

Activity of rezafungin against *Aspergillus* spp.

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Introduction

- Aspergillus* spp. is an environmental mould which is the causative agent of invasive aspergillosis (IA), chronic pulmonary aspergillosis, and allergic reactions
 - One year mortality of IA is up to 59% in solid organ transplant recipients and 25% in stem cell transplant recipients
- Rezafungin is a long-acting echinocandin with a pharmacodynamic/pharmacokinetic profile allowing a higher concentration in the bloodstream and at sites of infection in addition to weekly dosing
 - CLSI breakpoints are 2-3 doubling dilutions higher than for other echinocandins against *Candida* spp.
- Rezafungin is in a Phase 2 clinical trial for the treatment of chronic pulmonary aspergillosis (NCT06794554) and a Phase 3 clinical trial for the prevention of invasive fungal disease in adults undergoing allogeneic blood and marrow transplantation (ReSPECT, NCT04368559)
- We looked at the activity of rezafungin against *Aspergillus* spp. collected over 11 years during a worldwide surveillance program

Methods

- A total of 1,004 *Aspergillus* spp. isolates were collected from 2014-2024 in 60 different hospitals from 22 countries (Figure 1)
- Only 1 isolate per patient episode was included
- All isolates were identified by MALDI-TOF MS and/or DNA sequencing
- Isolates were tested by CLSI reference broth microdilution method (M38) for rezafungin, anidulafungin, micafungin, voriconazole, and amphotericin B
- Minimum effective concentration (MEC) was read for echinocandins and minimum inhibitory concentration (MIC) was read for voriconazole and amphotericin B

Results

- There were 814 *Aspergillus fumigatus* (81.1%), 145 *Aspergillus* section *Flavi* (14.4%), and 30 *Aspergillus* section *Nigri* (3.0%) isolates
- The rezafungin MEC_{50/90} was 0.015/0.03 mg/L among all isolates, which was the same as anidulafungin; micafungin MEC_{50/90} was ≤0.008/0.015 mg/L, voriconazole MIC_{50/90} was 0.5/1 mg/L, and amphotericin B was 1/2 mg/L (Table 1)
 - For *A. fumigatus*, rezafungin and anidulafungin MEC_{50/90} was 0.015/0.03 mg/L, micafungin ≤0.008/0.015 mg/L, voriconazole MIC_{50/90} 0.5/0.5 mg/L, and amphotericin B 1/2 mg/L
 - For *A. section Flavi*, rezafungin MEC_{50/90} was ≤0.008/0.03 mg/L, anidulafungin ≤0.008/0.015 mg/L, micafungin 0.015/0.03 mg/L, voriconazole MIC_{50/90} 0.5/1 mg/L, and amphotericin B 2/2 mg/L
 - For *A. section Nigri*, rezafungin and anidulafungin MEC_{50/90} was 0.004/0.008 mg/L, micafungin was 0.004/0.015 mg/L, voriconazole MIC_{50/90} was 1/2 mg/L, and amphotericin B was 0.25/0.25 mg/L
- Rezafungin MEC_{50/90} was unchanged across geographic regions (Figure 1)
 - Regional variability was seen for voriconazole among *A. fumigatus*; in North America 7.8% of isolates, in LATAM 13.5% of isolates, in Europe 8.4% of isolates, and in APAC 9.2% of isolates were non-susceptible to voriconazole (data not shown)
- There were 63 *A. fumigatus* isolates that were non-susceptible to voriconazole (MIC ≥1 mg/L)
 - Among these, rezafungin and comparator echinocandin MEC_{50/90}s were unchanged
- There were 3 *A. section Nigri* isolates that were non-wildtype to voriconazole (MIC >2 mg/L)
 - Among these rezafungin MECs were 0.002 to 0.008 mg/L, anidulafungin were 0.004 mg/L, micafungin were 0.008 to 0.015 mg/L, and amphotericin B MICs were 0.25 mg/L
- MECs and MICs were consistent across years of study with no trend towards increasing azole resistance (Table 2)

Conclusions

- Aspergillus* spp. isolates from 22 countries during 11 years of the SENTRY surveillance program showed low MECs to echinocandins including the novel agent rezafungin
- There was no change in MEC distributions for rezafungin across years of the study or in different geographical regions
- In contrast, voriconazole showed higher MICs and non-susceptible rates among *A. fumigatus* from LATAM and APAC compared to North America and Europe
- Rezafungin represents a promising agent for treatment and prevention of invasive Aspergillosis and chronic pulmonary Aspergillosis based on *in vitro* susceptibility results

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Table 1. Antimicrobial activity of rezafungin and select comparator agents in mg/L tested against 1,004 *Aspergillus* spp.

