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EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTIN

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ECOFFs:

Methods for Their Estimation

Definition

- An epidemiological cutoff value is the MIC (or other similar quantitative measure of bug-drug interaction) that has the highest probability of distinguishing the wild-type population from the non-wild-type population

Basic Assumptions

- ECOFFs are a feature of a single species
  - they cannot be applied or extrapolated to a genus or other larger grouping
- ECOFFs are “the same everywhere”
  - they do not change over time or vary geographically

Data Requirements

- The MICs must have been measured with a reference method
  - ISO 20776-1 in the case of bacteria
  - ISO 16256 in the case of yeasts
  - Other reference methods as they are developed and agreed upon internationally

Data Requirements

- All the MICs should, as far as is feasible, be on-scale
  - a small proportion of wild-type population values could be included as "≤"
    - ideally it should be <5%, although it is possible to provide a reasonable estimate of ECOFFs if the mode is not also the lowest concentration tested
  - ">" and "≥" values are acceptable in the data set provided they are clearly separated from the wild-type population

Data Pooling

- Because there is known variation between laboratories, as well as within laboratories, data from several laboratories are required for estimation of ECOFFs to ensure variation is accounted for
- The predictive power of ECOFFs increases as the number of laboratories increases
  - a working rule at the present is a minimum of 3 labs preferably with at least 35 presumptive wild-type values although a total of ≥100 overall is usually satisfactory

Issues with Pooling

CRNEO	Amphotericin B										
MIC	Log_2MIC	Gua	Cue	Os	An	Ful	Ann	Ter	Br	Mi	Con
0.0009765625	-10										
0.001953125	-9										
0.00390625	-8										
0.0078125	-7										
0.015625	-6										
0.03125	-5		2				1	1			
0.0625	-4		22				2	2	31		9
0.125	-3		59	2	6		34	4	25	2	25
0.25	-2	2	83	12	102	9	176	31	222	21	10
0.5	-1	7	21	10	97	50	84	41	300	267	
1	0	3	17		53	45	14	5	43	438	
2	1		1		9	4	2		2	13	
4	2		1							2	
8	3										
16	4										
32	5										
64	6										
128	7										
256	8										
512	9										
	Total	12	206	24	267	108	313	84	623	743	44
	Log_2 Mean	-1.4167	-2.7282	-2.1667	-1.6610	-1.0926	-2.2540	-2.0238	-2.0104	-0.9011	-3.4773
	Log_2 SD	0.6686	1.1440	0.6370	0.8844	0.6976	0.7805	0.8709	0.8873	0.6038	0.6643
	Log_2 Mode	-1	-2	-2	-2	-1	-2	-1	-1	0	-3
	Log_2 Median	-1	-2	-2	-1	-1	-2	-1	-1	0	-3
	Group	Non	Non	Non	Non	Non	Non	Non	Non	Non	Non

Issues with Pooling

CRNEO	Amphotericin B										
MIC	Log_2MIC	Gua	Cue	Os	An	Ful	Ann	Ter	Br	Mi	Con
	t-test p=	0.3302	0.0000	0.0315	0.4667	0.0000	0.0000	0.0062	0.0000	0.0000	0.0000
Comp Gp	`	2412	2218	2400	2157	2316	2111	2340	1801	1681	2380
	Mean	-1.2106	-1.1145	-1.2046	-1.2151	-1.2379	-1.1284	-1.1979	-1.1049	-1.5663	-1.1765
	SD	1.0407	0.9767	1.0416	1.0569	1.0437	1.0486	1.0432	1.0675	0.9901	1.0164
	t-test p=	0.4933	0.0000	0.0000	0.0000	0.1523	0.0000	0.0000	0.0000	0.0000	0.0000
	ECV 95.0		0.5		1	1	0.5		1	1	
	ECV 97.5		1		1	2	0.5		1	2	
	ECV 99.0		1		2	2	1		1	2	
	ECV 99.9		2		2	2	1		2	2	
	% 95.0		9.2		3.4	3.7	5.1		0.3	2	
	% 97.5		1.0		3.4	0	5.1		0.3	0.3	
	% 99.0		1.0		0	0	0.6		0.3	0.3	
	% 99.9		0.5		0	0	0.6		0	0.3	
	Mean est		-2.8		-1.75	-1.08	-2.32		-1.93	-0.87	
	SD Est		0.991		0.835	0.652	0.586		0.719	0.461	

