مرکز تحقیقات بیماری های عفونی و گرمسیری
برگزار می کند :

ژورنال کلاب

شیوع آسپرژیلوس فومیگاتوس مقاوم به تری آزول بالینی و محیطی در ایران: آیا این یک موضوع چالش برانگیز است؟

Prevalence of clinical and environmental triazole-resistant Aspergillus fumigatus in Iran: is it a challenging issue?

ارائه دهنده :

دکتر حامد فخیم

استادیار قارچ شناسی پزشکی دانشگاه علوم پزشکی اصفهان

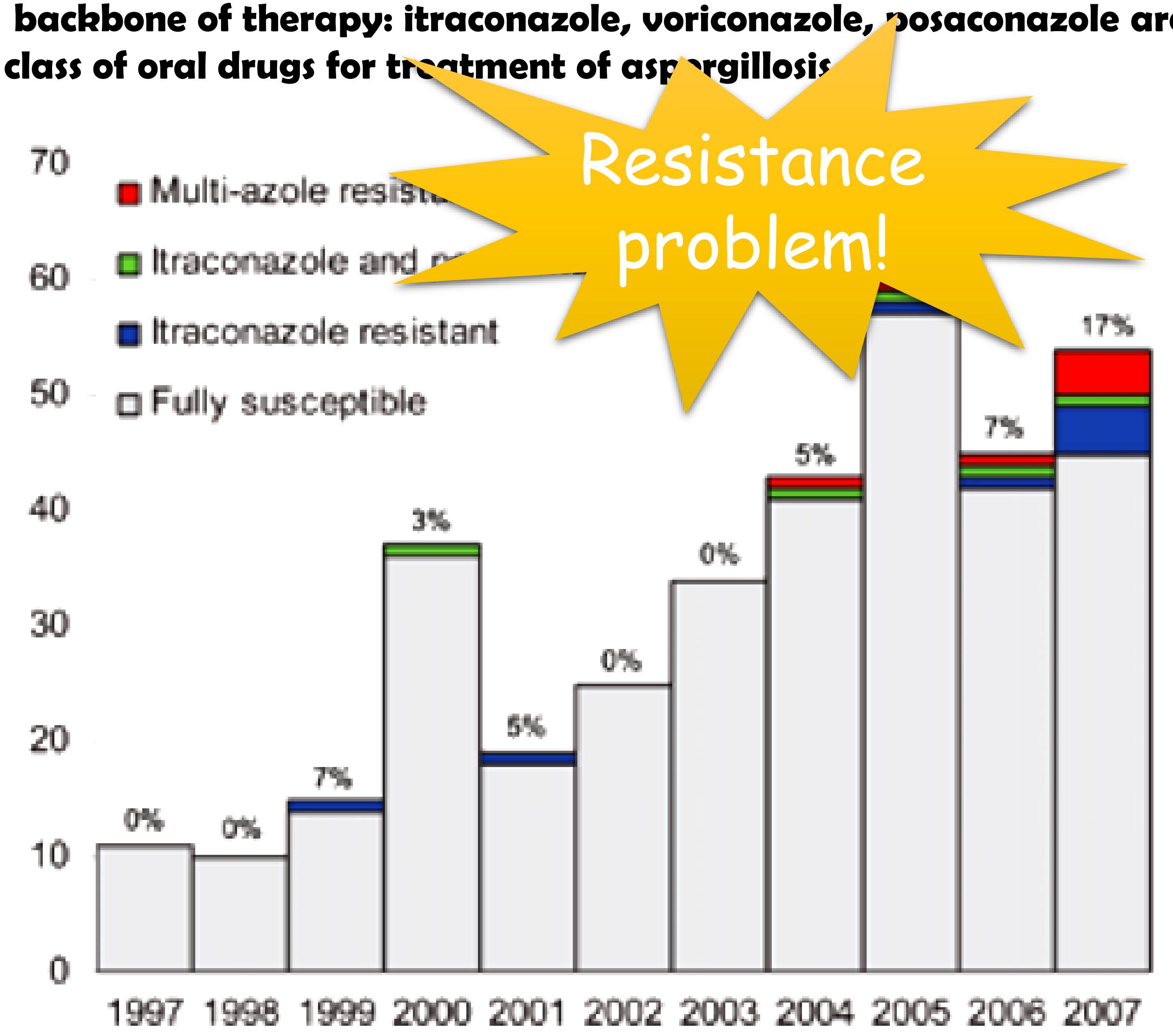
زمان: سه شنبه ۲۷ دی ماه ۱۴۰۱ - ساعت ۱۰ صبح

مکان: دانشگاه علوم پزشکی اصفهان

سالن کنفرانس آزمایشگاه جامع تحقیقاتی

Azole drugs are major agents for aspergillosis treatment

backbone of therapy: itraconazole, voriconazole, posaconazole are the only licensed class of oral drugs for treatment of aspergillosis



David W. Denning and et al.
Emerg. Infec. Dis 15:1068 (2009)

Main research question?

