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Trends on the Activity of Mould-active Agents Against *Aspergillus fumigatus* Clinical Isolates With and Without Cyp51 Alterations from Europe and North America (2017–2021)

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SENTRY ANTIMICROBIAL SURVEILLANCE

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Introduction

- Invasive aspergillosis is usually caused by *Aspergillus fumigatus* and exhibits high mortality rates.
- Azole resistance in *A. fumigatus* is increasing and is often associated with Cyp51 alterations.
- We evaluated the activity of isavuconazole and other mould-active azoles against *A. fumigatus* isolates causing invasive infections in Europe and North America.

Materials and Methods

- A total of 731 isolates were collected (1/patient) in 2017–2021 from 35 medical centres located in Europe (n=449; 17 centres; 11 countries) and North America (n=282; 18 centres; 2 countries; Figure 1).
- Isolates were identified by MALDI-TOF MS and/or ITS and β-tubulin sequencing and tested by CLSI broth microdilution method.
- CLSI (2022) epidemiological cut-off values (ECV) were applied, where available.
- Posaconazole ECVs of 0.5 mg/L was used.
- Azole non-wildtype (NWT) isolates were submitted for *cyp51* analysis by whole genome sequencing.

Results

- Overall, isavuconazole inhibited 92.7% and 94.0% of *A. fumigatus* isolates from Europe and North America, respectively, at the ECV of ≤1 mg/L.
- Table 1 displays the $MIC_{50/90}$ values for isavuconazole and other azoles.
- Isavuconazole activity was similar to other azoles regardless of the region (Table 1).
- Overall, 79 (10.8%) azole-NWT isolates were detected, 10.7% in Europe and 11.0% in North America (Table 2).
- However, azole-NWT rates increased in North America from 4.0% in 2017 to 24.4% in 2021, except for 2019 (2.4%; Figure 2).
- Azole-NWT rates varied from 4.9% (2019) to 20.6% (2018) in Europe without an observed trend (Figure 2).
- WT rates for itraconazole (14.6%/25.8% in Europe/North America), isavuconazole (31.2%/45.2%), voriconazole (58.3%/87.1%), and posaconazole (68.1%/87.1%) against azole-NWT isolates varied and were lower in Europe than North America for all azoles (Table 1).
- Cyp51 alterations occurred in 47.9%/48.4% of azole-NWT from Europe/North America, respectively (Table 2).
- Table 3 lists the *A. fumigatus* isolates displaying 11 different alterations in Cyp51 sequences and respective azole MIC ranges (Table 3).
- Cyp51A TR34/L98H alteration was observed in most European isolates (71.4% with Cyp51A alteration), while Cyp51A I242V occurred only in North American isolates (63.6% with Cyp51A alterations; Table 3).
- Isavuconazole remained active (MIC, ≤1 mg/L) against 21.7%/53.3% of azole-NWT *A. fumigatus* isolates exhibiting Cyp51 alterations in Europe/North America, along with voriconazole (34.8%/80.0%) and posaconazole (56.5%/86.7%; MIC, ≤0.5 mg/L; Figure 3).

Conclusions

- Although most *A. fumigatus* isolates were WT to azoles (89.2%), increasing azole-NWT rates were observed in North America.
- Eleven different Cyp51 alterations were detected in 38 of 79 NWT isolates.
- Only European isolates harboured the environmental alteration TR34/L98H.
- The *in vitro* activity of the azoles varied in *A. fumigatus* displaying Cyp51 alterations.

