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Evaluation of the *in vitro* activity of isavuconazole and comparator voriconazole against 2635 contemporary clinical *Candida* and *Aspergillus* isolates

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ABSTRACT

Objective: The *in vitro* activity of isavuconazole was determined for 1677 *Candida* and 958 *Aspergillus* isolates from 2012 to 2014 with voriconazole as comparator.
Methods: Aspergillus isolates were screened for resistance using azole-agar. *Aspergillus* isolates that screened positive and all *Candida* isolates underwent EUCAST broth microdilution testing. Isolates were categorized as wild-type (wt) or non-wt, adopting EUCAST epidemiological cut-off values (ECOFFs) (where available) or wt upper limits (wtULs; two two-fold dilutions above the MIC_{50}). The *CYP51A* gene was sequenced for non-wt *Aspergillus fumigatus* isolates. Itraconazole and posaconazole MICs were determined for selected *Aspergillus* isolates with isavuconazole MIC ≥2 mg/L.
Results: Isavuconazole MIC_{50} (range) (mg/L) against *Candida* species were: *Candida albicans*: ≤0.03 (≤0.03 to >4), *Candida dubliniensis*: ≤0.03 (≤0.03), *Candida glabrata*: ≤0.03 (≤0.03–4), *Candida krusei*: 0.06 (≤0.03–0.5), *Candida parapsilosis*: ≤0.03 (≤0.03–0.06), *Candida tropicalis*: ≤0.03 (≤0.03 to >4), *Saccharomyces cerevisiae* (anamorph: *Candida robusta*): ≤0.03 (≤0.03–0.5). Non-wt isavuconazole/voriconazole MICs were found for *C. albicans*: 0.8/1.0%, *C. dubliniensis*: 0/1.8%, *C. glabrata*: 14.9/9.5%, *C. krusei*: 2.7/1.4%, *C. parapsilosis*: 1.7/1.8%, *C. tropicalis*: 14.3/19.1% and *S. cerevisiae*: 10.0/0%. Isavuconazole MIC_{50} (range) (mg/L) against *Aspergillus* species were: *A. fumigatus*: 1 (≤0.125 to >16), *Aspergillus niger*: 2 (1–8), *Aspergillus terreus*: 1 (0.25–8), *Aspergillus flavus*: 1 (0.5–2), *Aspergillus nidulans*: ≤0.125 (≤0.125–0.25). Non-wt isavuconazole/voriconazole MICs were found for 13.7/15.2% *A. fumigatus*, 4.9/0% *A. niger* and 48.2/22.2% *A. terreus*.
Conclusion: Isavuconazole displayed broad *in vitro* activity, similar to that of voriconazole. Up to 15% of *C. glabrata*, *C. tropicalis* and *A. fumigatus* isolates were non-wt, reflecting increased resistance at a reference centre and technical issues. Significant CYP51A alterations were reliably detected applying the isavuconazole breakpoint. **K.M.T. Astvad, Clin Microbiol Infect 2017;23:882**

Introduction

Isavuconazole is a new triazole compound with broad-spectrum *in vitro* activity against *Aspergillus* species and a range of other medically important yeasts and moulds [1–5]. In 2015 it was licensed for invasive aspergillosis of adults by the EMA [6] and the FDA [7], following the phase III SECURE trial, which demonstrated non-inferiority compared with voriconazole regarding invasive mould infections [8]. The standard first-line treatment for invasive aspergillosis has until now been voriconazole [9,10]. Voriconazole has variable pharmacokinetics and a narrow therapeutic window, and as such, a proportion of patients are either under-dosed or experience adverse effects due to toxic levels [11]. Drug interactions can pose a problem, as can the cyclodextrin content of the intravenous formulation when treating patients who have renal impairment. Isavuconazole provides a welcomed expansion of the available armamentarium against mould infections and offers a

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favourable profile regarding drug interactions, toxicology, pharmacokinetics and with a spectrum at least partially including *Mucorales*.

Isavuconazole has been shown to be efficacious in oesophageal candidiasis [12] and has been investigated in the phase III clinical ACTIVE trial including patients with proven candidaemia or invasive candidiasis. Data evaluation failed to demonstrate non-inferiority compared with caspofungin but did show a similar overall success at the end of treatment, overall mortality and good tolerability (26th European Congress of Clinical Microbiology and Infectious Diseases, abstract 1239). Although these findings support the notion that echinocandins are superior to azoles for the treatment of candidaemia/invasive candidiasis, isavuconazole may remain relevant for selected patients with mixed infections, echinocandin-resistant infections, complicating factors, or for oral step down.