Estimation Methods

- The “eyeball” method (Kahlmeter)
- The 95% rule (Pfaller)
- The Normalised Resistance Interpretation (Kronvall)
- The iterative statistical method (Turnidge)
- Multimodal analysis (Meletiadis)
- Cluster analysis (Cantón)

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The "Eyeball" Method

Antimicrobial wild type distributions of microorganisms

Search

Method: (•) MIC ( ) Disk diffusion

Antimicrobial: Ampicillin Species: Species... Disk content: Disk

Antimicrobial: Ampicillin **(Method:** MIC)

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	S≤	R>	ECOFF≤
Acinetobacter baumannii	0	0	0	0	1	0	0	1	2	14	18	62	244	673	2720	111	3	35	1	ND	ND	ND
Acinetobacter lwoffii	0	0	0	0	0	0	4	6	13	32	62	44	42	32	118	0	0	0	0	ND	ND	ND
Acinetobacter spp	0	0	0	0	0	0	7	7	25	48	96	112	188	515	3224	1	1	0	0	ND	ND	ND
Bacteroides fragilis	0	0	0	0	0	0	0	0	0	4	8	11	50	123	185	37	34	70	120	0.5	2.0	ND
Bacteroides fragilis group	0	0	0	0	0	0	0	0	0	17	28	37	91	333	437	76	52	121	97	0.5	2.0	ND
Bacteroides ovatus	0	0	0	0	0	0	0	0	0	0	0	0	7	5	15	6	3	4	13	0.5	2.0	ND
Bacteroides thetaiotaomicron	0	0	0	0	0	0	0	0	0	0	1	0	3	9	24	16	4	12	16	0.5	2.0	ND
Bacteroides vulgatus	0	0	0	0	0	0	0	0	0	0	0	1	5	9	7	3	2	10	10	0.5	2.0	ND
Bifidobacterium longum	0	0	0	0	1	2	13	26	12	6	1	0	0	0	0	0	0	0	0	4.0	8.0	ND
Campylobacter coli	0	0	0	0	0	0	0	10	30	91	211	368	266	42	69	111	10	0	0	ND	ND	8.0
Campylobacter jejuni	0	0	0	0	0	0	3	6	29	143	223	172	83	78	55	12	1	3	0	ND	ND	8.0
Citrobacter freundii	0	0	0	0	0	0	0	0	0	1	17	44	30	8	3	84	17	0	0	8.0	8.0	8.0
Citrobacter spp	0	0	0	0	0	0	0	0	0	0	11	22	26	26	39	23	11	9	18	8.0	8.0	ND
Enterobacter agglomerans	0	0	0	0	0	0	0	0	0	5	8	52	66	16	13	14	7	0	1	8.0	8.0	ND
Enterobacter cloacae	0	0	0	0	0	0	0	0	0	0	3	5	12	20	19	18	14	8	11	8.0	8.0	ND

