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International Surveillance of *Candida* spp. and *Aspergillus* spp.: Report from the SENTRY Antimicrobial Surveillance Program (2003)

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During 2003, a total of 1,397 *Candida* isolates, 73 *Aspergillus* isolates, 53 *Cryptococcus neoformans* isolates, and 25 other fungal isolates from infected, normally sterile, body sites in patients hospitalized in North America, Europe, and Latin America were studied as a component of the longitudinal SENTRY Antimicrobial Surveillance Program. The MICs for seven antifungal agents were determined in a central laboratory (JMI Laboratories, North Liberty, IA) using testing methods promulgated by the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards). The rank order of *Candida* spp. occurrence was as follows: *C. albicans* (48.7%), *C. parapsilosis* (17.3%), *C. glabrata* (17.2%), *C. tropicalis* (10.9%), *C. krusei* (1.9%), and other *Candida* spp. (4.0%). *C. albicans* accounted for 51.5, 47.8, and 36.5% of candidal infections in North America, Europe, and Latin America, respectively. Ravuconazole, voriconazole, and fluconazole were highly active against *C. albicans*, *C. parapsilosis*, and *C. tropicalis*, with both former agents being more potent (MIC at which 90% of the isolates tested are inhibited [MIC_{90}] of ≤0.008 to 0.12 μg/ml) than fluconazole (MIC_{90} of 0.5 to 2 μg/ml). *C. glabrata* isolates were less susceptible to these agents, with MIC_{90}s of 1, 1, and 64 μg/ml, respectively. Ravuconazole and voriconazole were the most active agents tested against *C. krusei* (MIC_{90} of 0.5 μg/ml). Among *Aspergillus* spp., *A. fumigatus* was the most commonly (71.2% of isolates) recovered species; 96.2, 96.2, 84.6, and 11.5% of strains were inhibited by ≤1 μg/ml of ravuconazole, voriconazole, itraconazole, and amphotericin B, respectively. Of the antifungal agents tested, ravuconazole and voriconazole displayed the greatest spectrum of activity against pathogenic *Candida* and *Aspergillus* spp., regardless of geographic origin. These results extend upon previous findings from SENTRY Program reports (1997 to 2000), further characterizing species composition as seen in local clinical practice and demonstrating the potent activity of selected, newer triazole antifungal agents.

Fungal infections are associated with high rates of attributable morbidity and mortality (1, 5, 20). Limited therapeutic options for treating these infections, as well as concerns over selection of non-*Candida* species with reduced susceptibilities to the triazole agents (1, 4, 18), have warranted surveillance for potential resistance development and demonstrated the need for expansion of available antifungal regimens (16, 22). Emerging mold pathogens and rarely encountered yeast species with decreased susceptibility to current antifungal compounds (2, 3, 17) emphasize the sustained need for the generation of meaningful data to detect and monitor these etiologic agents. Standardized antifungal testing methodologies for *Candida* spp. and *Cryptococcus neoformans* development in the 1990s (7) and the implementation of methods for the filamentous fungi in 2002 (8) have facilitated the ability to assess the prevalence of resistance among these pathogens. These standardized methods, coupled with global longitudinal resistance surveillance, have further enabled analysis of potential changes in the efficacy of licensed and investigational antifungal agents (9, 11, 14, 15, 17). In addition, global-scale programs allow the detection of geographic differences in susceptibility, as well as the discovery of evolving trends in pathogen distributions secondary to changing patient demographics and clinical practice or drug exposure (11, 14, 17).

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We summarize here the results of the international SENTRY Antimicrobial Surveillance Program comparing the activity of investigational and currently marketed antifungal agents (one investigational agent, ravuconazole) against 1,548 clinical strains of yeast and filamentous fungi. The isolates were tested by Clinical and Laboratory Standards Institute (CLSI; formerly the National Committee for Clinical Laboratory Standards [NCCLS]) reference methods with susceptibilities to comparator agents interpreted by published breakpoint criteria, where available (7, 8).