In this study, we investigated the *in vitro* susceptibility to isavuconazole compared with voriconazole against a large contemporary clinical collection of *Aspergillus* and *Candida* isolates received at the Danish mycology reference centre, including azole-resistant isolates. MICs were interpreted using the recently established EUCAST clinical breakpoints and epidemiological cut-off values (ECOFFs).

Materials and methods

Isolates

A total of 958 *Aspergillus* and 1677 *Candida* isolates, from 683 and 1487 patients, respectively, were included. The collections contained all isolates from clinical samples or pure cultures received at the mycology reference laboratory at Statens Serum Institut for identification and susceptibility testing during the calendar years 2012–2014. No ethical restraints apply to studies of routinely obtained anonymized laboratory data. Identification was done using macro- and micromorphology, supplemented by thermo-tolerance (incubation at 37°C and 43°C) and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker, Bremen, Germany) for *Candida* [13] and by thermotolerance (incubation at 50°C) for *Aspergillus fumigatus* complex isolates and β-tubulin sequencing [14] for cryptic *Aspergillus* species. The use of the term 'complex' is acknowledged for *Aspergillus* species other than *A. fumigatus*, in the absence of detailed molecular identification, although for simplicity, it is not used throughout this manuscript.

Susceptibility testing

EUCAST susceptibility testing was performed according to E.Def 7.2 for *Candida* [15]. Voriconazole MIC determination was performed for 1647 of 1677 (98.2%) isolates and isavuconazole MIC determination for all 1677 isolates. For *Aspergillus*, screening for azole resistance was gradually introduced in routine laboratory practice during the collection period, using an azole containing four-well agar (containing itraconazole: 4 mg/L; voriconazole: 1 mg/L; posaconazole: 0.5 mg/l and an antifungal-free control well (Balis Laboratorium V.O.F., Bowen-Leeuwen, the Netherlands)) [14]. In brief, 25 μL of a McFarland 0.5 conidial suspension was added to each well and incubated for 48 hours before reading. Hence, EUCAST susceptibility testing [15] was performed for 306 of 958 *Aspergillus* isolates (227 patients) that grew on at least one of the azole agars, or were non-*A. fumigatus* isolates. For EUCAST susceptibility testing, stock solutions (5000 mg/L in dimethyl sulphoxide; Sigma-Aldrich, Brøndby, Denmark) of itraconazole (Sigma-Aldrich), voriconazole (Pfizer, Ballerup, Denmark), posaconazole (MSD, Ballerup, Denmark) and isavuconazole (Basilea Pharmaceutica Ltd., Basel, Switzerland) were prepared. Final drug concentration ranges for isavuconazole and voriconazole were 0.03–4 mg/L for *Candida* spp. and 0.125–16 mg/L for *Aspergillus* spp., respectively. MICs were determined spectrophotometrically at 24 hours as the lowest concentration giving a 50% growth reduction compared with an antifungal free control (*Candida*), or visually applying a no-growth endpoint after 48 hours of incubation (*Aspergillus*), as recommended. EUCAST control strains *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019 were routinely included and read after 24 hours [15]. Except for non-wild-type *A. fumigatus* isolates, only isavuconazole and voriconazole MICs are presented in this report. For interpretation of susceptibility, the following EUCAST clinical breakpoints were used for *A. fumigatus*: isavuconazole MIC $\leq$1 mg/L (susceptible) and >1 mg/L (resistant); and voriconazole MIC $\leq$1 mg/L (susceptible) and >2 mg/L (resistant).

ECOFF/wild-type definitions

Isolates were categorized as wild-type (wt) or non-wild-type (non-wt) adopting the EUCAST ECOFFs. These have been defined for *A. fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus* and *Aspergillus nidulans* (voriconazole and isavuconazole) [16,17] and for *Candida albicans*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis* and *Candida tropicalis* (voriconazole) [18]. For yeast species without a defined EUCAST ECOFF, a wild-type upper limit (wtUL) was determined as two two-fold dilution steps above the MIC_{50} (MIC_{50} value is the lowest concentration of the antifungal at which 50% of the isolates were inhibited) with the exception of species for which the entire population of MICs were less than or equal to the lowest concentration tested. In such cases, the lowest concentration tested was chosen as the wtUL [19].