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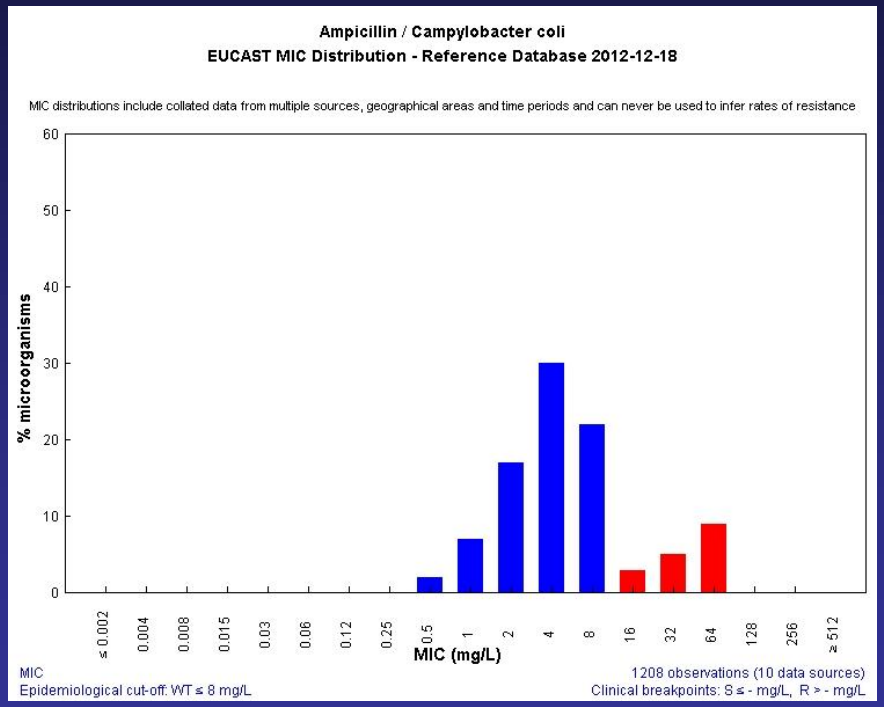
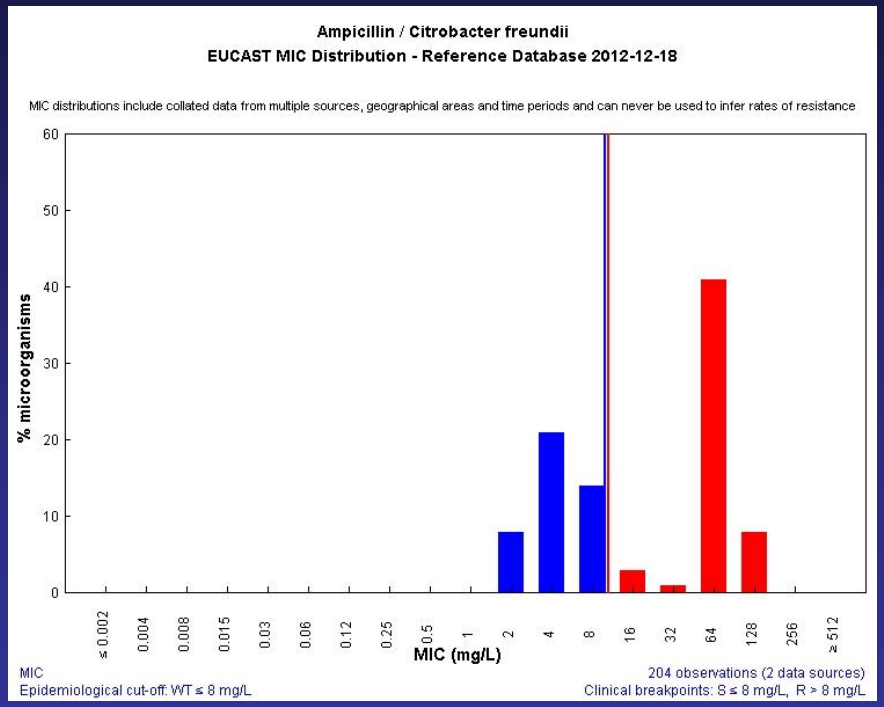
The "Eyeball" Method





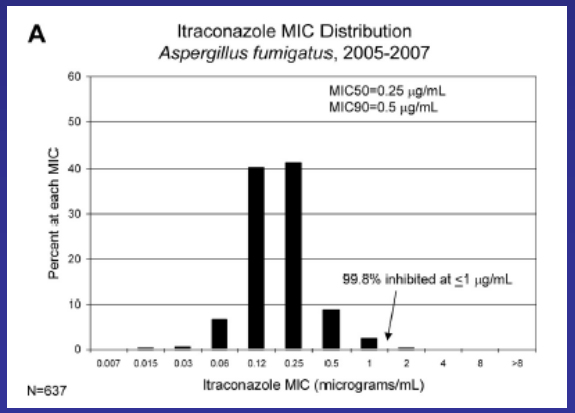
The "Eyeball" Method

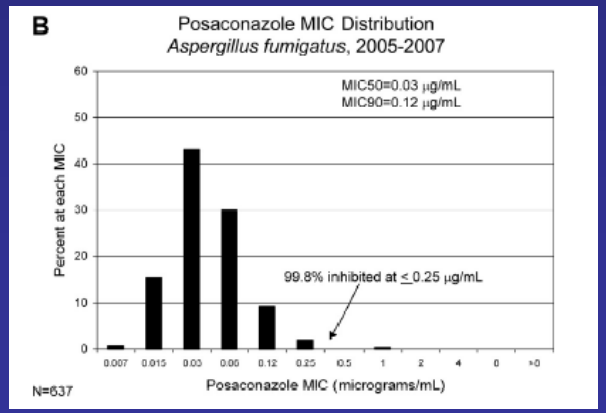
- Issues
  - Not necessarily reproducible between observers
  - No "objective" way of describing the selection