MATERIALS AND METHODS

Specimen collection. A total of 1,397 *Candida* spp. (predominantly from bloodstream infections), 73 *Aspergillus* spp. (lower respiratory tract infections), 53 *C. neoformans*, and 25 other isolates from infected sterile body sites were submitted from participating medical centers in North America (882 strains), Europe (350 strains), and Latin America (316 strains) to a central testing laboratory (JMI Laboratories, North Liberty, IA) for analysis. Applicable biochemical methods and use of the Vitek Identification System (bioMerieux, Hazelwood, MO) were performed to confirm species identification upon receipt. The collection of yeasts included 680 *C. albicans*; 242 *C. parapsilosis*; 240 *C. glabrata*; 152 *C. tropicalis*; 53 *Cryptococcus neoformans*; 27 *C. krusei*; 16 *C. lusitaniae*; 13 *C. guilliermondii*; eight *C. kefyr*; five *C. lipolytica*; three strains each of *C. pelliculosa*, *Hansenula anomala*, and *Saccharomyces cerevisiae*; two strains each of *C. dubliniensis*, *C. famata*, *Candida* spp., *Rhodotorula* spp., and *Trichosporon beigelii*; and one strain each of *C. humicola*, *C. pulcherrima*, *C. rugosa*, *C. sake*, *R. rubra*, and *T. asahii*. The collection of filamentous fungi included 52 *Aspergillus fumigatus*; seven *A. flavus*; six strains each of *A. niger* and *Penicillium* spp.; four *A. terreus*; and two strains each of *A. nidulans*, *A. versicolor*, *Curvularia* spp., *Fusarium* spp., and *Rhizopus* spp. Prior to susceptibility testing, yeast isolates were subcultured twice consecutively from storage in sterile water on potato dextrose agar (Remel, Inc., Lenexa, KS) and incubated for 24 h at 35 to 37°C to

ensure maximum viability. Mold isolates were subcultured on potato dextrose agar slants and incubated for 7 days at 35 to 37°C to ensure optimal conidial formation.

Susceptibility testing methods. All strains were tested by reference broth microdilution methods for yeasts and filamentous fungi as recommended by the NCCLS M27-A2 and M38-A Standards (7, 8). Broth microdilution panels containing antifungal agents were manufactured by TREK Diagnostics (Cleveland, OH) and stored at −80°C until used. The antifungal testing format consisted of 96-well round-bottom trays containing 100 μl of incremental 2× strength selected agents in RPMI 1640 growth medium buffered to pH 7.0 with 0.165 M morpholinepropanesulfonic acid. The antifungal agents included in the microdilution panel were flucytosine (range, 0.03 to 64 μg/ml), fluconazole (0.12 to 256 μg/ml), itraconazole (0.008 to 16 μg/ml), ketoconazole (0.008 to 16 μg/ml), voriconazole (0.008 to 16 μg/ml), ravuconazole (0.008 to 16), and amphotericin B (0.016 to 16 μg/ml). Quality control isolates *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 were tested in parallel for each batch of isolates tested; all results were within the published ranges for each antifungal agent tested.

Determination of MICs for yeasts. Microdilution panels were incubated at 35 to 37°C for 48 h in an enclosed container, and MIC results were visualized with the aid of a reading mirror. The MICs for amphotericin B were determined as the lowest concentration at which no visible growth was discerned. The MIC results for flucytosine, fluconazole, ketoconazole, itraconazole, voriconazole, and ravuconazole were recorded as the lowest concentration at which a significant (≥50%) decrease in growth was visualized compared to the growth control. Susceptible, intermediate (or susceptible, dose-dependent [SDD]), and resistant breakpoints for flucytosine (≤4 μg/ml, 8 to 16 μg/ml, and ≥ 32 μg/ml, respectively), fluconazole (≤8 μg/ml, 16 to 32 μg/ml [SDD], and ≥64 μg/ml), and itraconazole (≤0.12 μg/ml, 0.25 to 0.5 μg/ml [SDD], and ≥1 μg/ml) were those of Rex et al. (20) and the CLSI (7).

Determination of MIC results for molds. Panels were incubated for 48 h in an enclosed, moist chamber at 35 to 37°C. The MICs for amphotericin B, itraconazole, voriconazole, and ravuconazole were determined as the lowest concentration at which no growth was visualized. The MICs for fluconazole, ketoconazole, and flucytosine were determined as the lowest concentration in which significant growth inhibition (defined as ≤50% of the growth seen in the drug-free control well) was observed (8).

RESULTS AND DISCUSSION

The rank order of the 1,397 isolates of *Candida* spp. recovered during the 2003 surveillance year from all sources was as follows: *C. albicans* (48.7%), *C. parapsilosis* (17.3%), *C. glabrata* (17.2%), *C. tropicalis* (10.9%), *C. krusei* (1.9%), and other *Candida* spp. (5.2%), figures consistent with an increasing trend of non-*Candida* spp. recovered from prior SENTRY Program (1997 to 1999) and ARTEMIS Global Antifungal Surveillance Program (2001) monitoring periods (11, 12).