The MIC_{50}, MIC distribution range and number of isolates with MICs above the ECOFF/wtUL were determined and compared by species and antifungal compound.

PCR amplification and sequence analysis of the CYP51A gene

Isolates of *A. fumigatus* classified as non-susceptible or non-wt to itraconazole, posaconazole, isavuconazole or voriconazole were *CYP51A* sequenced as part of the routine procedures (as previously described [20]), except for one azole-resistant isolate from 2012, which was not available for *CYP51A* sequencing. Additionally, a few azole-susceptible isolates were sequenced as controls, or if the patient had previously harboured an azole-resistant *A. fumigatus*. In total, 57 *A. fumigatus* isolates were *CYP51A* sequenced, 45 of which had elevated MICs towards isavuconazole or voriconazole.

Nine *A. terreus* isolates were obtained from one patient with cystic fibrosis known since 2007 to repeatedly harbour isolates with an M217I alteration [21]. Eight of these isolates (one wt and seven resistant) were *CYP51A* sequenced as previously described [21].

Results

Isolates and MIC distributions

The normally azole-susceptible *Candida* species had very low and comparable MIC distributions for both compounds (Table 1 and Fig. 1). The following species-specific wtULs for isavuconazole MIC distributions were determined: *C. albicans*, *C. dubliniensis*, *C. parapsilosis* and *C. tropicalis*: 0.03 mg/L; *C. glabrata* and *Saccharomyces cerevisiae*: 0.125 mg/L, and *C. krusei:* 0.25 mg/L. For *C. glabrata*, *C. krusei*, *S. cerevisiae* and other *Candida* spp., for which the MIC distributions were not truncated, the isavuconazole MIC_{50}

Table 1
Total numbers and MIC distributions for *Candida* species

ID	Isolates tested	Isavuconazole MIC (mg/L)				Voriconazole (mg/L)				
	(ISA/VRZ)	MIC range	MIC_{50}	wtUL	MIC > wtUL (%)	MIC range	MIC_{50}	ECOFF	wtUL	MIC > ECOFF (%)
C. albicans	833/821	≤0.03–>4	≤0.03	0.03	0.8	≤0.03–>4	≤0.03	0.125	0.03	1.0
C. dubliniensis	56/56	≤0.03	≤0.03	0.03	0	≤0.03–0.25	≤0.03	0.125	0.03	1.8
C. glabrata	497/487	≤0.03–4	≤0.03	0.125	14.9	≤0.03–4	0.06	1	0.25	9.5
C. krusei	74/73	≤0.03–0.5	0.06	0.25	2.7	0.125–2	0.25	1	1	1.4
C. parapsilosis	59/56	≤0.03–0.06	≤0.03	0.03	1.7	≤0.03–2	≤0.03	0.125	0.03	1.8
C. tropicalis	70/68	≤0.03–>4	≤0.03	0.03	14.3	≤0.03–>4	≤0.03	0.125	0.03	19.1
S. cerevisiae	20/20	≤0.03–0.5	≤0.03	0.125	10	0.06–0.5	0.125	NA	0.5	0[b]
Other *Candida* spp.[a]	68/66	≤0.03–>4	≤0.03	0.125	11.8	≤0.03–>4	0.06	NA	0.25	15.2[b]

Abbreviations: NA, not available; MIC_{50}, the MIC value inhibiting the growth of ≥50% of isolates; wtUL, defined as a two-dilution step above the MIC_{50} (unless all isolates are at the truncated lower border of the MIC distribution in which case this MIC value is chosen); ISA, isavuconazole; VRZ, voriconazole.

[a] *Candida* species (isavuconazole/voriconazole (if different) MICs): *lusitaniae* (18/17), *kefyr* (13/12), *fermentati* (11), *guilliermondii* (6), *inconspicua* (5), *pelliculosa*, *nivariensis*, *norvegensis*, *magnoliae* (two each), *blankii*, *metapsilosis*, *orthopsilosis*, *palmioleophila*, *pararugosa*, *sphaerica*, *utilis* (one each).