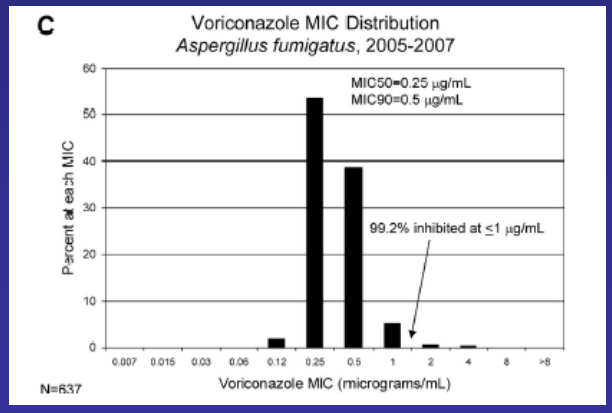
The 95% Rule

- Pfaller et al., J Clin Microbiol 2009

The ECV for each azole was obtained by considering the WT MIC distribution, the modal MIC for each distribution, and the inherent variability of the test (usually ±1 $\log_2$ dilution). In general, the ECV should encompass at least 95% of isolates in the WT distribution (43). Organisms with acquired resistance mechanisms may be identified as those with a MIC higher than the highest MIC of the WT (>ECV) (25, 44).







The 95% Rule

- Issues
  - Not clear direction about what should be done when a significant number of isolates in the population (i.e. >5%) are above wild-type

The Normalized Resistance Interpretation

JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2010, p. 4445–4452 Vol. 48, No. 12
0095-1137/10/$12.00 doi:10.1128/JCM.01101-10

Normalized Resistance Interpretation as a Tool for Establishing Epidemiological MIC Susceptibility Breakpoints▽

Göran Kronvall*

Department of Microbiology and Tumor Biology–MTC, Clinical Microbiology, Karolinska Institutet, Karolinska University Hospital Solna, Stockholm, Sweden

- Uses an adaptation of a method originally devised for "ECOFFs" for zone diameter distributions
  - Kronvall et al., Clin Micro Infect 2003