Antifungal activities (MIC at which 50% of the isolates are inhibited [MIC_{50}] and MIC_{90} values; categorical interpretations, where applicable) of the seven agents tested against these *Candida* spp. and *C. neoformans* (53 isolates) are presented in Table 1. The newer azoles, voriconazole and the investigational agent ravuconazole, demonstrated enhanced potency against *C. albicans* (MIC_{90} values [for both] of ≤0.008 μg/ml), *C. parapsilosis* (0.12 μg/ml [both]), *C. glabrata* (1 μg/ml [both]), *C. tropicalis* (0.12 μg/ml [both]), *C. krusei* (0.5 μg/ml [both]), and other *Candida* spp. (0.25 and 0.5 μg/ml, respectively). By comparison, currently licensed agents were generally less potent against these species (fluconazole MIC_{90} values of 0.5 to 128 μg/ml; itraconazole, 0.12 to 2 μg/ml; and flucytosine, 0.12 to 64 μg/ml). For agents with defined categorical breakpoints, *C. albicans*, *C. parapsilosis*, and *C. tropicalis* were most susceptible to fluconazole (≥98%) and flucytosine (>90%). Against species of *Candida* that express intrinsic resistance to fluconazole (*C. glabrata*, MIC_{90} of 64 μg/ml, 52.1% susceptible; *C. krusei*, MIC_{90} of 128 μg/ml, 25.9% susceptible), the newer triazoles displayed significantly greater potency (voriconazole and ravuconazole MIC_{90} values of 1 and 0.5 μg/ml for *C. glabrata* and *C. krusei*, respectively). Flucytosine was the single most active agent against *C. glabrata* (MIC_{90} of 0.12 μg/ml; 100.0% susceptible) and was eightfold more active than either voriconazole or ravuconazole.

Breakpoints have not been established for any drug targeting *C. neoformans*. The potencies of tested agents do vary significantly for this species (Table 1), with the newer triazole agents displaying the greatest potencies (voriconizole and ravuconazole, MIC_{90} of 0.5 μg/ml), 64-fold more potent than fluconazole (MIC_{90} of 32 μg/ml). Itraconazole and amphotericin B demonstrated identical in vitro activities (MIC_{90} of 1 μg/ml). Compared to a prior study (in 1999) of 566 *C. neoformans* isolates from the United States and Africa, the potencies (i.e., the MIC_{90} results) for fluconazole, itraconazole, and voriconazole decreased twofold (19).

The MIC_{50} and MIC_{90} results for antifungal agents tested and analyzed by species and by continent of origin are presented in Table 2. The most frequently encountered *Candida* spp. in all regions, *C. albicans*, occurred at rates of 51.5, 47.8, and 36.5% among candidal infections in North America, Europe, and Latin America, respectively. *C. parapsilosis* accounted for 15.5, 16.3, and 23.4% of isolates, respectively. Although further study on the nosocomial spread of this species may be of clinical interest, this finding emphasizes the utility of longitudinal surveillance results, since *C. parapsilosis* has been associated with poor infection control practices (1, 6). Reducing the frequency of infection caused by this organism, as well as the associated healthcare costs, has been attainable with improved hospital hygiene practices. *C. glabrata* was ranked second among *Candida* species isolated from North America but ranked third in Europe and fourth in Latin America, with 21.3, 12.7, and 10.8% of isolates, respectively. This species generally possesses reduced susceptibility to the azoles, an added challenge in the development of new agents. During the surveillance period, *C. glabrata* from Latin America were found to be less susceptible to amphotericin B (MIC_{90} of 2 μg/ml) and ravuconazole (MIC_{90} of 2 μg/ml). *C. tropicalis*, ranked fourth in occurrence among *Candida* spp. isolates overall, was the third-ranking organism in Latin America (21.3% of isolates).

Among *Aspergillus* spp., *A. fumigatus* was predominant (71.2% [Table 3]). *A. fumigatus* was resistant to most antifungals, with voriconazole (MIC_{90} of 1 μg/ml), ravuconazole (MIC_{90} of 1 μg/ml), and itraconazole (MIC_{90} of 2 μg/ml) being the most active agents with inhibition of 96.2, 96.2, and 84.6% of isolates at MICs of ≤1 μg/ml, respectively. Amphotericin B, fluconazole, and ketoconazole showed limited activity against *Aspergillus* spp. (MIC_{90} range, 4 to >256 μg/ml).