[b] wtUL used instead of the ECOFF as no ECOFF has been determined for these species.

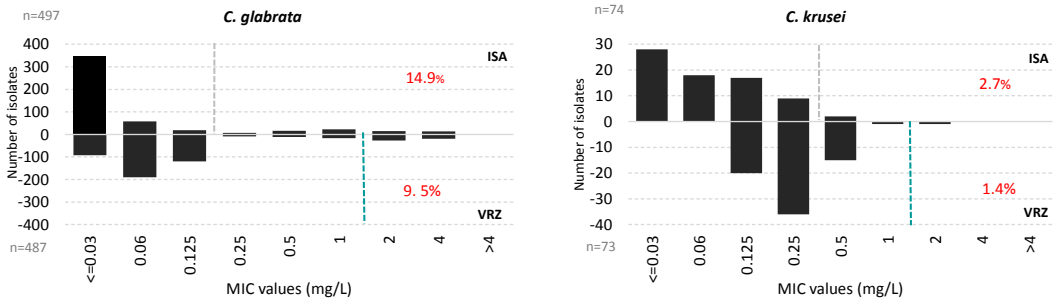

Fig. 1. MIC distributions for selected *Candida* species.

and wtULs were one or two dilution steps lower than those for voriconazole. The percentage of non-wt isolates for the two compounds (isavuconazole/voriconazole) was as follow: *C. albicans* (0.8/1.0), *C. dubliniensis* (0/1.8), *C. glabrata* (14.9/9.5), *C. krusei* (2.7/1.4), *C. parapsilosis* (1.7/1.8), *C. tropicalis* (14.3/19.1) and *S. cerevisiae* (10.0/0). For voriconazole, the species-specific wtULs defined in this study were at least two dilution steps lower than the EUCAST ECOFFs for all species, with the exception of *C. krusei* (Table 1).

For the 306 (32%) *Aspergillus* isolates that underwent EUCAST susceptibility testing due to a non-*fumigatus Aspergillus* species identification or growth at the screening agar, the species-specific MIC_{50} values for isavuconazole and voriconazole were again within one two-fold dilution step of each other (Table 2). Hence, the isavuconazole MIC distributions were approximately one dilution step higher for *A. fumigatus* and *A. niger* (including *A. tubingensis*) compared with those for voriconazole and one dilution step lower for *A. nidulans*. The percentage of MICs above the ECOFFs for the two compounds (isavuconazole/voriconazole) were as follows: *A. fumigatus* (13.7/15.2); *A. niger* (4.9/0); *A. terreus* (48.2/22.2; but 27.8/0 if excluding all isolates from a patient with the previously detected M217I alteration); *A. flavus* (0/0) and *A. nidulans* (0/0) (Fig. 2). Applying the clinical breakpoints for the 26.3% of *A. fumigatus* isolates that underwent EUCAST susceptibility testing, the susceptibility profiles were as follows: isavuconazole: 78.2% (susceptible; S)/21.8% (resistant; R), voriconazole: 84.8% (S)/6.intermediate; 6% (I)/8.5% (R); overall, 24.2% were found to be non-susceptible to at least one mould-active azole. The overall isavuconazole and voriconazole non-susceptibility rates among *A. fumigatus* (when including the 592 isolates found susceptible using the azole agar screenings test) were 5.7% ($n = 46$) and 4.0%

Table 2
Total numbers and MIC distributions for *Aspergillus* species

	n (%)	Isavuconazole MIC (mg/L)				Voriconazole (mg/L)			
		MIC range	MIC_{50}	ECOFF	MIC > ECOFF (%)	MIC range	MIC_{50}	ECOFF	MIC > ECOFF (%)
A. fumigatus sensu stricto	211 (69.0)	≤0.125–>16	1	2	13.7	≤0.125–>16	0.5	1	15.2
A. niger species complex[a]	41 (13.4)	1–8	2	4	4.9	0.25–2	1	2	0
A. terreus species complex	27 (8.8)	0.25–8	1	1	48.2/27.8[b]	0.25–8	1	2	22.2/0[b]
A. flavus species complex	19 (6.2)	0.5–2	1	2	0	0.5–2	1	2	0
A. nidulans species complex[c]	5 (1.6)	≤0.125–0.25	≤0.125	0.25	0	0.25–0.5	0.25	1	0
A. calidostus	1 (0.3)	4	NA	NA	NA	>16	NA	NA	NA
A. quadrilineatus	1 (0.3)	≤0.125	NA	NA	NA	≤0.125	NA	NA	NA
A. tamarii	1 (0.3)	0.25	NA	NA	NA	1	NA	NA	NA

Abbreviations: NA, not available; MIC_{50}, the MIC value inhibiting the growth of ≥50% of isolates.