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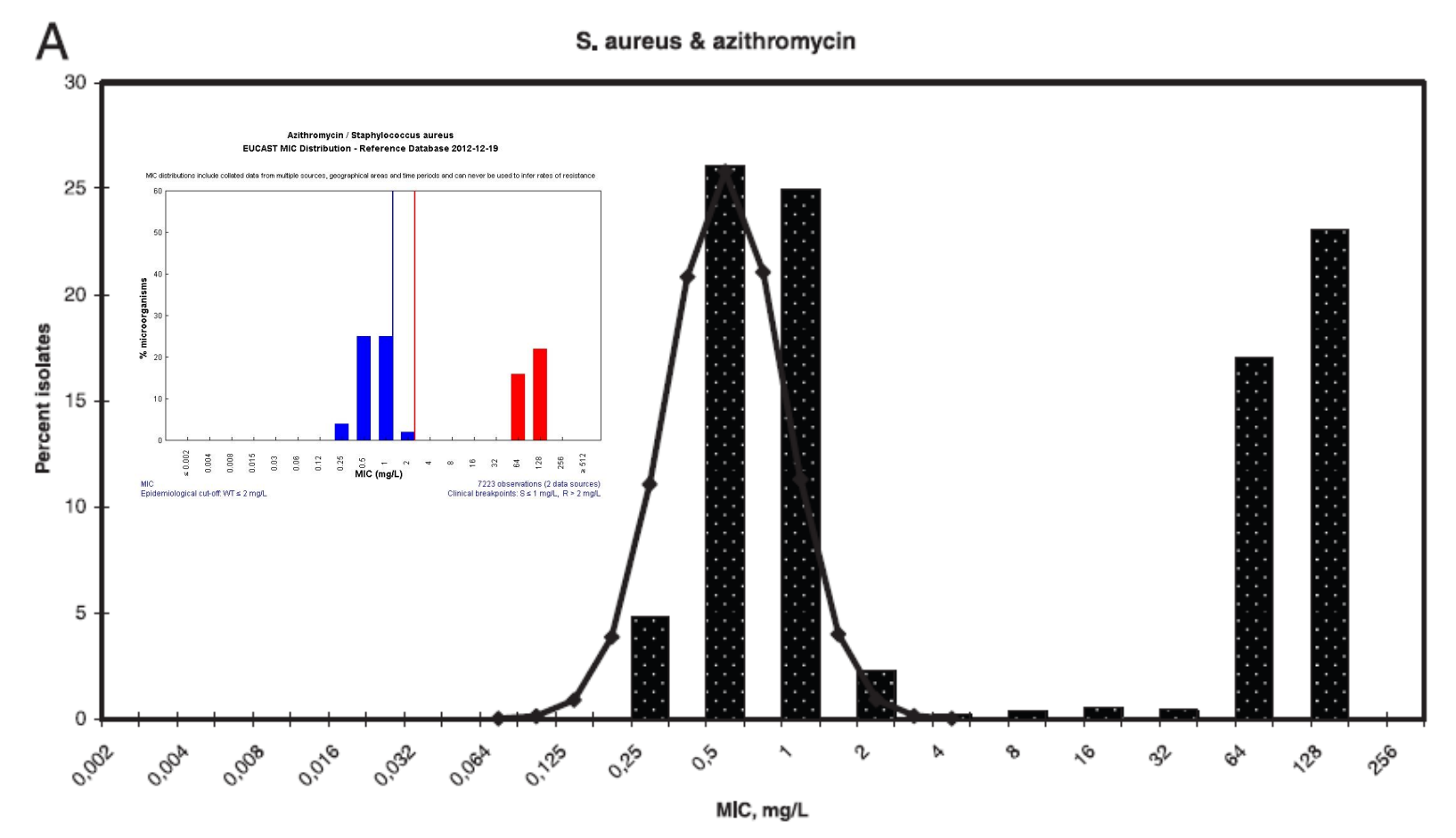
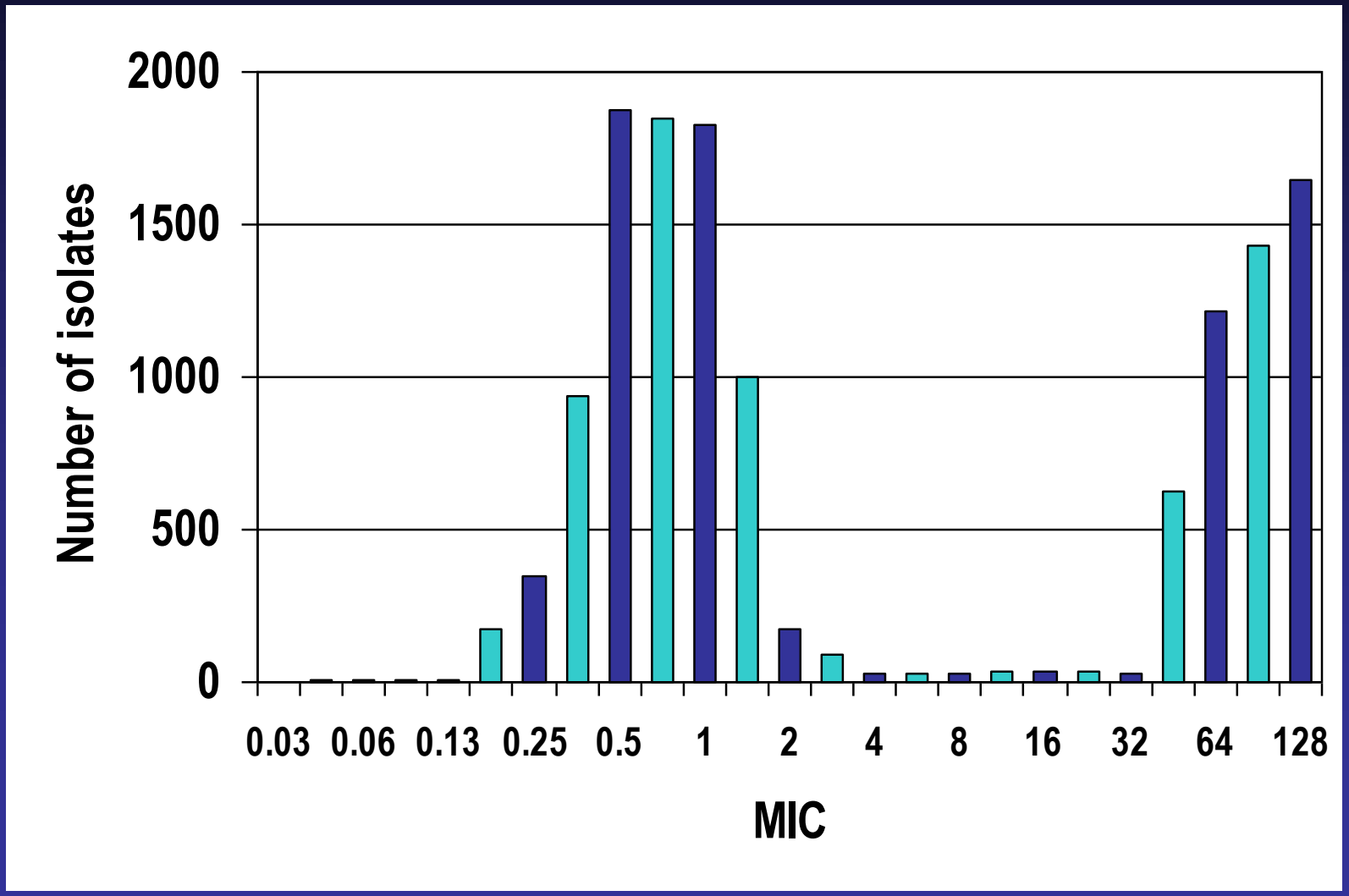
The Normalized Resistance Interpretation



