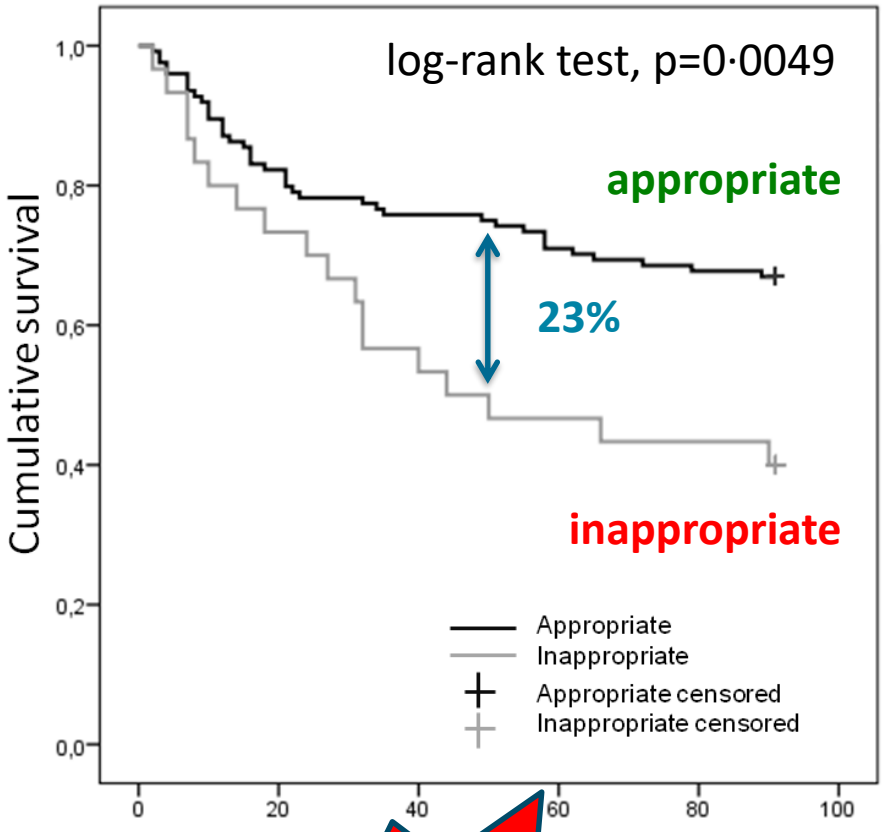
Mixed infections



Azole susceptible

Azole resistant

Resistance diagnosis and appropriateness of antifungal therapy



Intensive R-screening of cultures

Diagnosis IA (154)

VCZ therapy

Culture *A. fumigatus*

MIC-test

VCZ-S

VCZ-R

continue VCZ (124)