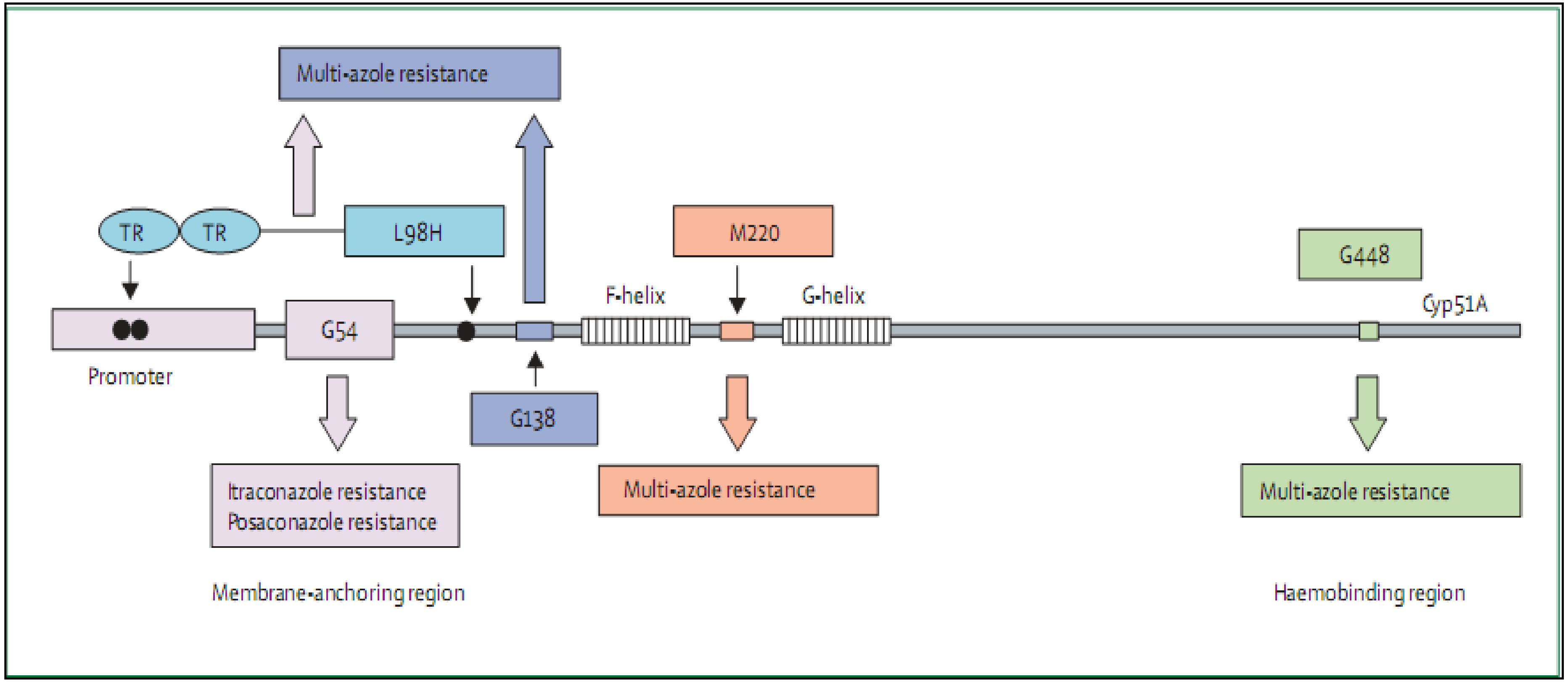
Is Azole resistance in *Aspergillus fumigatus* a public health problem?

