Activity of Isavuconazole and Other Mould-Active Triazoles Against With and Without Alterations

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AbbVie / Allergan
Achaogen
Allecra
Amplyx
Antabio
Arietis Corp.
Arixa Pharmaceuticals
Artugen Therapeutics
Astellas Pharma
Athelas
Basilea
Bayer
Boston Pharmaceuticals
Bugworks Research
Cidara
Cipla
Contrafect
Cormedix
Crestone
Curza,
CXC7
DePuy Synthes
Destiny Pharma
Discuva Ltd.
Dr. Falk Pharma GmbH
Emery Pharma
Entasis Therapeutics
F. Hoffmann-La Roche Ltd.
Fedora Pharmaceutical
Fimbrion Therapeutics
Gateway Pharmaceutical
GenePOC Inc.
Geom Therapeutics, Inc.
GSK
Harvard University
Helperby
HiMedia Laboratories
Janssen
ICON plc
Idorsia Pharmaceuticals
Iterum Therapeutics
Janssen Research & Development
Johnson & Johnson
Kaleido Biosciences,
KBP Biosciences
Melinta Therapeutics
Menarini
Merck & Co
Meridian Bioscience Inc.
Micromyx
Microchem Laboratory
MicuRx Pharmaceuticals
Mutabilis Co.
Nabriva
Novartis
NAEJA-RGM
Paratek
Pfizer
Polyphor
Prokaryotics Inc
Qpex Biopharma
Ra Pharmaceuticals
Roche
Roivant

Background

In *A. fumigatus*, there are 2 types of environments that produce resistance selection:

- Single nucleotide mutations in *cyp51* genes, which are related to long-term azole therapy.
- Specific amino acid changes in the Cyp51A protein in combination with tandem repeats (TR) in the gene promoter, which are related to environmental selection, such as:
  - TR_{34}/L98H
  - TR_{46}/Y121F/T289A

Castanheira et al., Mycoses. 2021 Oct;64(10):1279-1290
Lestrade et al., Clin Microbiol Infect. 2019;25(7):799-806

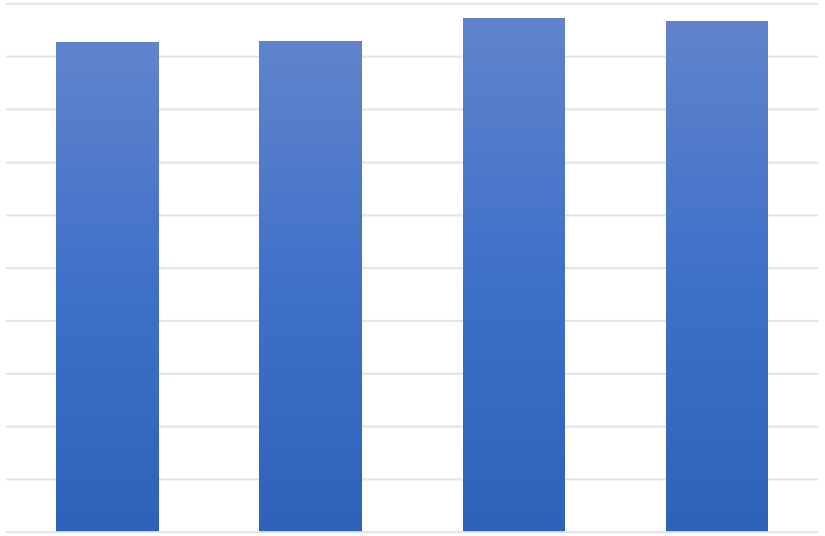
Methods

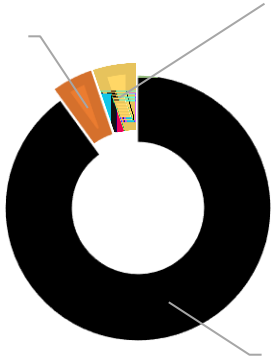
Collected by the SENTRY Antifungal Surveillance Program 2017

Methods

Used CLSI (M38) broth microdilution method.