Since its inception in 1997, one of the objectives of the SENTRY Program has been to examine frequencies of occurrence and antifungal resistance among yeast species from bloodstream infections and normally sterile body sites in the North American, European, and Latin American regions (11, 14). The frequencies of the recovered species over the intervening years (1997 to 1999 and 2003) have consistently demonstrated a trend toward a decreasing prevalence of *C. albicans* in all regions (North America, 55 to 51%, respectively; Europe, 58 to 52%; Latin America, 45 to 36%) and an increasing

TABLE 1. In vitro susceptibilities of *Candida* spp. and *C. neoformans* isolates to seven antifungal agents (SENTRY Program, 2003)

Species (no. of isolates tested) and drug	MIC (μg/ml)			% of isolates[a]		
	50%	90%	Range	Susceptible	SDD	Resistant
All *Candida* spp. (1,397)						
Amphotericin B	1	1	0.25–2			
5-FC[b]	0.12	1	≤0.03–>64	95.3	(1.4)	3.3
Fluconazole	0.5	16	≤0.12–256	88.5	7.3	4.2
Ketoconazole	0.03	1	≤0.008–4			
Itraconazole	0.12	1	≤0.008–>16	55.6	28.9	15.5
Voriconazole	0.016	0.25	≤0.008–8			
Ravuconazole	0.016	0.25	≤0.008–4			
C. albicans (680)						
Amphotericin B	1	1	0.25–2			
5-FC	0.12	2	≤0.03–>64	97.8	(0.4)	1.8
Fluconazole	≤0.25	0.5	≤0.12–128	99.4	0.1	0.4
Ketoconazole	≤0.008	0.016	≤0.008–2			
Itraconazole	0.06	0.12	≤0.008–2	92.8	6.9	0.3
Voriconazole	≤0.008	≤0.008	≤0.008–4			
Ravuconazole	≤0.008	≤0.008	≤0.008–4			
C. parapsilosis (242)						
Amphotericin B	1	1	0.5–2			
5-FC	0.12	0.5	≤0.03–2	100.0	(0.0)	0.0
Fluconazole	1	2	0.25–64	98.8	0.8	0.4
Ketoconazole	0.12	0.25	0.016–1			
Itraconazole	0.25	0.5	0.03–1	32.6	65.7	1.7
Voriconazole	0.03	0.12	≤0.008–1			
Ravuconazole	0.03	0.12	≤0.008–0.5			
C. glabrata (240)						
Amphotericin B	1	1	0.25–2			
5-FC	0.06	0.12	≤0.03–2	100.0	(0.0)	0.0
Fluconazole	8	64	1–128	52.1	35.8	12.1
Ketoconazole	0.5	2	0.12–4			
Itraconazole	1	2	0.25–>16	0.0	26.3	73.7
Voriconazole	0.25	1	0.03–4			
Ravuconazole	0.25	1	0.03–4			
C. tropicalis (152)						
Amphotericin B	1	1	0.5–2			
5-FC	0.25	1	≤0.03–>64	90.1	(0.7)	9.2
Fluconazole	1	2	≤0.12–128	98.0	0.7	1.3
Ketoconazole	0.03	0.12	≤0.008–4			
Itraconazole	0.25	0.5	0.016–2	32.2	64.5	3.3
Voriconazole	0.06	0.12	≤0.008–8			
Ravuconazole	0.03	0.12	≤0.008–4			
C. krusei (27)						
Amphotericin B	1	2	1–2			
5-FC	32	64	8–>64	0.0	(44.4)	55.6
Fluconazole	64	128	16–256	0.0	25.9	74.1
Ketoconazole	1	2	0.5–4			
Itraconazole	1	1	0.25–2	0.0	40.7	59.3
Voriconazole	0.5	0.5	0.12–4			
Ravuconazole	0.5	0.5	0.12–2			
Candida spp. (56)						
Amphotericin B	1	1	0.25–2			
5-FC	0.12	16	≤0.03–>64	83.9	(7.2)	8.9
Fluconazole	0.12	16	≤0.12–128	83.9	10.7	5.4
Ketoconazole	0.12	0.5	≤0.008–2			
Itraconazole	0.25	1	0.03–2	32.1	46.5	21.4
Voriconazole	0.03	0.25	≤0.008–1			
Ravuconazole	0.03	0.5	≤0.008–1			
C. neoformans (53)[c]						
Amphotericin B	1	1	0.25–2			
5-FC	8	16	2–16			
Fluconazole	16	32	4–64			
Ketoconazole	0.5	1	0.12–1			
Itraconazole	0.5	1	0.25–1			
Voriconazole	0.12	0.5	0.03–0.5			
Ravuconazole	0.12	0.5	0.016–0.5			

[a] The breakpoint criteria are those of the NCCLS/CLSI (7). Numbers in parentheses indicate the percent intermediate, not the susceptibility dose dependent (SDD) (7).
[b] 5-FC, 5-fluorocytosine.
[c] Breakpoint criteria have not been established for cryptococcal organisms.