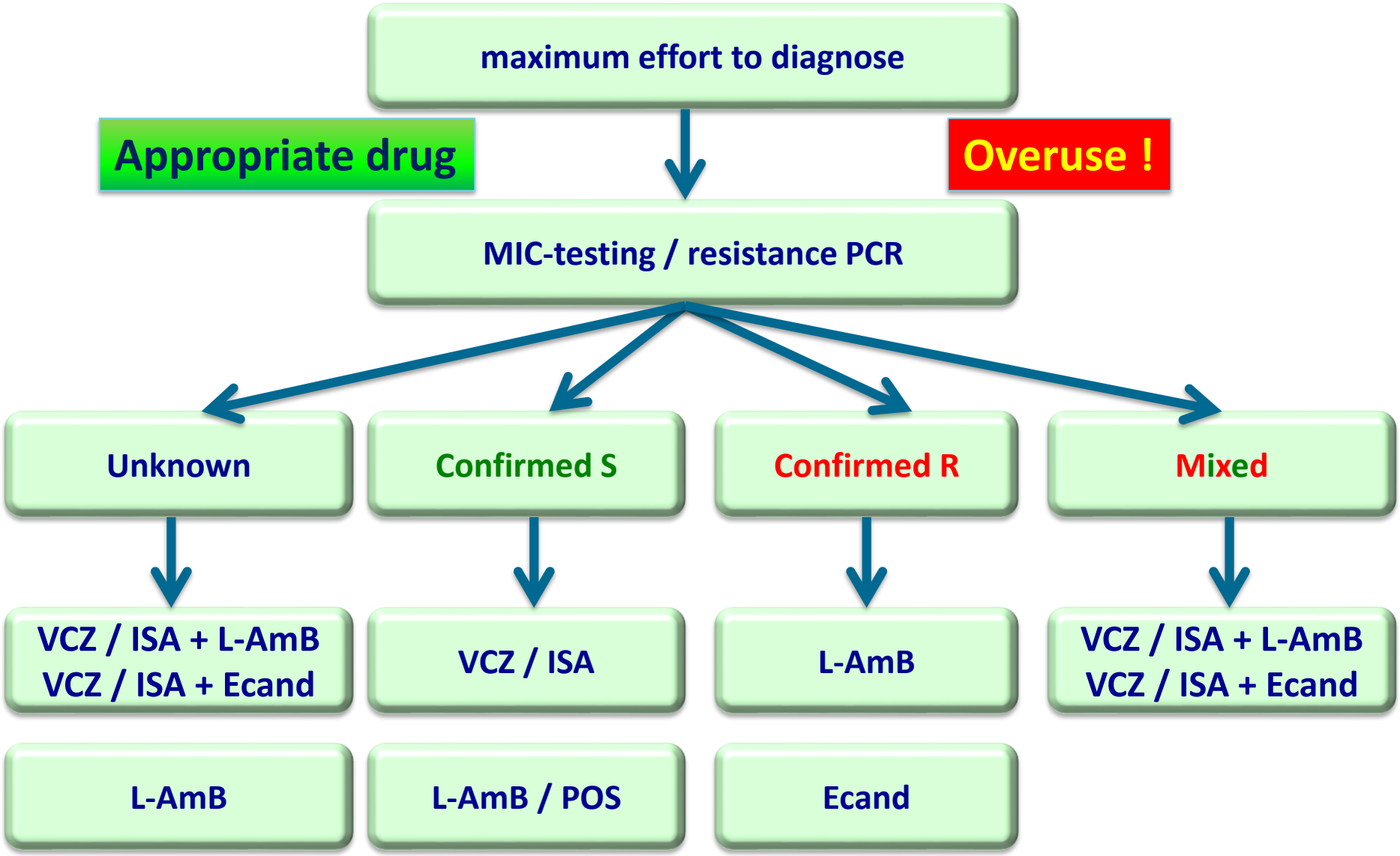
Switch to appropriate AF therapy (30)

appropriate

inappropriate

Clin Infect Dis 2019;68:1463–1471.