The Normalized Resistance Interpretation



The Normalized Resistance Interpretation

- Issues
  - Requires the introduction of a ‘helper variable’ (dummy data) into the observed data to work on MIC values in the two-fold dilution ($\log_2$) scale.

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Iterative Statistical Method

ORIGINAL ARTICLE 10.1111/j.1469-0691.2006.01377.x

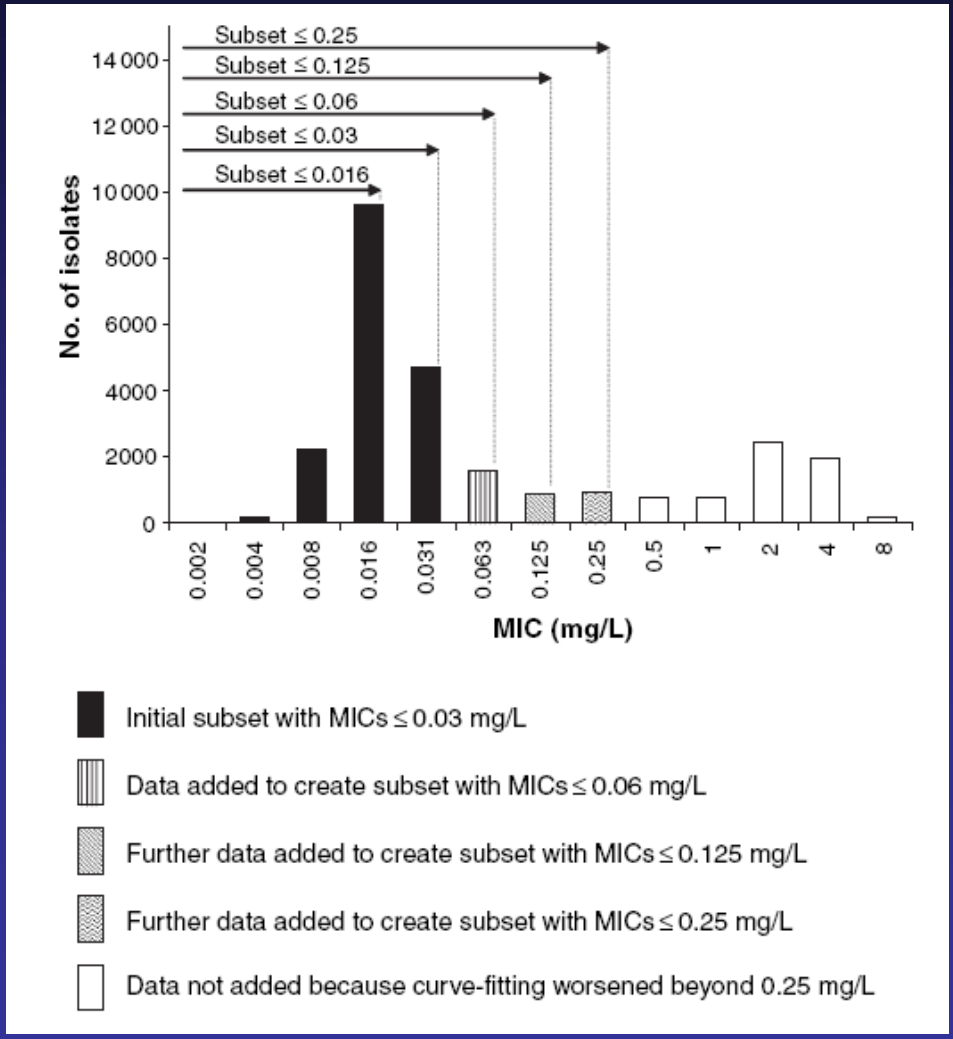
Statistical characterisation of bacterial wild-type MIC value distributions and the determination of epidemiological cut-off values