Species distribution (isolates submitted to either azole screening or EUCAST susceptibility testing): *A. fumigatus* (803), *A. niger* (60), *A. terreus* (41), *A. flavus* (35), *A. nidulans* (6), *A. nidulans var. echinulatus* (4), *A. tubingensis* (2), *A. sydowii* (2), *A. calidoustus* (1), *A. ochraceus* (1), *A. tamarii* (1), *A. versicolor* (1), and *A. quadrilineatus* (1).

[a] Including the two isolates of *A. tubingensis*.

[b] When excluding isolates from a cystic fibrosis patient with a known M217I alteration.

[c] Including three isolates of *A. nidulans var. echinulatus*.

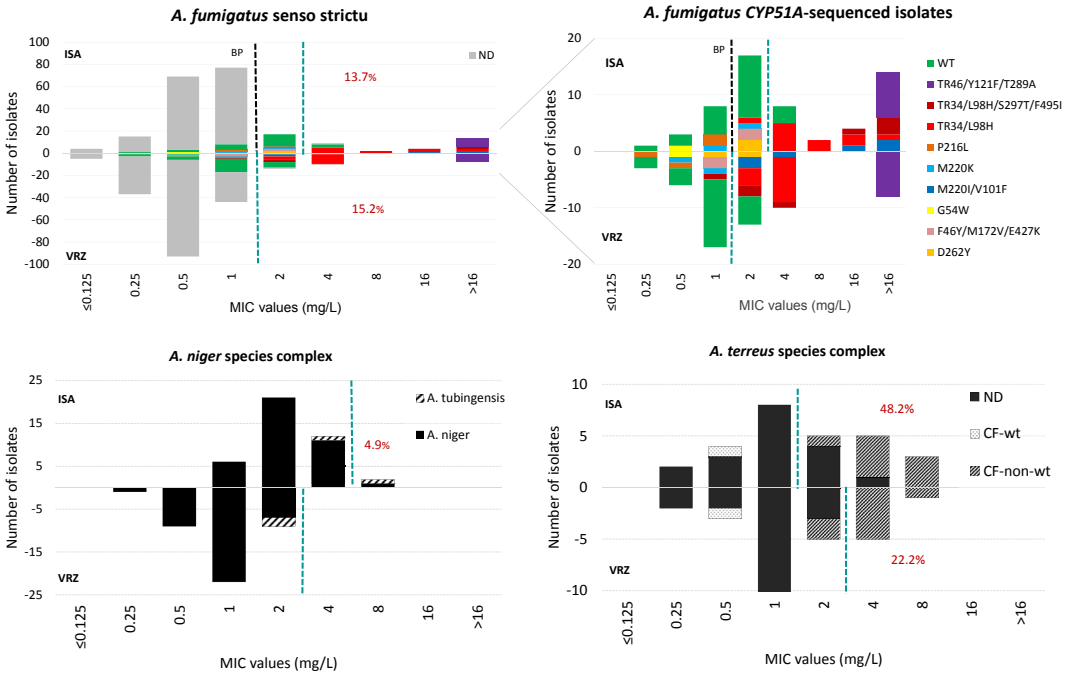

Fig. 2. MIC distributions for selected *Aspergillus* species and *Aspergillus fumigatus CYP51A* genotypes.

($n = 32$), respectively; 6.4% ($n = 51$) exhibited resistance to at least one mould-active azole. The detailed triazole MIC and *CYP51A* profile for the individual *A. fumigatus* and *A. terreus* isolates with an MIC of 2 mg/L are available in the Supplementary material (Tables S1 and S2).