Management strategy……New SWAB guideline



Multidisciplinary mycology team

- ID physician
- Pharmacist
- Microbiologist
- Pulmonologist
- Hematologist

Acquired resistance frequency in *A. fumigatus* 2013 - 2017

5 university medical centers

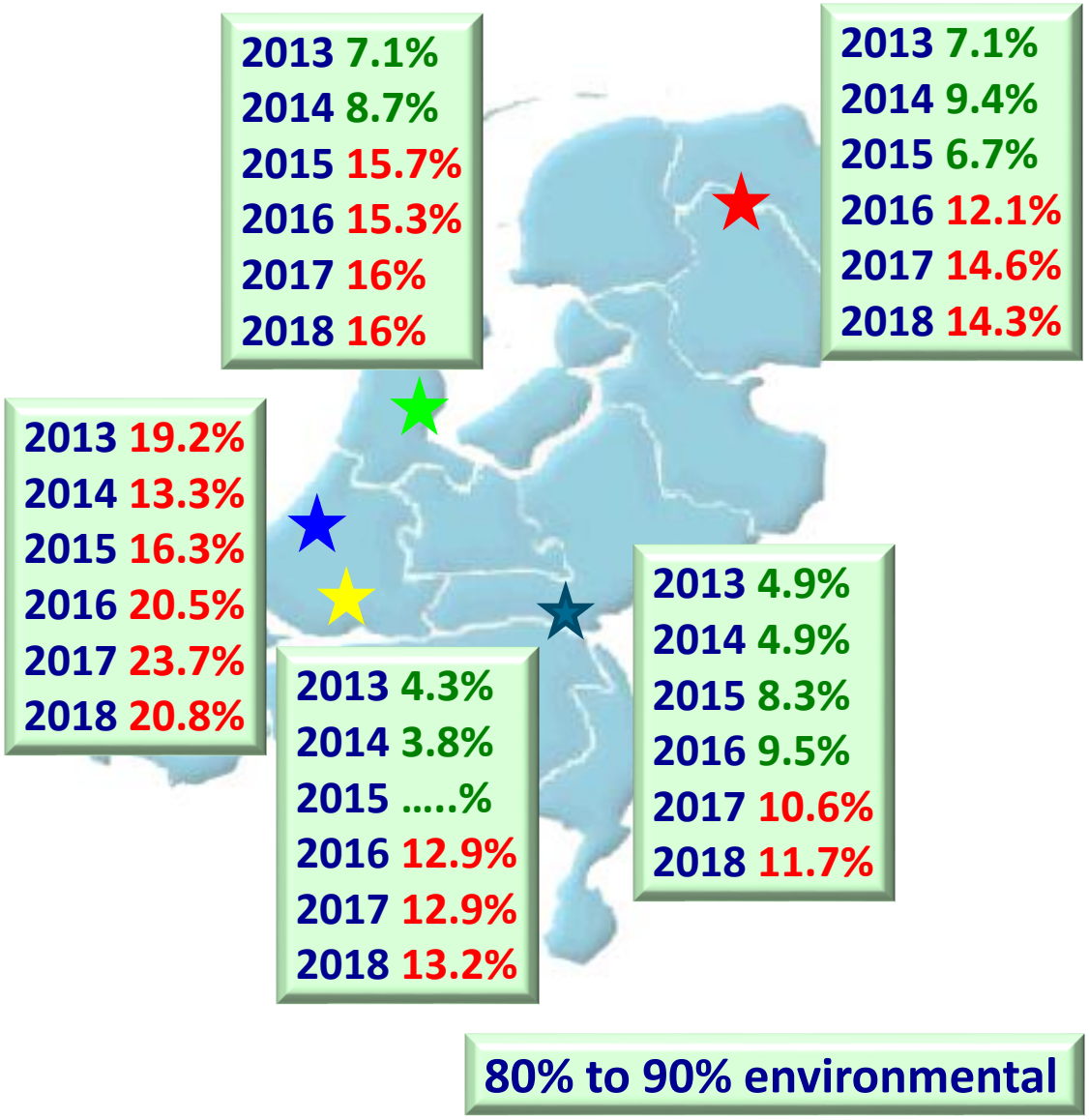
Screening for resistance of unselected clinical isolates using VIPcheck™