long term use of azole drugs

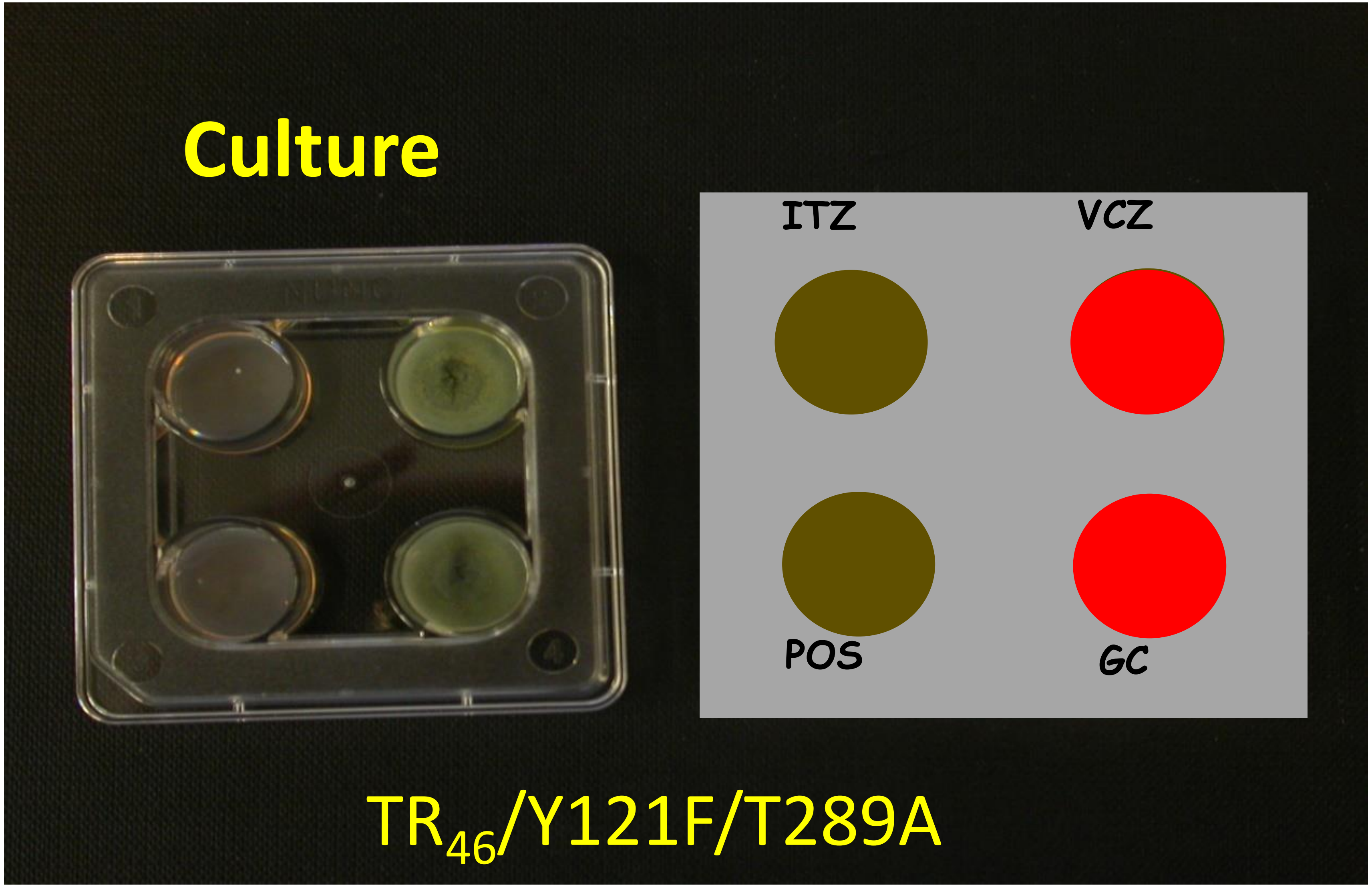
Use of fungicides repeatedly in environment

Use of fungicides repeatedly in environment

Aspergillus fumigatus cyp51A-related resistance mechanisms to azole antifungal



Screening of clinical isolates

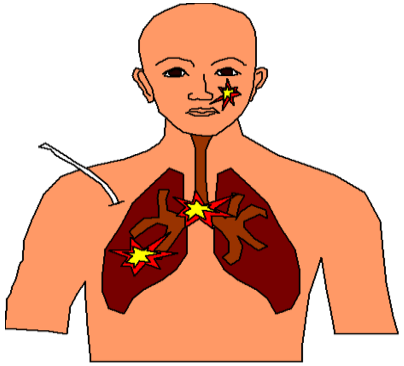


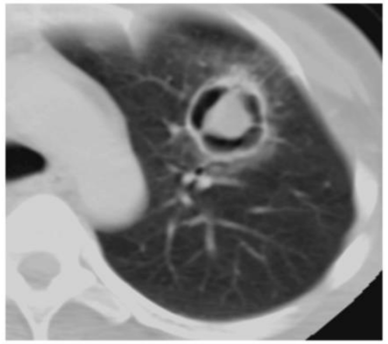
Potential Magnitude of the Problem

- CPA and ABPA are the principal patient groups potentially impacted by therapeutic failures due to **triazole resistance.**

No other class of antifungals is orally active against *Aspergillus* .

- Patients with multi-azole resistant invasive aspergillosis have an 88% risk of dying.