J. Turnidge[1], *G. Kahlmeter*[2] *and G. Kronvall*[3]

[1]Division of Laboratory Medicine, Women's and Children's Hospital, North Adelaide, South Australia, Australia, [2]Department of Clinical Microbiology, Central Hospital, Växjö and [3]Department of Microbiology and Tumour Biology, MTC, Clinical Microbiology, Karolinska Institute, Karolinska Hospital, Stockholm, Sweden

Iterative Statistical Method

Recalculate (log2) mean and SD for each subset above the (left-hand) mode



Iterative Statistical Method - COFinder

Step 1. Population Data | *CRGAT* | FLUC All

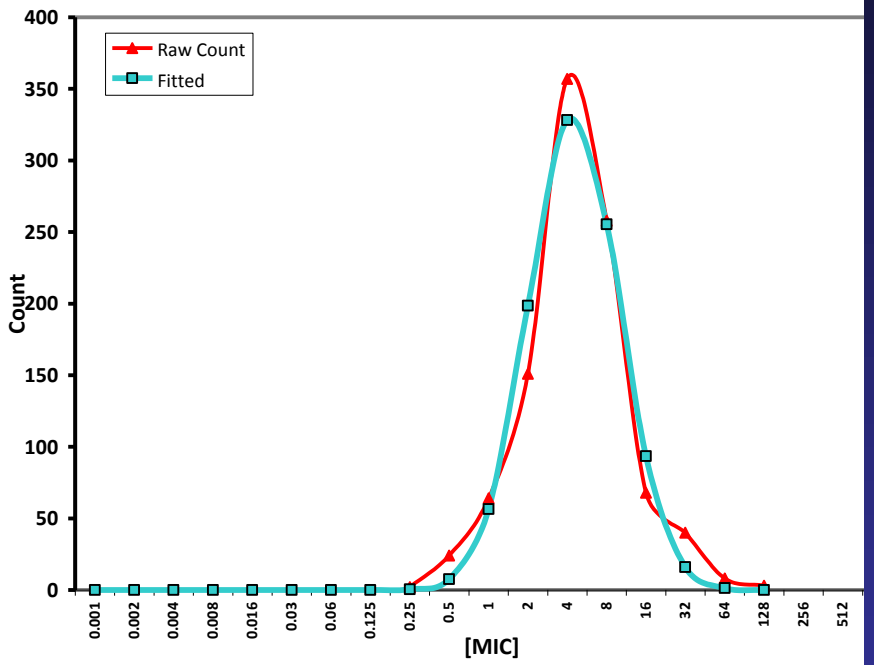
MIC	Log_2MIC	Raw Count	Cum. Count	Fitted
0.001	-10		0	0.0
0.002	-9		0	0.0
0.004	-8		0	0.0
0.008	-7		0	0.0
0.016	-6		0	0.0
0.03	-5		0	0.0
0.06	-4		0	0.0
0.125	-3		0	0.0
0.25	-2	2	2	0.5
0.5	-1	24	26	7.5
1	0	64	90	56.5
2	1	151	241	198.7
4	2	357	598	328.2
8	3	258	856	255.3
16	4	68	924	93.5
32	5	40	964	16.0
64	6	8	972	1.3
128	7	3	975	0.0
256	8		975	
512	9		975	
1024	10		975	
		?		

Enter/paste data in this column

Modal MIC	4
Log_2MIC Mode	2
Max Log_2MIC	7
Selected Log2 Mean	1.6667 =3.17
Selected Log2 SD	1.1145

Selected CO_{WT} Values		%>
CO_{WT} 95%	16	5.2%
CO_{WT} 97.5%	16	5.2%
CO_{WT} 99%	32	1.1%
CO_{WT} 99.9%	64	0.3%

REVIEW AREA



Data from 10 laboratories

Selected CO_{WT} Values		%>
CO_{WT} 95%	16	5.2%
CO_{WT} 97.5%	16	5.2%
CO_{WT} 99%	32	1.1%
CO_{WT} 99.9%	64	0.3%

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Iterative Statistical Method - MicDat