Includes clinically not-relevant isolates

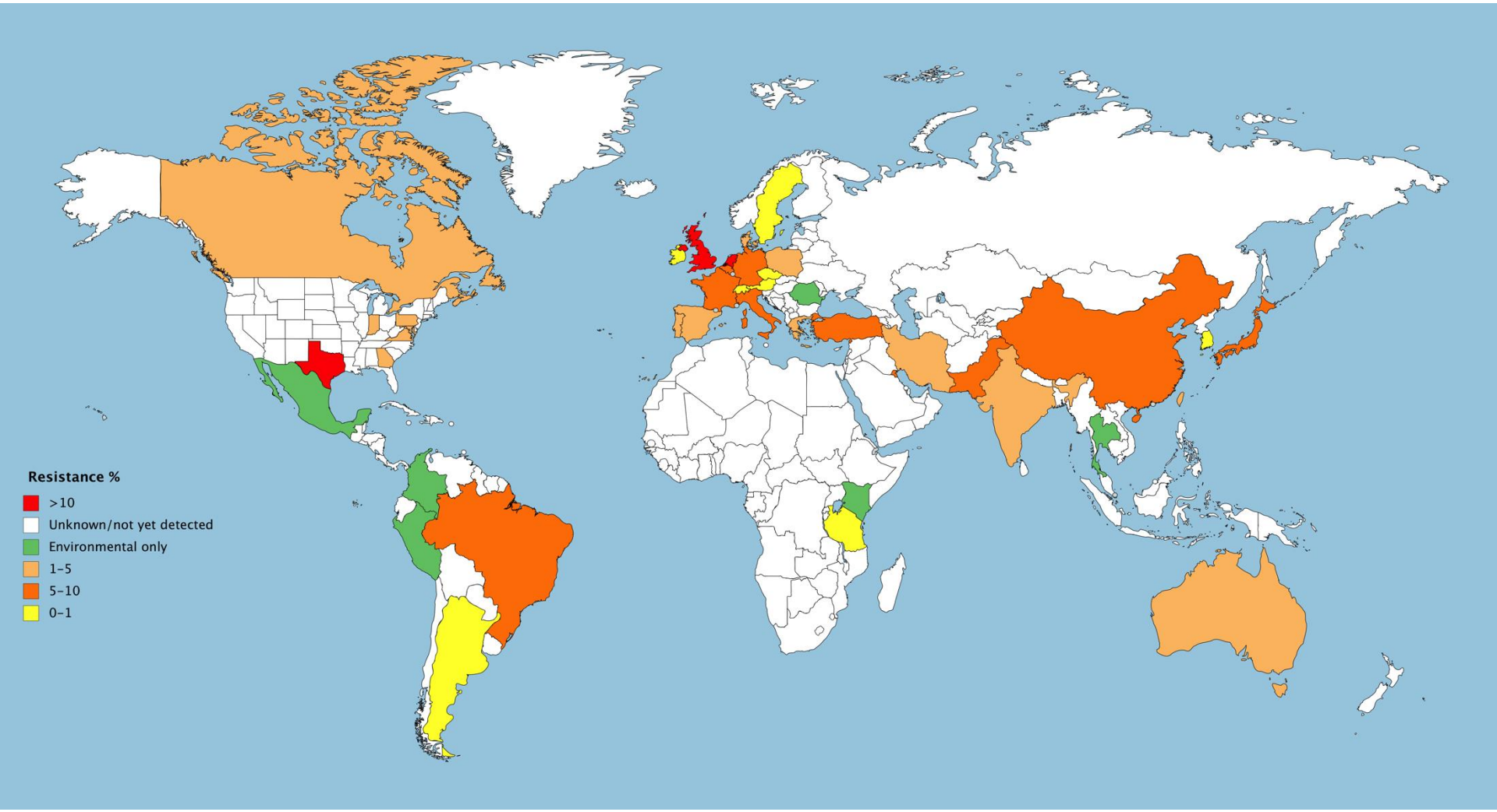
Number of patients screened 600 to 814 per annum

$$\text{Resistance frequency} = \frac{\text{number of patients with azoleR isolate}}{\text{number of screened patients}}$$

Anticipated risk: Aspergillus resistance surveillance



Acquired resistance: global?



Clin Microbiol Infect. 2019;25:799-806.

Do you worry about AMR ?

An antibiotic is an antimicrobial drug used to treat bacterial infections in humans and animals.

Like humans, animals (including farm animals) carry bacteria. when antibiotics are given to animals, the drugs kill most of the bacteria, but resistant bacteria can survive and multiply.