Day 10

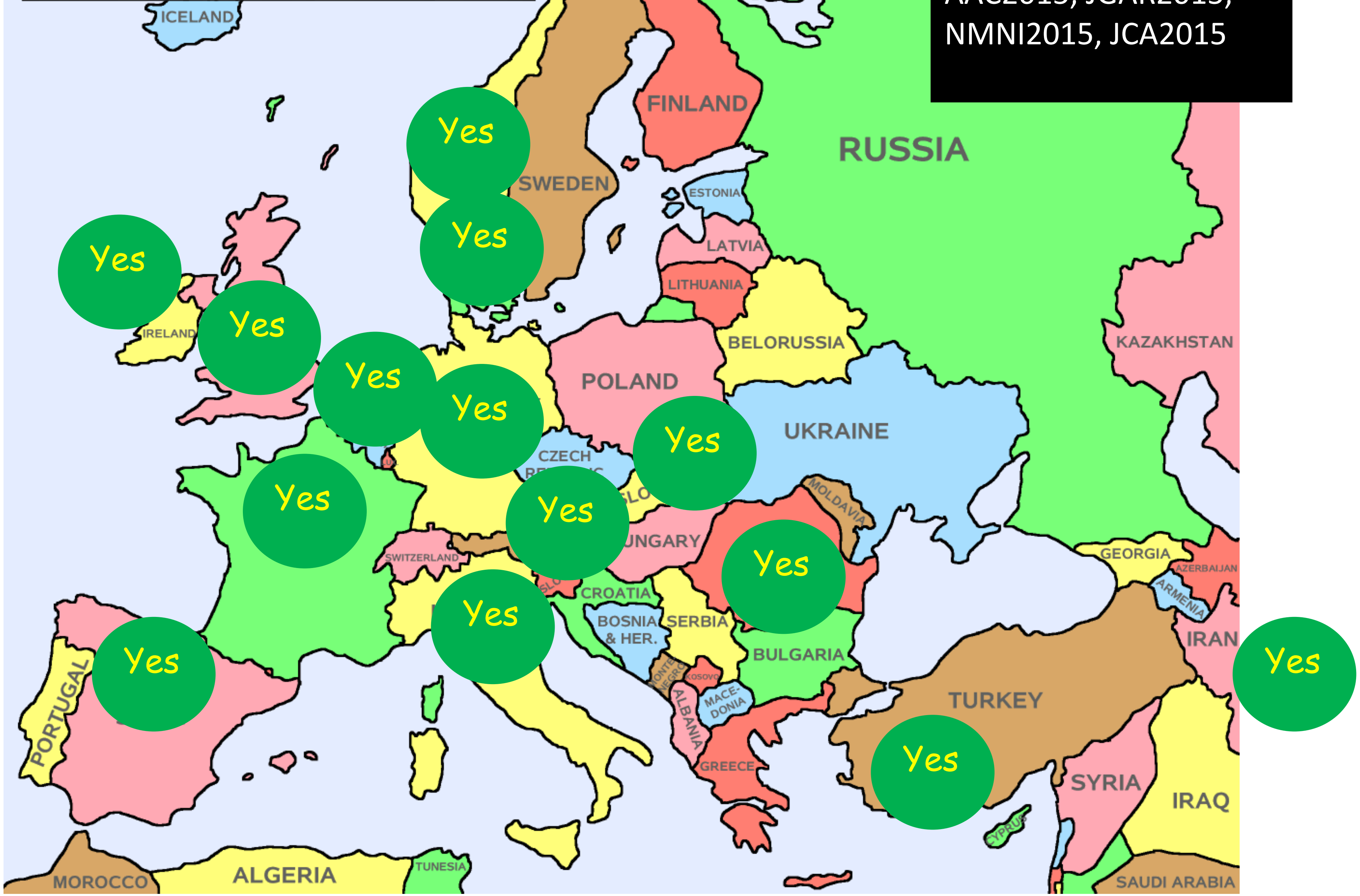
According to the European Centre for Disease Control (ECDC)