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Figure 1. Distribution of 731 *A. fumigatus* isolates stratified by continent and country

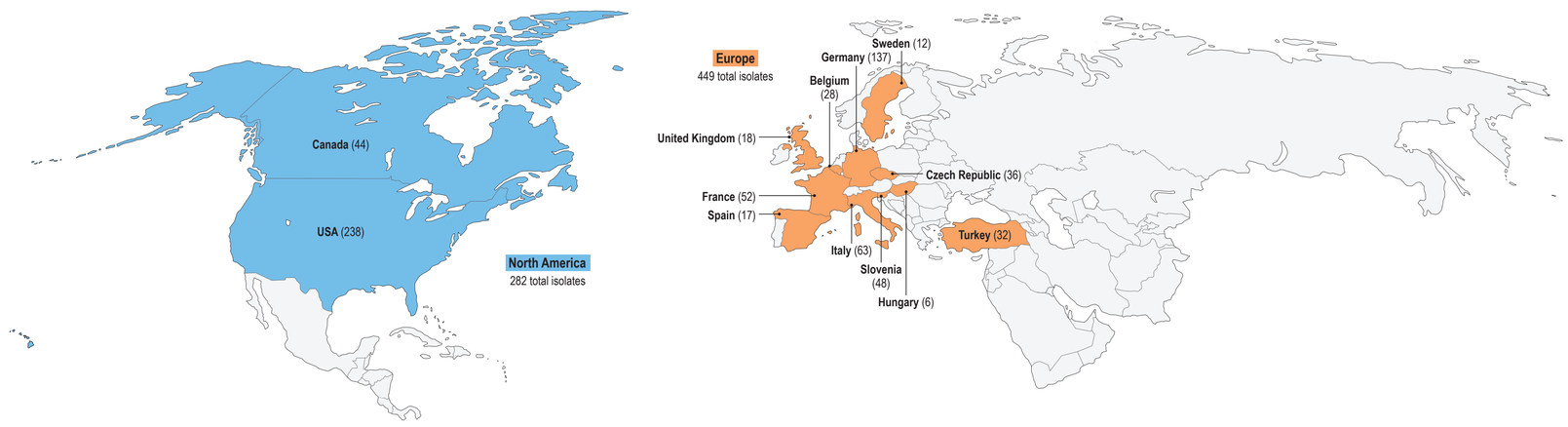


Figure 2. Azole-NWT *A. fumigatus* isolates stratified by continent and year

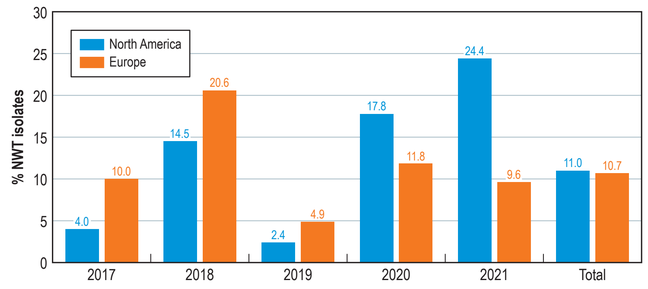
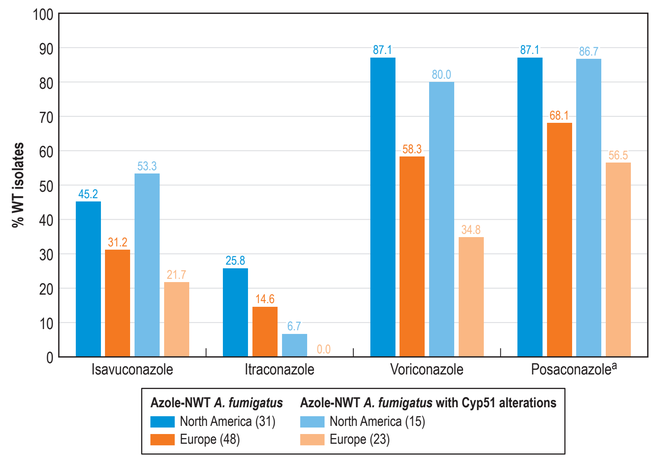


Figure 3. Isavuconazole and comparator agents WT rates against azole-NWT *A. fumigatus* isolates



Abbreviations: WT, wildtype; NWT, non-wildtype.
[a] A posaconazole ECV of 0.5 mg/L was applied.

