

# EUCAST Susceptibility Testing of F901318: MIC Data for Contemporary Clinical Mould Isolates



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## Objectives

The new antifungal F901318 is an orotomide with potent activity against various moulds. Here, we performed EUCAST AFST on moulds received for identification and susceptibility determination at the national reference mycology laboratory to generate contemporary MIC data for this compound and for future ECOFF and clinical breakpoint setting.

## Material & methods

The MICs of F901318 and four comparator antimycotics against 273-278 clinical mould isolates from 217 patients were determined generating 1380 MICs in total. Methods in brief:

1. EUCAST E.Def 9.3.1 using cell-culture treated Nunc plates
2. Plates stored at -80 °C for ≥24 h prior to inoculation
3. Antimycotics and concentration ranges used: F901318; 1-0.002 mg/L and 0.5-0.0005 mg/L, amphotericin B and posaconazole; 4-0.004 mg/L, itraconazole and voriconazole; 16-0.016 mg/L
4. Full inhibition MICs determined visually by two observers

Single centre ECOFF was determined using the EUCAST ECOFF finder programme adopting 97.5% as threshold.

## Results

### Isolates

Over an 18-month period, 278 clinical mould isolates were tested. Of these, 255 were *Aspergillus* including 216 *A. fumigatus*. Three were dermatophytes, 10 were Mucorales and 10 were various other moulds. Among the *A. fumigatus* isolates, 21 (9.7%) were non-wild type to at least one azole.

### *Aspergillus*

F901318 displayed overall uniform activity across all *Aspergillus* isolates (EUCAST MIC<sub>50</sub>=0.06 mg/L, range ≤0.004 - >0.5 mg/L). This was also the case for *A. fumigatus* independent of whether the isolates were wild type (MIC<sub>50</sub>=0.06 mg/L, range <0.004-0.5 mg/L) or non-wild type (MIC<sub>50</sub>=0.06 mg/L, range 0.004->0.5 mg/L) for azoles (Table). The statistical single-centre ECOFF for *A. fumigatus* was 0.25 mg/L.

### Dermatophytes and other moulds

The MICs were low against the *M. canis*, *T. rubrum* and *T. interdigitale* isolates (0.03, 0.03 and 0.06 mg/L, respectively) and 0.5 mg/L for *A. pinkertoniae*.

MICs against the other moulds were all above 0.5 mg/L. However, although not meeting the full inhibition endpoint in the drug concentrations tested, F901318 showed *in vitro* activity against *F. solani* with approx. 50% growth inhibition at ~1 mg/L and against *F. dimerum* at ~0.06 mg/L (Fig 4). In contrast, no inhibition was observed against the remaining moulds in the 0.002-0.5 mg/L concentration range, including Mucorales for which the drug target is known to be absent.

## Conclusion

F901318 displayed uniform and potent activity with a single-centre ECOFF of 0.25 mg/L against all tested *Aspergillus* isolates including those resistant to azoles. This is promising as no other oral options are available for such isolates. Moreover, F901318 was active against the three dermatophytes suggesting further investigation this of activity is warranted. Although full growth inhibition was not achieved against the *Fusarium* isolates in the concentration range included here, partial growth inhibition was observed, the clinical implication of which remains to be investigated.