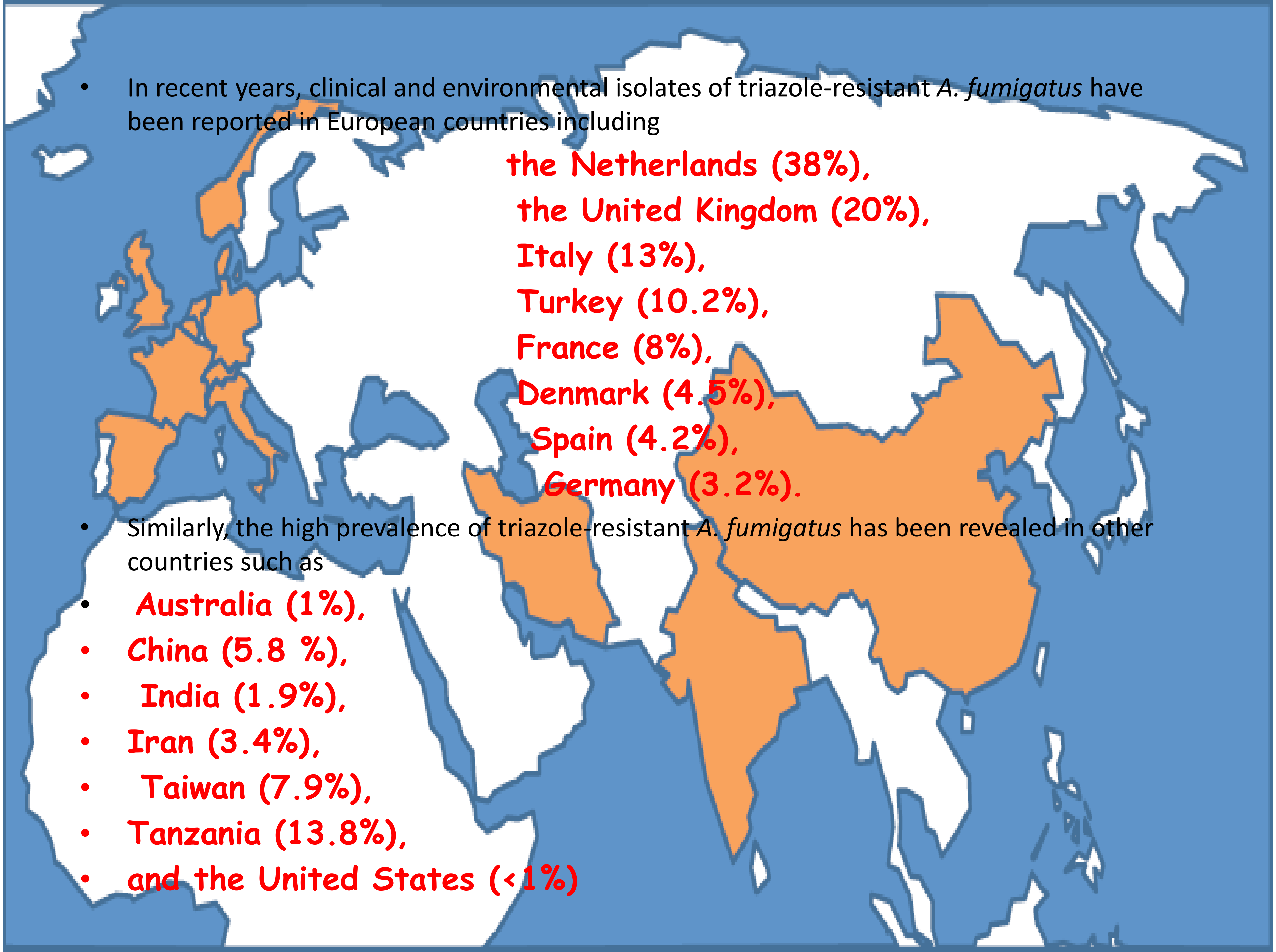
- The overall mean burden estimate of all forms of as... Europe is approximately 2 400 000 affected indivi...
- We estimate that 63... ...p 1A, a disease with a high morta... ...apy.
- Slig... ...an 2.3 million patients with allergic or chronic asper...osis could potentially benefit from long-term oral azole therapy.

Azole resistance is therefore potentially highly problematic for both groups of patients.