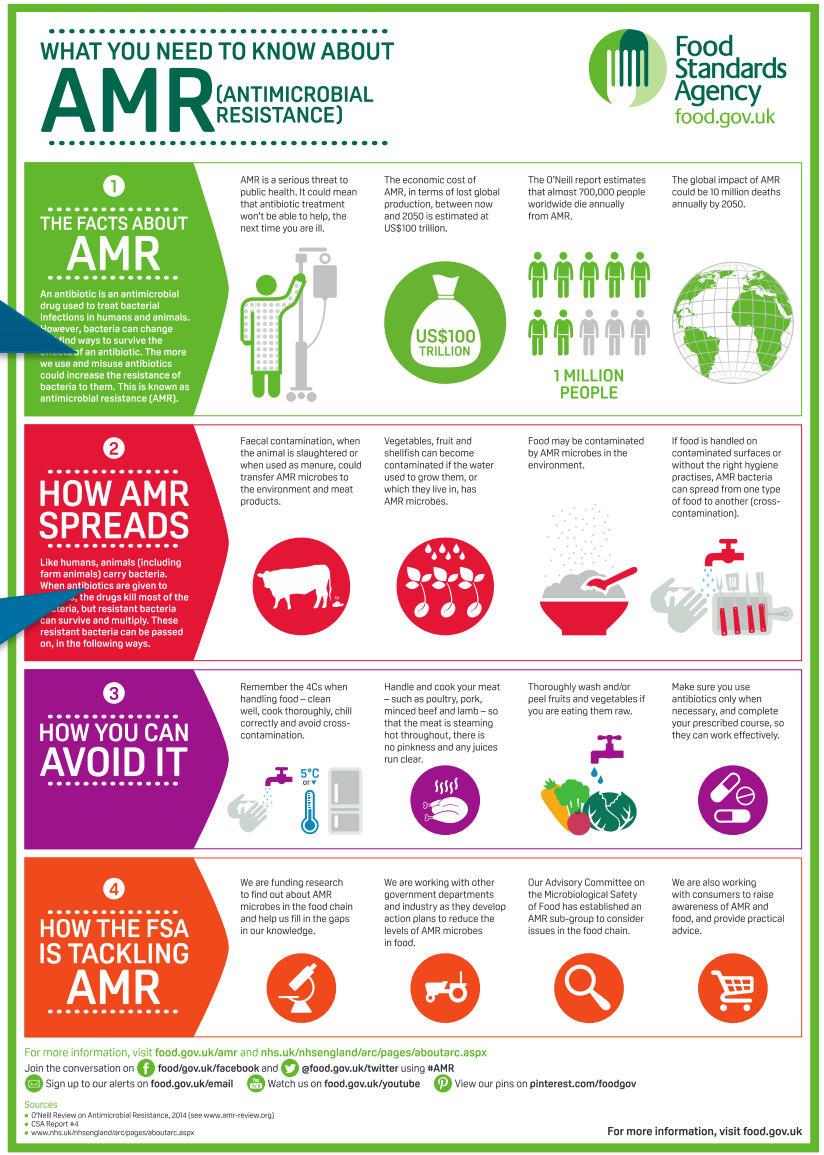


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