Organism (no. isolates)	Rezafungin		Anidulafungin		Micafungin		Voriconazole		Amphotericin B	
	MEC _{50/90}	MEC Range	MEC _{50/90}	MEC Range	MEC _{50/90}	MEC Range	MIC _{50/90} (%S/WT) ^b	MIC Range	MIC _{50/90} (%S/WT) ^b	MIC Range
<i>Aspergillus</i> spp. (1,004) ^a	0.015/0.03	≤0.008 to 0.12	0.015/0.03	≤0.008 to 0.12	≤0.008/0.015	≤0.008 to 0.12	0.5/1	0.12 to >8	1/2	≤0.03 to >2
<i>Aspergillus fumigatus</i> (814)	0.015/0.03	≤0.008 to 0.12	0.015/0.03	≤0.008 to 0.12	≤0.008/0.015	≤0.008 to 0.12	0.5/0.5 (92.3/97.8)	0.12 to >8	1/2 (NA/99.8)	0.06 to 4
<i>Aspergillus fumigatus</i> NS to VRC (63)	0.015/0.03	≤0.008 to 0.12	0.015/0.03	≤0.008 to 0.12	≤0.008/0.015	≤0.008 to 0.06	1/8 (0.0/0.0)	1 to >8	1/2	0.06 to 2
<i>Aspergillus</i> section <i>Flavi</i> (145)	≤0.008/0.03	≤0.008 to 0.06	≤0.008/0.015	≤0.008 to 0.03	0.015/0.03	≤0.008 to 0.03	0.5/1 (NA/100.0)	0.25 to 2	2/2 (NA/99.3)	0.12 to >2
<i>Aspergillus</i> section <i>Nigri</i> (30)	0.004/0.008	0.001 to 0.03	0.004/0.008	≤0.002 to 0.06	0.004/0.015	≤0.002 to 0.06	1/2 (NA/90.0)	0.12 to >8	0.25/0.25 (NA/100.0)	≤0.03 to 0.5
<i>Aspergillus</i> section <i>Nigri</i> NWT to VRC (3)	0.004/NA	0.002 to 0.008	0.004/NA	0.004	0.008/NA	0.008 to 0.015	4/NA	4 to >8	0.25/NA	0.25