Azole-resistant *A. fumigatus* due to TR_{34}/L98H

EID 2015, JAC2015, AAC2015, JGAR2015, NMNI2015, JCA2015



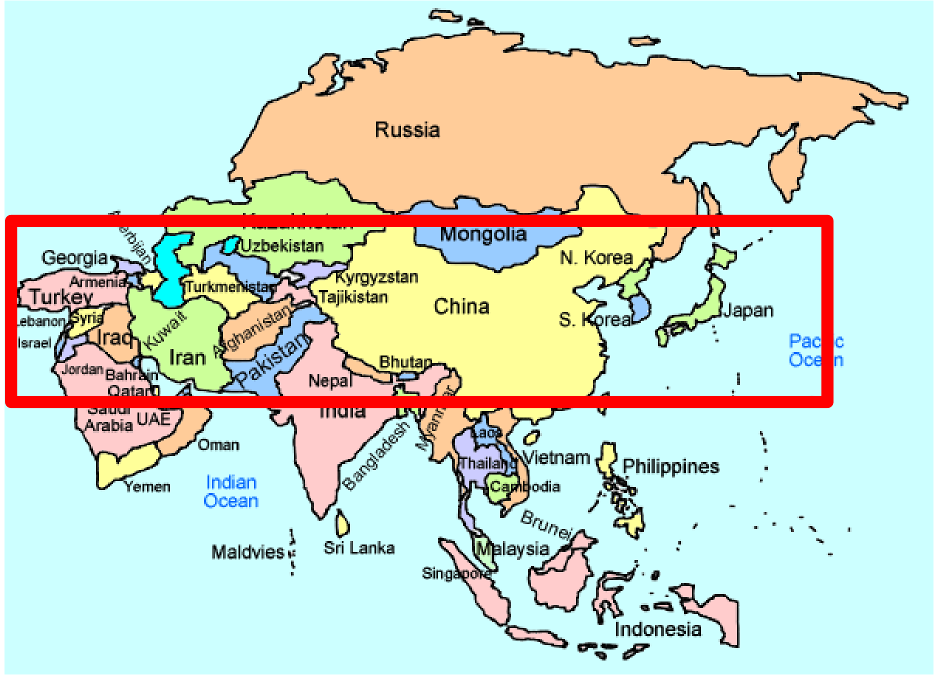


- In recent years, clinical and environmental isolates of triazole-resistant *A. fumigatus* have been reported in European countries including

the Netherlands (38%),
the United Kingdom (20%),
Italy (13%),
Turkey (10.2%),
France (8%),
Denmark (4.5%),
Spain (4.2%),
Germany (3.2%).

- Similarly, the high prevalence of triazole-resistant *A. fumigatus* has been revealed in other countries such as
- Australia (1%),
- China (5.8 %),
- India (1.9%),
- Iran (3.4%),
- Taiwan (7.9%),
- Tanzania (13.8%),
- and the United States (<1%)

Asian scenario



Turkey, TR34
Iran, TR34
Kuwait, TR34
India, TR34/TR46
China, TR34/TR46
Taiwan, TR34
Australia, TR34

- According to previous research in Iran,

- the prevalence of clinical and environmental azole-resistant *A. fumigatus* isolates 3.2% and 3.3%, respectively (Badali et al., 2013)

- In contrast with the present findings, in previous studies, with the increased rate of azole resistance (4.2% and 7.6% for clinical and environmental *A. fumigatus* isolates, respectively),

Routes of resistance development

- Azole resistance observed in azole naïve patients.
- A dominant resistance mechanism is found in the Netherlands.
- The presence of two genomic changes (including a tandem repeat).
- Isolates harbouring the TR34/L98H resistance mechanism are found in the environment.
- Triazole fungicides used in agriculture have a similar molecular structure to medical triazoles.
- Absence of genotypical wild-type isolates related to those with TR34/L98H.

(van der Linden et al., 2013).

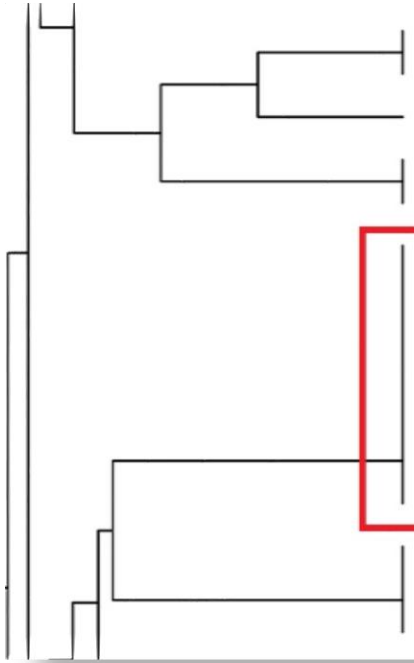
- novel *CYP51A*-mediated resistance mechanism,
- consisting of two amino acid substitutions and a 46-bp tandem repeat in the TR_{46}/Y121F/T289A gene promoter region
- reduce susceptibility to voriconazole (MIC> 16 µg/ml),
- while reducing resistance to itraconazole and posaconazole (MIC: 0.25-0.2 µg/ml).
- They revealed that 20.6% of patients harbored azole-resistant strains due to TR46/Y121F/T289A mutations

Typing

- **recently numerous fingerprinting techniques, i.e., RFLP, AFLP, RAPD, and MLST for genotyping of *A. fumigatus* with high discriminatory power and inter-laboratory reproducibility have been described**
- **they either lack the necessary reproducibility between experiments.**
- **de Valk *et al,* newly described a novel panel of nine short tandem repeat (STRs) for genotyping of *A. fumigatus* with highly discriminatory power, unambiguous assignment, inter-laboratory exchangeability of the results**
- de Valk HA, Meis JF. Journal of clinical microbiology. 2005;43(8):4112-20.