CYP51A sequencing

Thirty-two isolates of *A. fumigatus* isolates with non-wt MIC values towards voriconazole ($n = 31$) or isavuconazole ($n = 28$) were sequenced (Fig. 2). Isolates with an isavuconazole MIC value of ≥4 mg/L also had elevated MIC values for voriconazole and/or at least one other triazole. In 25 of these isolates (89.3%), *CYP51A* mutations known to confer pan-azole resistance were found (M220I + V101F ($n = 3$), TR_{34}/L98H ($n = 10$), TR_{34}/L98H/S297T/F495I ($n = 4$), and TR_{46}/Y121F/T289A ($n = 8$)) (Fig. 2).

Seventeen isolates had an isavuconazole MIC of 2 mg/L (8.1% of EUCAST susceptibility tested and 2.1% of all *A. fumigatus* isolates). Five of these (29.4%) also had an elevated MIC value towards one of the other triazoles (see Supplementary material, Table S1). Overall, six of the 17 isolates (35.3%) harboured a *CYP51A* mutation (M220K ($n = 1$), D262Y ($n = 2$), F46Y/M172V/E427K ($n = 2$) and TR_{34}/L98H ($n = 1$)). Five isolates with MICs of voriconazole and isavuconazole ≤1 mg/L were sequenced due to elevated MICs for posaconazole and itraconazole, four of which harboured G54W ($n = 1$), P216L ($n = 2$) or M220K ($n = 1$) alterations.

A high number of non-wt *A. terreus* isolates (≈50% for isavuconazole) were found (Fig. 2). One patient with cystic fibrosis contributed with eight resistant isolates and one phenotypically azole-susceptible isolate; all sequenced resistant isolates had the M217I alteration, synonymous with the M220I alteration in *A. fumigatus*. The phenotypically pan-azole susceptible isolate harboured an Y491H alteration. In *A. fumigatus*, this alteration has been associated with elevated itraconazole MICs [22] but its significance in *A. terreus* is unknown. The eight resistant isolates from this patient were all identified as non-wt applying the isavuconazole ECOFF, whereas six were non-wt applying the voriconazole EUCAST ECOFF (see Supplementary material, Table S2).

Discussion

Overall, the *in vitro* activities of isavuconazole and voriconazole against *Candida* and *Aspergillus* isolates were comparable and consistent with previously published EUCAST [2] and CLSI [1,5,23,24] MICs. However, for *C. krusei* and *C. glabrata* our wt distributions were two to three dilution steps lower than those reported by CLSI, which may reflect the inter-laboratory variability previously associated with MIC testing of these species (*C. glabrata* especially [2]).

Elevated MICs were not uncommon. Indeed, up to 15% of *C. glabrata* and *C. tropicalis* displayed non-wt MICs for isavuconazole, whereas this was the case for 5.7% of all included *A. fumigatus* isolates. Reports of azole resistance rates in *A. fumigatus* vary. In an international surveillance study from 2009 to 2011 the prevalence in Denmark was 3.3% and equal to the overall average [25]. A subsequent retrospective laboratory-based documented an increase in azole resistance from 1.4% to 6% in clinical samples in the time period 2010–2014, suggesting that the resistance rate in Denmark may be increasing [26].

The proportion of isolates with an isavuconazole MIC of 2 mg/L (categorized as resistant but still within the wt MIC range) was comparable to the proportion reported from a recent multicentre study (~8%; 34/401 isolates), but higher than in the data set used for setting the EUCAST ECOFFS (3%) [2,17]. This may reflect the selected proportion of isolates undergoing EUCAST susceptibility testing after azole agar screening (for which a higher proportion of resistance is expected) and the fact that isolates received at a reference laboratory constitute a selected subset of isolates that may not be fully representative for the national epidemiology.

All *A. fumigatus* isolates with *CYP51A* mutations consistently known to confer voriconazole or pan-azole resistance were classified as resistant applying the isavuconazole breakpoint. One M220K alteration resulted in discreet MIC elevations (isavuconazole MIC of 2 mg/L), but whether this is clinically relevant is unclear. However, one TR_{34}/L98H was found within the wt MIC range (isavuconazole MIC of 2 mg/L). In comparison, one TR_{34}/L98H/S297T/F495I was classified as voriconazole susceptible, illustrating

that perfect discrimination of susceptible and mutant isolates is challenging to achieve due to the overlapping MIC distributions for wt and mutant isolates for both compounds.