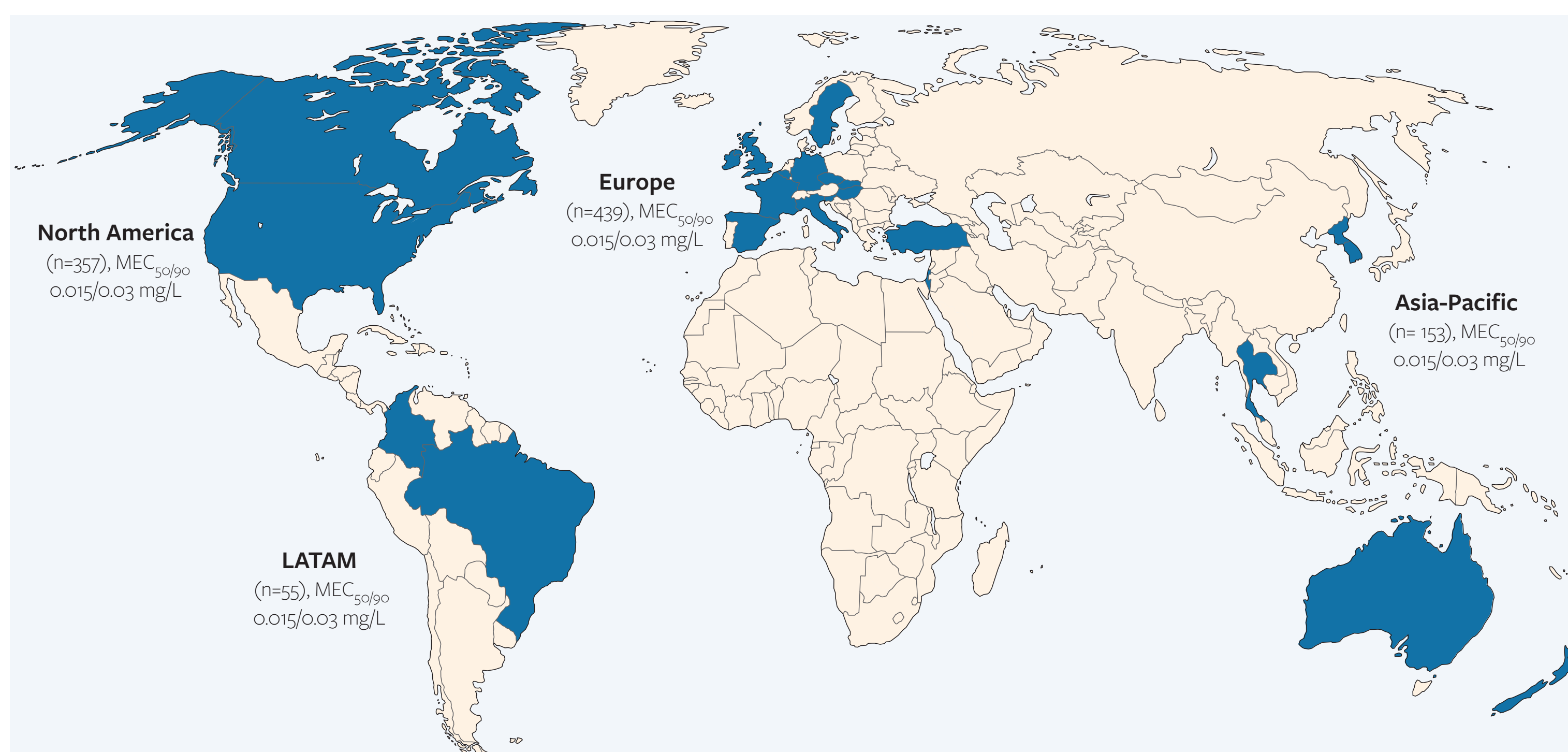
MEC, minimum effective concentration; MIC, minimum inhibitory concentration; S, susceptible; WT, wildtype; NS, non-susceptible; VRC, voriconazole; NWT, non-wildtype
^a Organisms include *Aspergillus flavus* (5), *A. flavus* species complex (135), *A. fumigatus* (814), *A. hirsutiae* (1), *A. nidulans* (3), *A. nidulans* species complex (1), *A. niger* (10), *A. niger* species complex (20), *A. nomius* (2), *A. parasiticus* (2), *A. tamarii* (1), *A. terreus* (6), *A. terreus* species complex (3), and unspiciated *Aspergillus* (1).
^b Breakpoint criteria published in CLSI M38M51S (2022) and epidemiological cutoff value (ECV) criteria published in CLSI M57S (2022).

Table 2. Antifungal activity (MIC/MEC_{50/90}) of rezafungin and select comparator agents tested against 1,004 *Aspergillus* spp. across years of study

Antifungal agent	MIC/MEC _{50/90} (mg/L) per year of testing (number of isolates per year)										
	2014 (56)	2015 (110)	2016 (60)	2017 (78)	2018 (90)	2019 (121)	2020 (93)	2021 (70)	2022 (123)	2023 (103)	2024 (100)
Rezafungin	0.015/0.015	0.015/0.03	0.015/0.015	0.015/0.015	0.015/0.03	0.015/0.03	0.015/0.03	0.03/0.06	0.015/0.03	0.008/0.015	0.008/0.015
Anidulafungin	≤0.008/0.015	≤0.008/0.015	≤0.008/0.015	0.015/0.03	0.015/0.015	0.015/0.06	0.015/0.06	0.03/0.06	0.015/0.03	0.015/0.03	0.008/0.015
Micafungin	0.015/0.015	≤0.008/0.015	≤0.008/0.015	≤0.008/0.015	0.008/0.015	0.008/0.008	0.008/0.015	0.008/0.015	0.008/0.03	0.004/0.008	0.008/0.008
Voriconazole	0.25/0.5	0.5/1	0.5/1	0.25/0.5	0.5/1	0.25/0.5	0.5/1	0.5/1	0.5/1	0.5/1	0.5/1
Amphotericin B	2/2	1/2	2/2	1/2	1/2	2/2	2/2	1/1	1/1	1/2	1/2

MEC, minimum effective concentration; MIC, minimum inhibitory concentration

Figure 1. Rezafungin MEC_{50/90} from *Aspergillus* spp. isolates by region



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