Notably, We report similar genotype in 4 isolates:
Sari Hospital soil sample (IFRC794)
Sari Hospital (BAL sample) (IFRC 540, 547,548)

Maybe source of transmission: Environmental



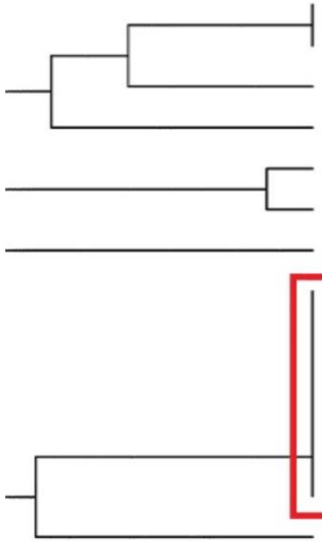
20.0	16.0	13.0	26.0	16.0	7.0	8.0	12.0	10.0	IFRC277	Clinical	Mashhad
20.0	16.0	13.0	26.0	16.0	7.0	8.0	12.0	10.0	IFRC538	Clinical	Tehran
20.0	16.0	13.0	13.0	29.0	7.0	12.0	12.0	10.0	IFRC799	Environment	Tehran
22.0	16.0	8.0	29.0	9.0	7.0	18.0	12.0	10.0	IFRC202	Clinical	Shiraz
22.0	16.0	8.0	29.0	9.0	7.0	18.0	12.0	10.0	IFRC204	Clinical	Shiraz
23.0	19.0	15.0	48.0	13.0	7.0	10.0	28.0	5.0	IFRC518	Clinical	Mashhad
23.0	19.0	15.0	48.0	13.0	7.0	10.0	28.0	5.0	IFRC535	Clinical	Tehran
23.0	19.0	15.0	48.0	13.0	7.0	10.0	28.0	5.0	IFRC540	Clinical	Sari
23.0	19.0	15.0	48.0	13.0	7.0	10.0	28.0	5.0	IFRC541	Clinical	Tehran
23.0	19.0	15.0	48.0	13.0	7.0	10.0	28.0	5.0	IFRC547	Clinical	Sari
23.0	19.0	15.0	48.0	13.0	7.0	10.0	28.0	5.0	IFRC548	Clinical	Sari
23.0	19.0	15.0	48.0	13.0	7.0	10.0	28.0	5.0	IFRC794	Environment	Sari
23.0	23.0	15.0	37.0	11.0	52.0	10.0	26.0	8.0	IFRC203	Clinical	Shiraz
23.0	23.0	15.0	37.0	11.0	52.0	10.0	26.0	8.0	IFRC206	Clinical	Shiraz
23.0	23.0	15.0	37.0	11.0	52.0	10.0	26.0	8.0	IFRC201	Clinical	Shiraz

- **In the present study, we reported TR34/L98H mutations as the responsible resistant mechanism**
- **Molecular epidemiology studies indicated that:**
- **TR34/L98H isolates might have a common ancestor and have subsequently migrated widely through airborne conidia and ascospores, as observed across Europe,**
- **or may be an adaptive recombinant progeny that developed locally,**
- **as observed in India where a unique genotype distinct from the Chinese, Middle East and European TR34/L98H strains was identified**

- In another cluster:
- 4 isolates from Tehran
- 1 isolate from Sari
- 1 isolate from Mashhad