Table 1. Activity of isavuconazole and other mould-active azoles against *A. fumigatus* from Europe and North America

Organism (no. of isolates in all years)	MIC_{50}/MIC_{90} (mg/L) CLSI %WT			
	ISC	ITC	VRC	PSC[a]
A. fumigatus				
Europe (449)	0.5/1 92.7	1/1 90.9	0.5/0.5 95.5	0.25/0.5 96.4
North America (282)	0.5/1 94.0	1/1 91.8	0.5/0.5 98.6	0.25/0.5 97.5
Azole-WT *A. fumigatus*				
Europe (401)	0.5/1 100.0	1/1 100.0	0.5/0.5 100.0	0.25/0.5 99.8
North America (251)	0.5/1 100.0	1/1 100.0	0.5/0.5 100.0	0.25/0.5 98.8
Azole-NWT *A. fumigatus*				
Europe (48)	2/8 31.2	2/>8 14.6	1/4 58.3	0.5/1 68.1
North America (31)	2/2 45.2	2/4 25.8	0.5/2 87.1	0.5/1 87.1
Azole-NWT *A. fumigatus* with Cyp51 alterations				
Europe (23)	4/8 21.7	4/>8 0.0	2/4 34.8	0.5/1 56.5
North America (15)	1/2 53.3	2/4 6.7	1/2 80.0	0.5/1 86.7

Abbreviations: WT, wildtype; NWT, non-wildtype; ISC, isavuconazole; ITC, itraconazole; VRC, voriconazole; PSC, posaconazole.
[a] Posaconazole ECV of 0.5 mg/L was applied.

Table 2. Occurrence of Cyp51 alterations in azole-NWT *A. fumigatus* isolates stratified by region

	Europe		North America	
	no. of isolates		no. of isolates	
A. fumigatus	449		282	
Azole-NWT *A. fumigatus*	48	10.7%	31	11.0%
Cyp51 alterations	23	47.9%	15	48.4%
Cyp51A alterations	21	91.3%	11	73.3%
Cyp51B alterations	2	8.7%	6	40.0%
Cyp51A & Cyp51B alterations	0	0%	2	13.3%

Table 3. Summary of *A. fumigatus* isolates carrying Cyp51 alterations

Cyp51 alteration		Country (no. of occurrences)	Study Years	MIC range (mg/L)			
Cyp51A	Cyp51B			ISC	ITC	VRC	PSC
F46Y, M172V, E427K	WT	Czech Republic (3), USA (2)	2018, 2020, 2021	1-2	2	0.5-1	0.5
F46Y, M172V, E427K with N248T, D255E	WT	Czech Republic (1), USA (1)	2018, 2020	1-2	2	0.5-1	0.5
G448S	WT	USA (1)	2019	>8	>8	4	0.5
I242V	WT	USA (6), Canada (1)	2018, 2020, 2021	1-2	1-4	0.5-1	0.25-1
I242V alone	WT	USA (4), Canada (1)	2018, 2020	1	2	0.5	0.25-1
I242V with Cyp51B alteration	Q42L, S501Q	USA (2)	2021	1-2	1-4	1	0.5
K67Q	WT	France (1), USA (1)	2021	0.5-2	2	0.5-2	0.5-1
L98H, TR34[a]	WT	Belgium (1), Czech Republic (1), Germany (1), Italy (7), Slovenia (1), UK (4)	2018, 2019, 2020, 2021	2->8	2->8	1->8	0.5-4
M172V	WT	Czech Republic (1)	2021	1	2	0.5	0.5
Y121F, T289A, TR46[a], M172I, G448S	WT	Belgium (1)	2019	>8	8	>8	0.5
WT	Q42L	France (1), USA (4)	2019, 2020, 2021	0.5-4	2-4	0.5-2	0.25-1
WT	F149V	France (1)	2021	1	2	0.5	0.5

Abbreviations: WT, wildtype; ISC, isavuconazole; ITC, itraconazole; VRC, voriconazole; PSC, posaconazole.
[a] 34 or 46 base pair tandem repeat sequence upstream of the *cyp51A*

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