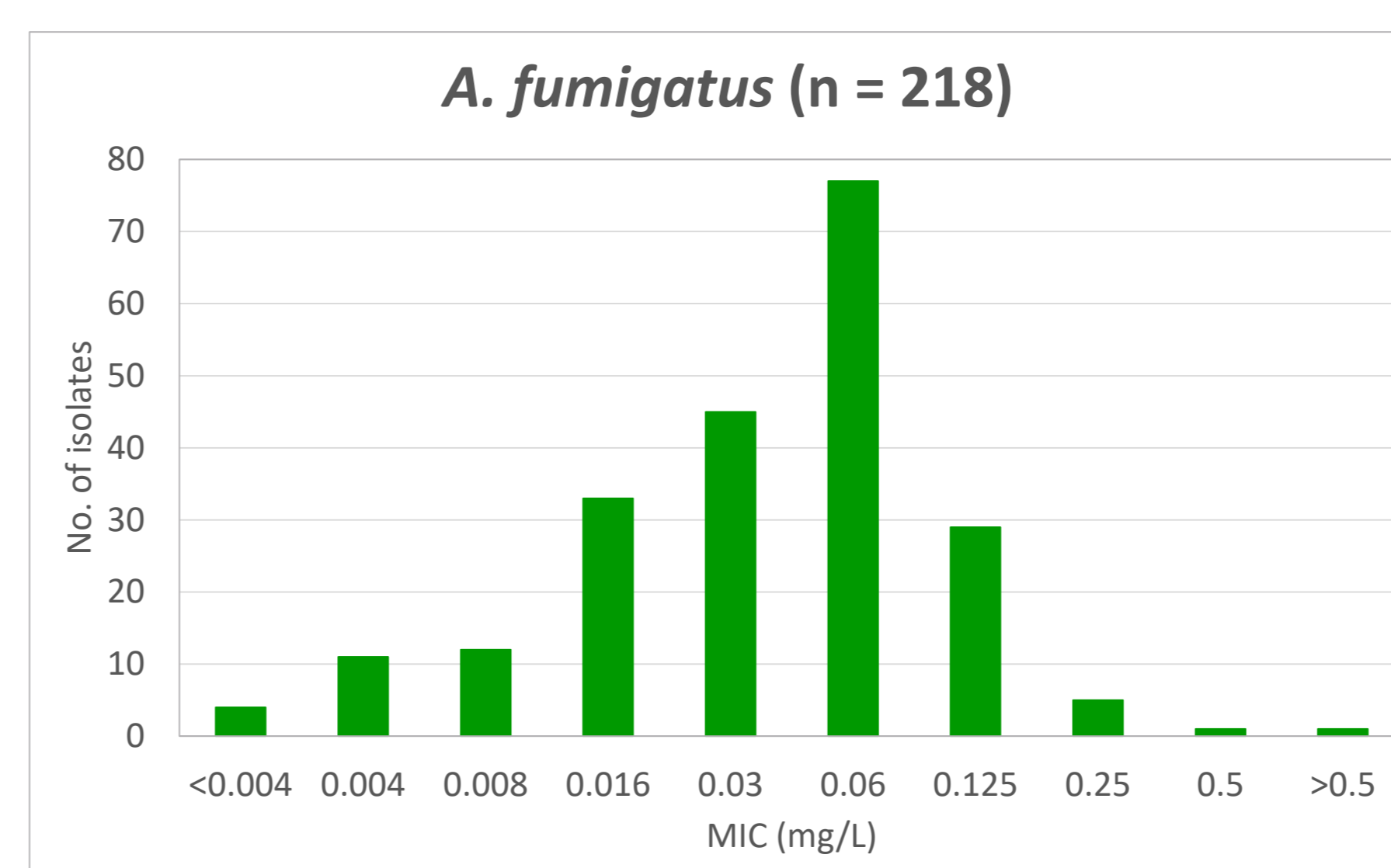


Fig. 1. MIC-distribution of F901318 for the 216 tested *A. fumigatus* isolates.