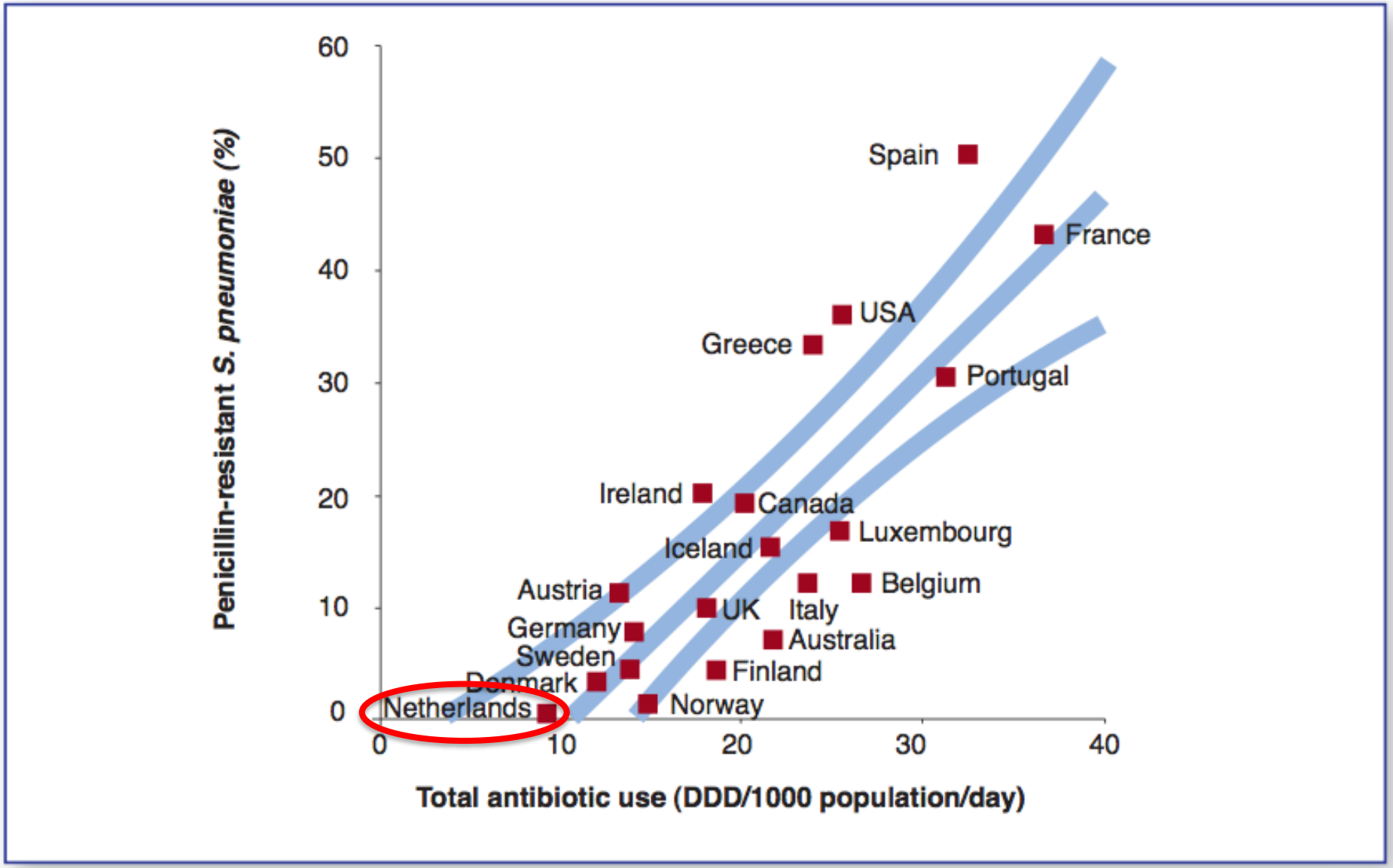
Figure 2.6 Antibiotic use and AMR from 1990–2000 in selected countries