Are the Same genotype

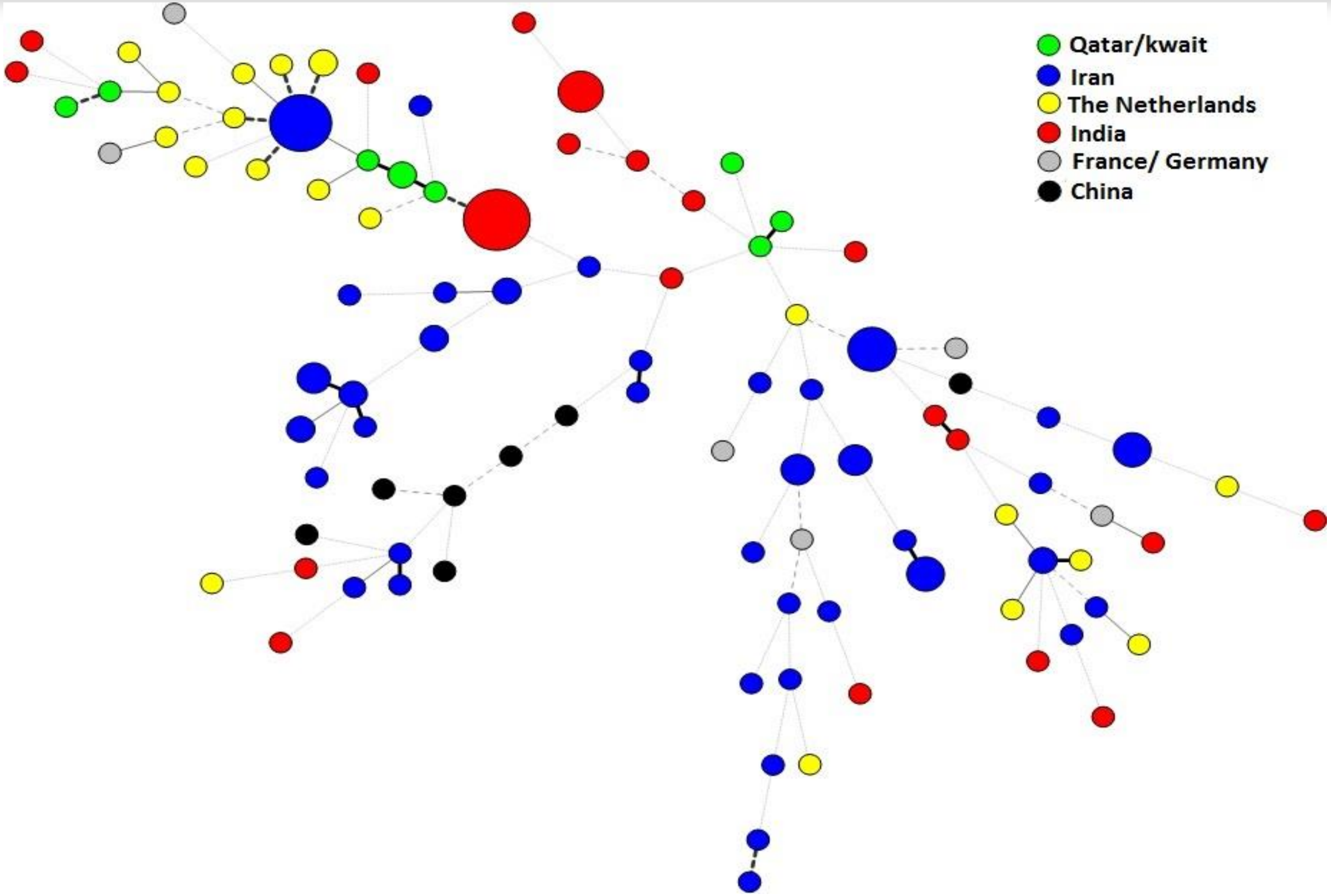
- Its possible to migration of resistant isolate



10.0	16.0	10.0	24.0	11.0	8.0	7.0	5.0	5.0	IFRC199	Clinical	Shiraz
10.0	16.0	10.0	24.0	11.0	8.0	7.0	5.0	5.0	IFRC198	Clinical	Shiraz
10.0	17.0	10.0	17.0	11.0	13.0	7.0	5.0	6.0	IFRC521	Clinical	Mashhad
11.0	16.0	9.0	14.0	24.0	5.0	7.0	5.0	5.0	IFRC836	Environment	
24.0	12.0	28.0	12.0	12.0	15.0	9.0	9.0	6.0	IFRC210	Clinical	Sari
24.0	12.0	28.0	12.0	12.0	17.0	9.0	9.0	6.0	IFRC384	Clinical	Babol
24.0	20.0	17.0	31.0	13.0	16.0	9.0	11.0	11.0	IFRC789	Environment	Mashhad
14.0	20.0	8.0	32.0	9.0	6.0	8.0	10.0	20.0	IFRC442	Environment	Tehran
14.0	20.0	8.0	32.0	9.0	6.0	8.0	10.0	20.0	IFRC387	Clinical	Sari
14.0	20.0	8.0	32.0	9.0	6.0	8.0	10.0	20.0	IFRC795	Environment	Tehran
14.0	20.0	8.0	32.0	9.0	6.0	8.0	10.0	20.0	IFRC441	Clinical	Tehran
14.0	20.0	8.0	32.0	9.0	6.0	8.0	10.0	20.0	IFRC103	Environment	Mashhad
14.0	20.0	8.0	32.0	9.0	6.0	8.0	10.0	20.0	IFRC435	Environment	Tehran
14.0	10.0	9.0	26.0	12.0	7.0	8.0	10.0	10.0	IFRC396	Clinical	Tehran

The STR typing depicted no genotypic correlation of Iranian *A. fumigatus* with isolates from other countries.

a unique genotype distinct from other countries



Recommendations

- Routine triazole susceptibility testing for clinical isolates (if antifungal treatment is indicated);
- Develop molecular methods to detect triazole resistance in culture-negative specimens and implement them in laboratory practice.
- Extensive and continued environmental studies;
- In the era of increasing azole resistance, systematic and periodic surveillance of antifungal resistance in environmental and clinical *A. fumigatus* strains are important.
- In addition, agricultural fungicide usage strategies contributing to a lower resistance selection pressure should be investigated
- monitor disease frequency and triazole resistance