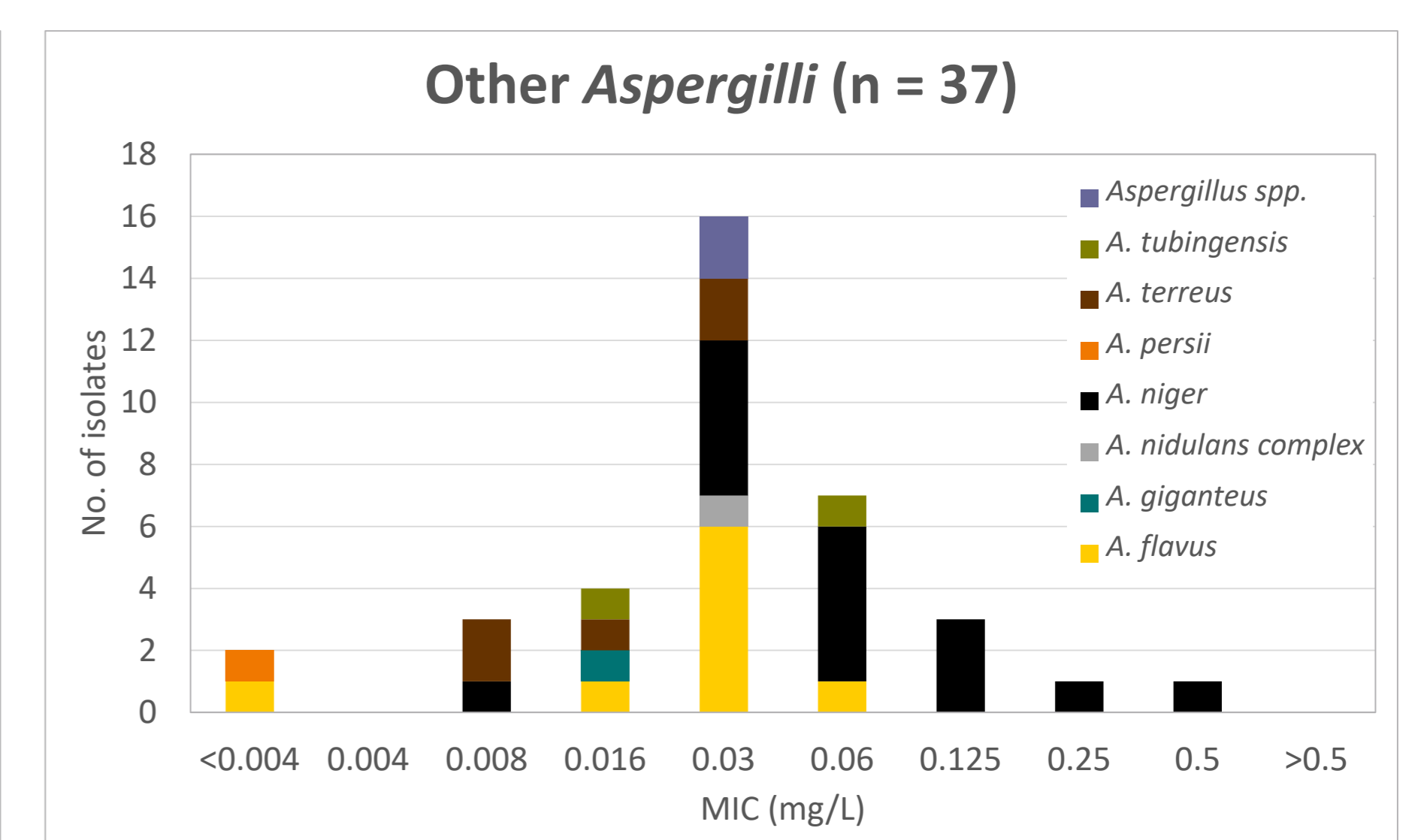


Fig. 2. MIC-distribution of F901318 for the 39 other *Aspergilli* tested.