For *A. terreus*, we found a high proportion of non-wt isolates for both drugs and notably higher (27.8%) for isavuconazole compared with voriconazole (0%), even after excluding a patient known to harbour isolates with an M217I alteration. These differences are most likely not reflecting efficacy differences between the two compounds, but rather technical issues related to MIC testing and categorization, as the MIC distributions were symmetric with an MIC_{50} of 1 mg/L and produced an almost identical categorization if an isavuconazole ECOFF of 2 mg/L was applied.

Two *A. niger* complex isolates (4.9%) were non-wt for isavuconazole, one of which belonged to the intrinsically less susceptible cryptic species *A. tubingensis*. This is in line with a previous report and within the percentage of wild-type isolates expected to be above the ECOFF [2,27].

Technical challenges regarding MIC endpoint reading were encountered. For *C. tropicalis*, we found a tail of high MIC values for both compounds, primarily consisting of isolates with trailing phenotype, i.e. with residual growth over a broad range of MIC values. Whether such isolates are truly resistant is still unresolved and the phenomenon implies a risk of variation in MIC and random susceptibility classification. Moreover, the growth curves for *C. krusei* were less steep for isavuconazole around the 50% growth inhibition target, resulting in less reproducible MIC determination (and less well-defined normal distributions for isavuconazole than for voriconazole). This may, at least in part, explain the higher degree of inter-laboratory variation previously observed for this species [2]. Finally, the MIC distributions for the two compounds against *A. terreus* mirrored one another with a modal MIC of 1 mg/L. In contrast, the modal MIC from the data set used to set EUCAST ECOFFs for isavuconazole was 0.5 mg/L and CLSI modal MICs are reported to be 0.25–0.5 mg/L [1,23]. These discrepancies (± one dilution) are all within the expected variation for susceptibility testing, yet lead to interpretative disagreement when a restrictive endpoint is adopted. Of note, inter-laboratory discrepancies in MIC testing of *A. terreus* in particular have previously been reported, but the underlying mechanism remain unclear [2].

Our study has limitations. For *Candida* species, the truncation of the MIC distribution interfered with definitive MIC and wtUL determination, particularly for the normally azole-susceptible species. The discrepancy between wtULs for isavuconazole and voriconazole ECOFFs did result in some non-wt classification differences. For *C. glabrata*, the difference is most likely artificial and due to our strict definition of an wtUL, in combination with a truncated MIC interval. If we applied our strict definition of an wtUL on voriconazole, 15% of isolates would be non-wt for both compounds, suggesting comparable activity of the two.

One concern could be that we may have overlooked resistant *A. fumigatus* isolates, as confirmatory EUCAST AFST was only performed for isolates that grew on the screening agar (in which isavuconazole is not incorporated). We have EUCAST susceptibility tested one-quarter of all *A. fumigatus* isolates as they were originally screening positive, but only confirmed resistance in under one-quarter. Moreover, a recent multicentre study confirmed a specificity of 95%–100% (27th European Congress of Clinical Microbiology and Infectious Diseases, abstract P1750). On this background, we find it unlikely that the isavuconazole resistance rate was underestimated despite not performing EUCAST microdilution testing on all isolates. However, as isavuconazole was not licensed in our country in the years of isolate collection, it remains to be seen if isavuconazole mono-resistance mutations may occur once the compound is in clinical use.

In conclusion, the *in vitro* activity of voriconazole and isavuconazole is similar, with observed differences in *Candida* species being primarily due to methodological issues. This suggests that isavuconazole will be a promising new alternative in most cases where voriconazole is indicated, particularly in patients with invasive aspergillosis, and that susceptibility testing is important for clinical management.

Transparency declaration

This study was supported by an unrestricted grant from Basilea. Some of these data were presented at the 26th ECCMID 2016 in Amsterdam, the Netherlands, 9–12 April 2016 (#O227). Outside this study, the authors declare the following potential conflicts of interest: MCA has received research grants or speaker honoraria from Amplyx, Astellas, Basilea, Cidara, F2G, Gilead, MSD, Novartis, Pfizer and T2Biosystems. She is the current chairman for the EUCAST-AFST and before this served on advisory boards for MSD (until 2014), and Pfizer (until 2012). KMTA has received travel grants from Pfizer and Gilead. RKH has received research grant from Gilead and travel grants from Astellas, MSD and Pfizer.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2017.03.023.

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