DDD: Defined Daily Doses

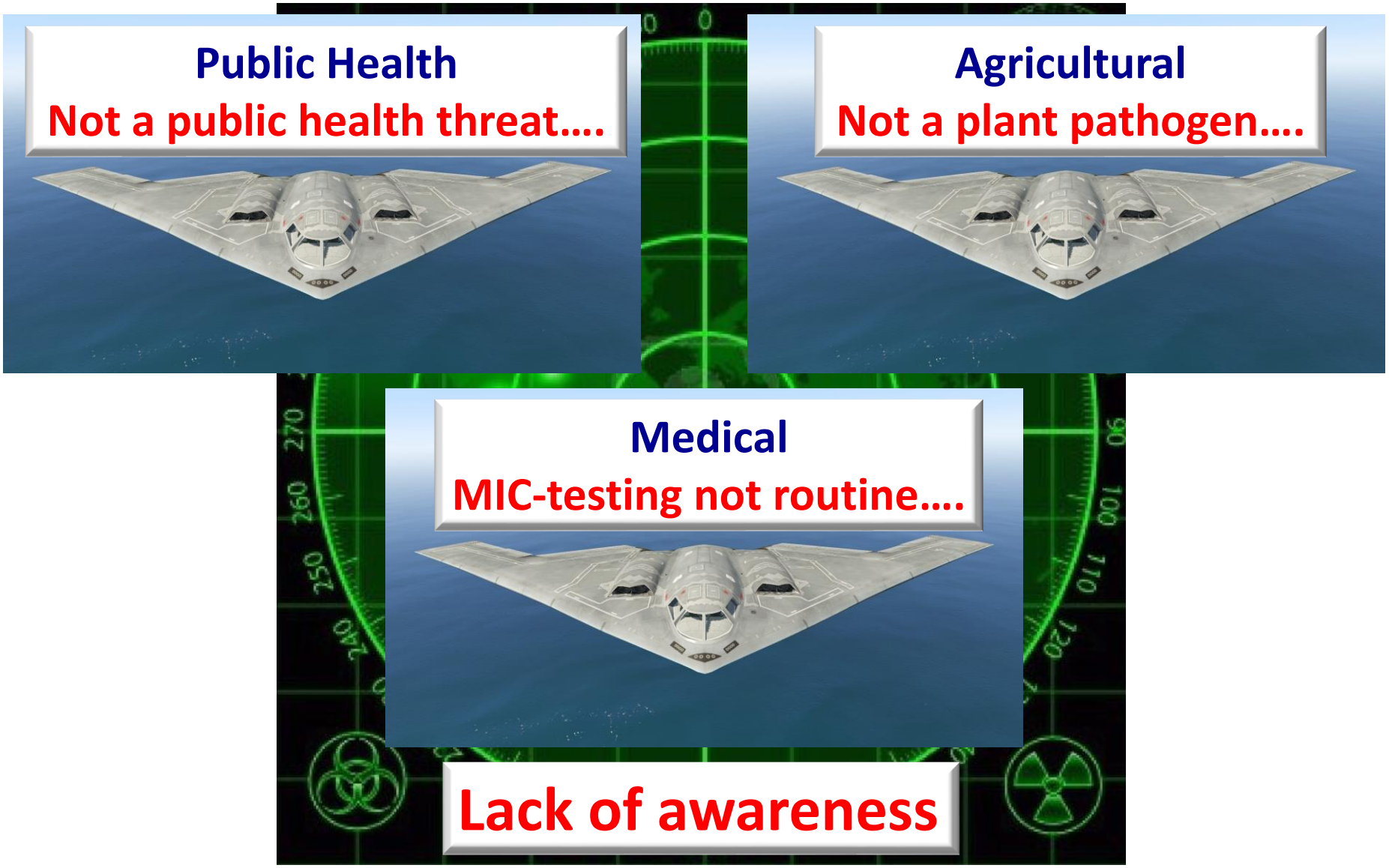
Total antibiotic use in outpatients versus prevalence of penicillin-nonsusceptible *Streptococcus pneumoniae* in 20 industrialized countries.

AMR ≠ ABR

Funding of infectious disease projects by ZonMw – last 14 years!

Program	Period	Budget (M€)	Molds included?	No projects awarded	No fungal projects
Infectieziektebestrijding	2006 - 2011	12.6	Tolerated	**33**	**1**
Q-koorts	2010-2014	3	No	**14**	**0**
Infectieziektebestrijding	2014 - 2017	17	Fungal resistance excluded		
Ronde 1 (Non-alimentaire zoönosen)				**6**	**0**
Ronde 2				**14**	**0**
Ronde 3 (Non-alimentaire zoönosen)				**9**	**0**
Ronde 4				**9**	**0**
Priority Medicines Antimicrobiële Resistentie	2009 - 2018	14.76	Fungi excluded	**28**	**0**
Antibioticaresistentie	2016 - 2023	16	Fungi excluded		
Ronde 1				**10**	**0**
Ronde 2				**6**	**0**
Totaal		**63.36**		**129**	**1 (0.8%)**

Azole resistance in *A. fumigatus*: Under the radar……



CDC – antibiotic resistance threats

Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris (C. auris)*
- *Clostridioides difficile (C. difficile)*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)*

Serious Threats

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- Extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae
- Vancomycin-resistant *Enterococci* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa (P. aeruginosa)*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae (S. pneumoniae)*
- Drug-resistant Tuberculosis (TB)

Concerning Threats

- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

Watch List

- Azole-resistant *Aspergillus fumigatus (A. fumigatus)*
- Drug-resistant *Mycoplasma genitalium (M. genitalium)*
- Drug-resistant *Bordetella pertussis (B. pertussis)*

The environment: Deadly flower power?