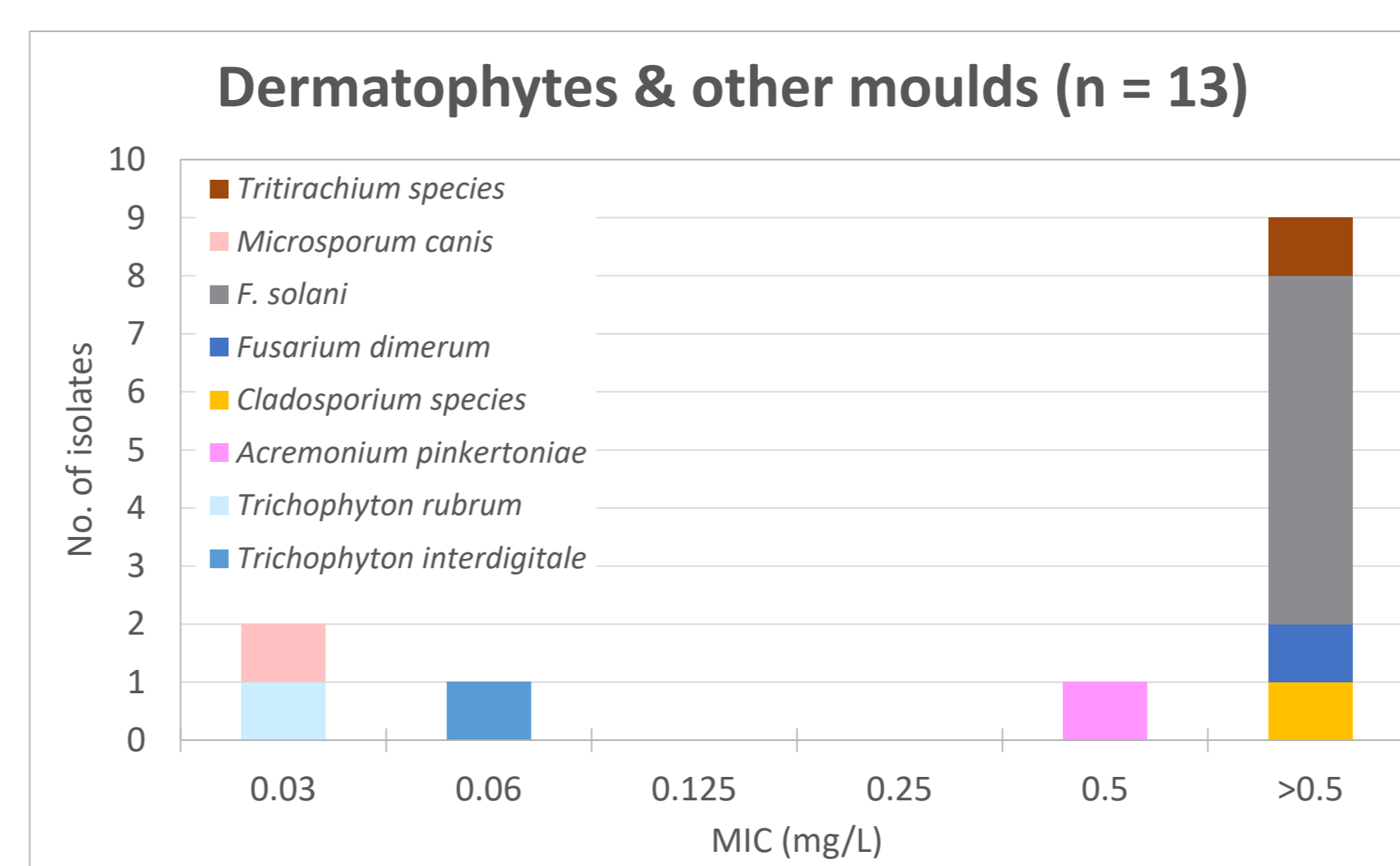


Fig. 3. MIC-distribution of F901318 for the tested non-*Aspergillus* and non-*Mucorales* mould isolates.