TABLE 2. In vitro susceptibilities of *Candida* spp. and *C. neoformans* isolates from North America, Europe, and Latin America to seven antifungal agents (SENTRY Program, 2003)

Species (no. of isolates tested in North America, Europe, and Latin America) and drug	MIC (μg/ml) or % of isolates susceptible[a]								
	North America			Europe			Latin America		
	50%	90%	%S	50%	90%	%S	50%	90%	%S
All *Candida* spp. (784, 336, 277)									
Amphotericin B	1	1		1	1		1	1	
5-FC[b]	0.12	2	95.9	0.25	8	92.6	0.12	1	96.8
Fluconazole	0.5	16	86.4	0.5	16	89.3	0.5	8	93.5
Ketoconazole	0.016	1		0.016	0.5		0.03	0.5	
Itraconazole	0.12	1	57.1	0.12	1	59.5	0.25	1	46.6
Voriconazole	0.016	0.25		≤0.008	0.25		0.03	0.25	
Ravuconazole	≤0.008	0.5		≤0.008	0.25		0.03	0.25	
C. albicans (404, 175, 101)									
Amphotericin B	1	1		1	1		1	1	
5-FC	0.25	2	97.0	0.12	0.5	98.9	0.12	2	99.0
Fluconazole	0.25	0.5	99.0	0.25	0.5	100.0	≤0.12	0.5	100.0
Ketoconazole	≤0.008	0.016		≤0.008	0.016		≤0.008	0.03	
Itraconazole	0.06	0.12	92.8	0.06	0.12	94.3	0.06	0.12	90.1
Voriconazole	≤0.008	≤0.008		≤0.008	≤0.008		≤0.008	0.016	
Ravuconazole	≤0.008	≤0.008		≤0.008	≤0.008		≤0.008	≤0.008	
C. parapsilosis (122, 55, 65)									
Amphotericin B	1	1		1	1		1	1	
5-FC	0.12	0.5	100.0	0.25	0.5	100.0	0.12	0.25	100.0
Fluconazole	1	2	97.5	1	2	100.0	1	8	100.0
Ketoconazole	0.12	0.25		0.12	0.25		0.12	0.5	
Itraconazole	0.25	0.5	37.7	0.25	0.5	30.9	0.25	0.5	24.6
Voriconazole	0.03	0.12		0.03	0.06		0.03	0.12	
Ravuconazole	0.03	0.12		0.03	0.06		0.03	0.12	
C. glabrata (167, 43, 30)									
Amphotericin B	1	2		1	1		1	2	
5-FC	0.06	0.12	100.0	0.12	0.12	100.0	0.12	0.12	100.0
Fluconazole	8	64	52.1	8	128	53.5	8	64	50.0
Ketoconazole	0.5	2		0.5	2		1	2	
Itraconazole	1	2	0.0	1	2	0.0	1	4	0.0
Voriconazole	0.25	1		0.25	2		0.5	1	
Ravuconazole	0.25	1		0.25	1		0.5	2	
C. tropicalis (59, 34, 59)									
Amphotericin B	1	1		1	1		1	1	
5-FC	0.25	0.5	94.9	0.25	>64	76.5	0.25	0.5	93.2
Fluconazole	1	2	96.6	1	4	97.1	1	2	100.0
Ketoconazole	0.03	0.12		0.03	0.12		0.06	0.12	
Itraconazole	0.25	0.5	39.0	0.25	0.5	29.4	0.25	0.5	27.1
Voriconazole	0.03	0.12		0.06	0.25		0.06	0.12	
Ravuconazole	0.03	0.12		0.03	0.25		0.03	0.12	
C. neoformans[c] (23, 3, 27)									
Amphotericin B	1	1		1			1	1	
5-FC	8	16		8			8	16	
Fluconazole	16	32		8			16	32	
Ketoconazole	0.5	1		0.5			0.5	1	
Itraconazole	0.5	1		0.5			0.5	1	
Voriconazole	0.12	0.5		0.12			0.25	0.25	
Ravuconazole	0.12	0.5		0.12			0.12	0.25	