Results





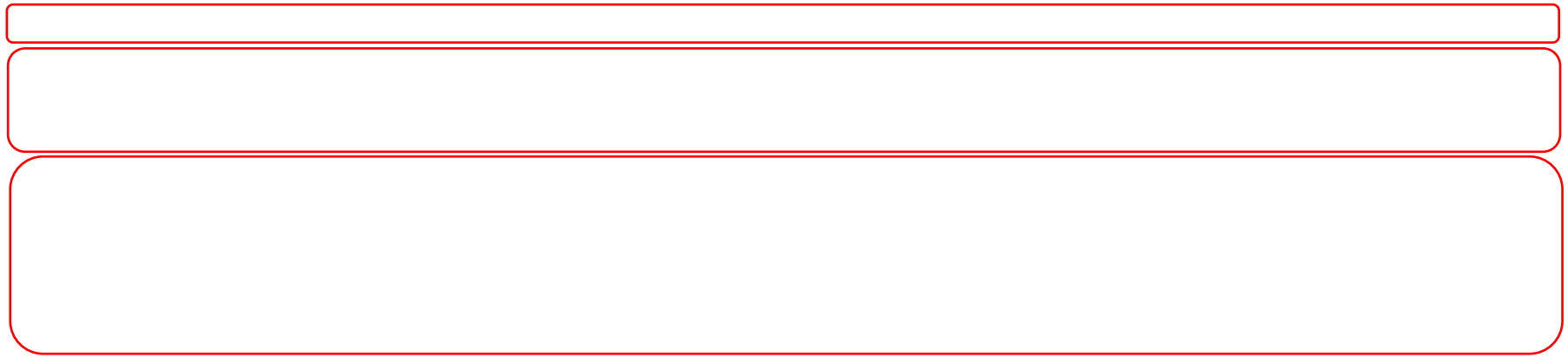
Isolates displaying alterations (=32)

Region	Total # of isolates	*cyp51* alterations	
		# of isolates	% of isolate
Asia-W. Pacific	84	4	4.8%
Europe	324	17	5.2%
North America	241	11	4.6%
Latin America	11	0	0.0%

Study Year	Continent	Country	MIC (mg/L)				CYP51A	CYP51B
			ISC	ITC	VRC	PSC		
			2	2				
			8	>8	4	1		
			4	4	2	1		
			>8	>8	>8	4		
			8	8	2	1		
			4	4	2	1		
			4	4	2	1		
			4	2	2			
			2	2	2			
			4	4				
			4	>8	2			
			8	8	2	1		
			4	4	2	1		
			4	>8	2			
			4	4	2			
			4	4		1		
			>8	8	>8			

Isolates displaying alterations (=32)

Single resistance mutations in *cyp51A*



1 isolate carried G138C and was NWT to all 4 azoles

**4 NA isolates carried I242V
All NWT to ITC
but WT to ISC and VRC**

**1 isolate carried G448S
and
1 carried A9T**

Isolates displaying alterations (=32)

5 isolates displayed multiple alterations in *cyp51A*

Study Year	Continent	Country	MIC (mg/L)				CYP51A	CYP51B
			ISC	ITC	VRC	PSC		
			2					
			2	2				
			>8	8	>8			
			2	2				
				2				

4/5 NWT to ISC or ITC

All WT to PSC

Isolates displaying alterations (=32)

7 isolates showed alterations in *cyp51B*

Study Year	Continent	Country	MIC (mg/L)				CYP51A	CYP51B
			ISC	ITC	VRC	PSC		
			2	2				
			2					
					2			
			4	4		1		
			2	2				
			2	2				
				2				

6/7 carried Q42L
and
5/7 NWT to ISC or ITC

Acknowledgements

JMI Fungal Team