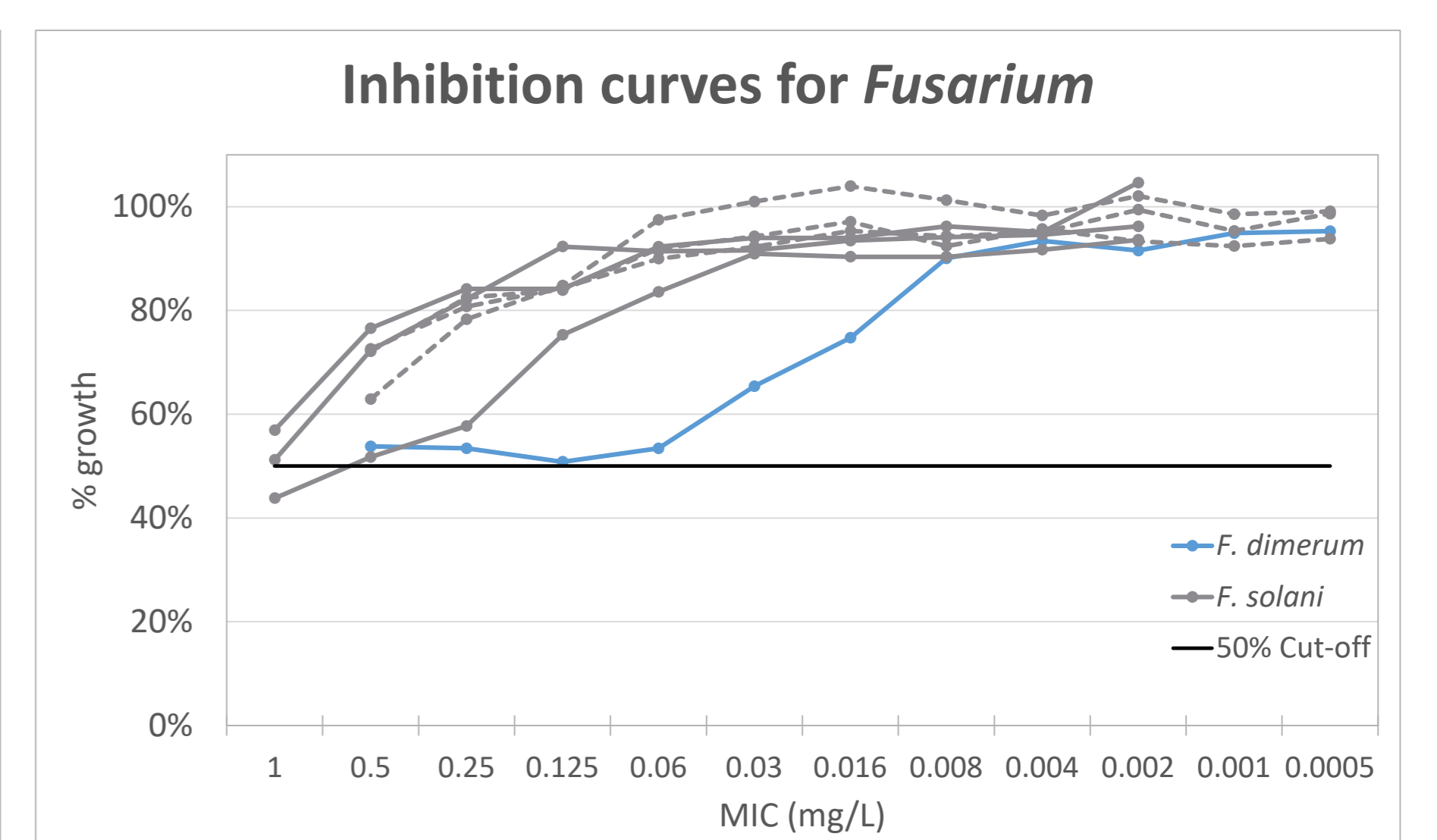


Fig. 4. Inhibition growth curves for the *F. dimerum* isolate (blue) and the *F. solani* isolates (grey) under exposure to F901318. Stipled lines: *F. solani* isolates from the same patient.

Table. F901318 MIC<sub>50</sub>/MIC<sub>90</sub> and ranges for the *Aspergillus* species tested. For *A. fumigatus*, % sensitivity and ranges are given.

	No.	MIC <sub>50</sub> /MIC <sub>90</sub> (mg/L) or % sensitive and (range) (mg/L)				
		F901318	Amphotericin B	Itraconazole	Posaconazole	Voriconazole
<b><i>Aspergillus</i> all</b>	255*	0.06/0.125 (<0.004 - >0.5)				
<i>A. flavus</i>	9	0.03/0.06 (<0.004 - 0.06)	1/4 (1-4)	0.125/0.5 (0.125 - 0.5)	0.06/0.125 (0.06 - 0.125)	0.5/1 (0.5 - 1)
<i>A. fumigatus</i> all	218	0.06/0.125 (<0.004 - >0.5)	0.5/0.5 (0.125 - 1)	91.3 % sensitive (<0.125 - >16)	90.8 % sensitive (<0.06 - >4)	95.0 % sensitive (0.25 - 16)
Azole WT	196	0.06/0.125 (<0.004 - 0.5)	0.5/0.5 (0.125 - 1)	100 % sensitive (<0.125 - 1)	100 % sensitive (<0.06 - 0.125)	100 % sensitive (0.25 - 1)
Azole non-WT	22	0.06/0.125 (0.004 - >0.5)	0.5/1 (0.25 - 1)	>16/>16 (0.5 - >16)	0.5/>4 (0.06 - >4)	1/8 (0.25 - 16)
<i>A. giganteus</i>	1	-/ (0.016)	-/ (0.125)	-/ (0.5)	-/ (0.125)	-/ (1)
<i>A. nidulans</i> complex	1	-/ (0.03)	-/ (0.5)	-/ (0.125)	-/ (0.06)	-/ (0.25)
<i>A. niger</i>	16*	0.06/0.25 (0.008 - 0.5)	0.25/0.5 (0.125 - 4)	1/>16 (0.5 - >16)	0.25/0.5 (0.125 - 0.5)	2/4 (0.5 - 8)
<i>A. persii</i>	1	-/ (<0.004)	-/ (>4)	-/ (2)	-/ (0.5)	-/ (1)
<i>A. terreus</i>	5	0.016/0.03 (0.008 - 0.03)	1/4 (1 - 4)	0.125/0.5 (<0.125 - 0.5)	0.06/0.25 (<0.06 - 0.25)	1/1 (0.5 - 1)
<i>A. tubingensis</i>	2	0.016/0.06 (0.016 - 0.06)	0.125/0.125 (0.125)	>16/>16 (>16)	0.25/0.5 (0.25 - 0.5)	2/2 (2)
<i>Aspergillus</i> spp.	2	0.03/0.03 (0.03)	0.5/4 (0.5 - 4)	0.125/0.25 (0.125 - 0.25)	0.125/0.25 (0.125 - 0.25)	1/1 (1)

\* 16 *A. niger* isolates for F901318, AMB and itraconazole and 11 isolates for posaconazole and voriconazole.