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Deadly flower power? Imported tulip bulbs spread anti-fungal resistance

Date: May 18, 2017

Source: Trinity College Dublin

Summary: Tulip and narcissus bulbs imported into Ireland from the Netherlands may be acting as vehicles for the international spread of a drug-resistant fungus -- with potentially fatal consequences. Experts advise people not to plant bulbs near hospitals or to gift them to at-risk patients.

Share:

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Plants & Animals

FULL STORY

Tulip bulbs imported into Ireland from the Netherlands may be helping to spread resistance to vital antifungal medicines called Triazoles that treat potentially fatal fungal infections. That is according to research showing that the inter-country transfer of bulbs of Holland's iconic flowers may inadvertently have opened up a new transport route for a particularly nasty fungal pathogen called *Aspergillus fumigatus*

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

presence of azole residues

Flower bulb waste

Green waste

Wood chippings waste

Strawberry waste

Azole fungicide residues in hotspots

40 samples analyzed – 34 contained azole fungicide residues (85%)

Median of 2.5 compounds per sample – range 1 to 8

11 different azole fungicide compounds and 3 metabolites

tebuconazole (24 samples)
prothioconazole (13)
epoxiconazole (11)
azaconazole (8)
propiconazole (7)

Median concentration 0.036 mg/l (range 0.01 mg/l to 6.4 mg/l)

Each gram of compost contained >1x10^6 *A. fumigatus* spores

Emerg Infect Dis. 2019;25:1347-1353

Where?

application of fungicides

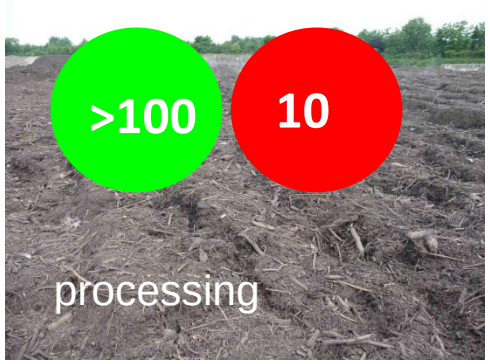
collection of organic waste

composting

mature compost

Commercial composting

65-70 ° C



50-60 ° C

Where?

application of fungicides

collection of organic waste

composting

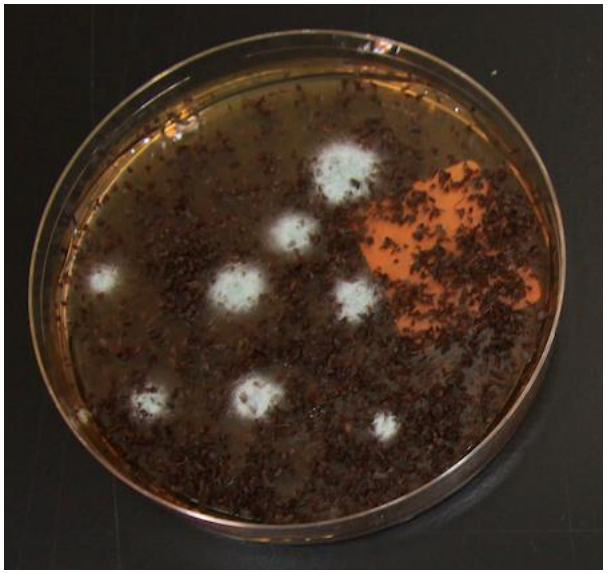
mature compost

How are patients infected? – potential sources

other?

How ?

How are patients infected? – potential sources



tea

pepper

onions

coffee

carrots

How are patients infected? – water?

Conclusions – azole-resistant aspergillosis

Threat?	**yes**	Develop better diagnostic tests New drug targets
Global?	**yes**	Set up international surveillance Include fungal resistance in One-health programs
Forgotten?	**yes**	Prioritize fungal resistance research Include fungal resistance in AMR initiatives