[a] The breakpoint criteria are those of the NCCLS/CLSI (7); %S, percent susceptible.
[b] 5-FC, 5-fluorocytosine.
[c] Breakpoint criteria have not been established for cryptococcal organisms (7).

prevalence of non-*C. albicans Candida* species, specifically *C. parapsilosis*, *C. glabrata*, and *C. tropicalis*. This trend is also apparent when we review the results from the ARTEMIS Program (12) and is a worrisome development. When we compare the combined results from 1997 to 1999 (11) for all *Candida* spp. to those presented here (Table 2), fluconazole, voriconazole, and ravuconazole all display up to twofold less activity in all regions, and this reflects the inherent resistances (especially to the azole agents) documented with these increasingly more common non-*C. albicans Candida* species. Within each species

TABLE 3. Activities of six antifungal agents to *A. fumigatus* and other *Aspergillus* spp. (SENTRY Program, 2003)

Species (no. of isolates tested) and drug	MIC (μg/ml)			% Inhibited at ≤1 μg/ml[a]
	50%	90%	Range	
A. fumigatus (52)				
Amphotericin B	2	4	1–16	11.5
Fluconazole	256	>256	64–>256	
Ketoconazole	4	8	0.5–8	
Itraconazole	1	2	0.25–2	84.6
Voriconazole	0.5	1	0.12–2	96.2
Ravuconazole	0.5	1	0.12–2	96.2
Other *Aspergillus* spp. (21)				
Amphotericin B	2	4	1–4	9.5
Fluconazole	256	>256	64–>256	
Ketoconazole	2	8	0.5–8	
Itraconazole	1	2	0.5–2	71.4
Voriconazole	0.5	2	0.06–4	81.0
Ravuconazole	1	2	0.25–4	76.2

[a] Breakpoint criteria have not been established by the CLSI; for comparison purposes, a susceptible breakpoint only was used at ≤1 μg/ml (8, 17).

and for all agents tested, changes in potency (MIC_{90} values) between regions were not apparent, except for flucytosine with *C. tropicalis* (>64 μg/ml in Europe versus 0.5 μg/ml in North and Latin America) and with *C. albicans* (2 μg/ml in North and Latin America versus 0.5 μg/ml in Europe).

Importantly, increases in resistance among individual *Candida* species to the triazoles has not been detected in the current surveillance period. The ongoing shift to the non-*C. albicans Candida* species does, however, require further study to better understand the changing epidemiology that is generally attributed to the widespread therapeutic and prophylactic use of fluconazole in immunocompromised patients (12, 21). This shift will require continued assessment of the potency and spectrum of the currently licensed agents, as well as investigational agents, to better characterize their current and future utility, especially after the introduction of novel agents into clinical practice.

As with yeast species, the emergence of invasive *Aspergillus* spp. and other molds as causes of morbidity and mortality emphasizes the importance of performing periodic surveillance among these fungi as well (4, 10). Difficulties in performing antifungal susceptibility testing by clinical laboratories has, however, limited its routine performance. With the recent introduction of standardized methods, greater utilization of testing is now being realized, although categorical interpretive criteria are still lacking (8). Compared to a previous surveillance study from 2000, the *A. fumigatus* isolates studied here were generally less susceptible to amphotericin B (MIC_{90} of 4 μg/ml; two- to fourfold change) and the azoles, voriconazole and ravuconazole (MIC_{90} of 1 μg/ml; twofold higher); the itraconazole MIC_{90} value (2 μg/ml) remained unchanged from that reported in the earlier study (17). The newer triazole agents continue to offer excellent in vitro activity against *Aspergillus* spp. and other less common filamentous fungi; fortunately, cross-resistance between itraconazole and the newer triazoles has not been found to be complete and varies according to the particular tested strain (17).

This report extends in time the available data for antifungal resistance surveillance for these important yeast and mold pathogens. The newer triazoles (e.g., voriconazole and an investigational agent, ravuconazole) displayed the greatest spectrum of activity and potency across all species, regardless of geographic region, although some minor inter-regional differences were observed. These results are congruent with earlier reports (11, 14, 15, 17), demonstrating that the use of currently available antifungals has had little appreciable influence on the prevalence of antifungal resistance. However, the potential for the emergence of yeast and mold species with reduced susceptibilities to currently marketed and investigational compounds warrants continued, prudent monitoring.

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