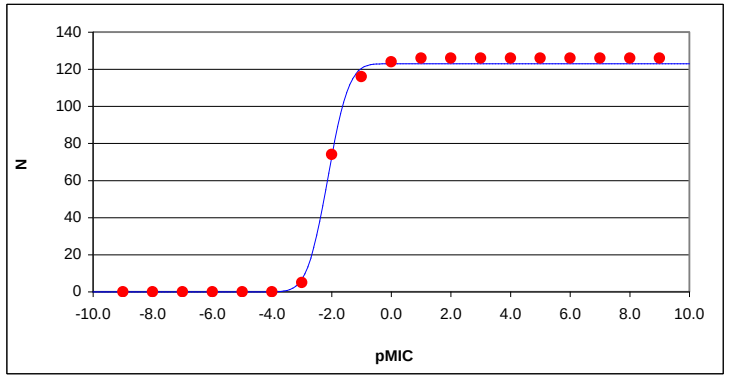
MAIN

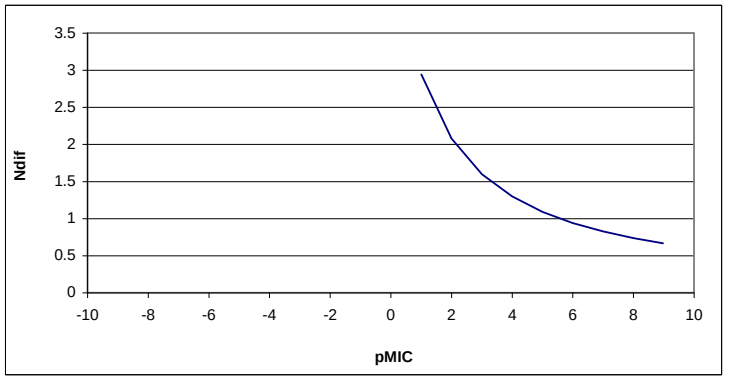
	Auto	User
Mean	-2.0000	-2.1281
Sd	0.7420	0.5502
Ntot	126	123
From	7	7
To	9	11
Ndata	19	
Mode	8	
SoSq	36	
Nit	10	

Database | Datasets | Fit | Reset | ? | Analyze | Archive

No	MIC	pMIC	Nobs	Ncum	Npre	Sq
1	0.00195313	-9.0		0	0	0
2	0.00390625	-8.0		0	0	0
3	0.0078125	-7.0		0	0	0
4	0.015625	-6.0		0	0	0
5	0.03125	-5.0		0	0	0
6	0.0625	-4.0		0	0	0
7	0.125	-3.0	5	5	7	4
8	0.25	-2.0	69	74	73	1
9	0.5	-1.0	42	116	121	21
10	1	0.0	8	124	123	1
11	2	1.0	2	126	123	9
12	4	2.0		126	123	9
13	8	3.0		126	123	9
14	16	4.0		126	123	9
15	32	5.0		126	123	9
16	64	6.0		126	123	9
17	128	7.0		126	123	9
18	256	8.0		126	123	9
19	512	9.0		126	123	9

Trimethoprim (S. agalactiae)





Dataset	From	To	pMIC	Mean	Sd	Nest	Nobs	Ndif
1	7	11	1	-2.1281	0.5502	123	126	2.950851
2	7	12	2	-2.1218	0.5626	124	126	2.080609
3	7	13	3	-2.1181	0.5697	124	126	1.599968
4	7	14	4	-2.1158	0.5743	125	126	1.297617
5	7	15	5	-2.1141	0.5775	125	126	1.090579
6	7	16	6	-2.1129	0.5799	125	126	0.940163

Set	1	2	3	4
CUT-lo (%)	5.0	2.5	1.0	0.1
CUT-hi (%)	95.0	97.5	99.0	99.9
MIC-lo	0.063	0.063	0.063	0.063
MIC-hi	0.500	0.500	1.000	1.000
P-lo (%)	0.0334	0.0334	0.0334	0.0334
P-hi (%)	2.0162	2.0162	0.0055	0.0055

Iterative Statistical Method

- Issues
  - Works well on bi- and tri-modal populations, but struggles when wild-type is 5% or less (uncommon!)

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Multimodal Analysis

Epidemiological Cutoff Values for Azoles and *Aspergillus fumigatus* Based on a Novel Mathematical Approach Incorporating *cyp51A* Sequence Analysis

J. Meletiadis,[a] E. Mavridou,[b,c] W. J. G. Melchers,[b,c] J. W. Mouton,[b,c,d] and P. E. Verweij[b,c]

Clinical Microbiology Laboratory, Attikon University General Hospital, Medical School, University of Athens, Athens, Greece[a]; Department of Medical Microbiology[b] and Nijmegen Institute for Infection, Inflammation and Immunity,[c] Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands; and Canisius Wilhelmina Hospital, Nijmegen, the Netherlands[d]

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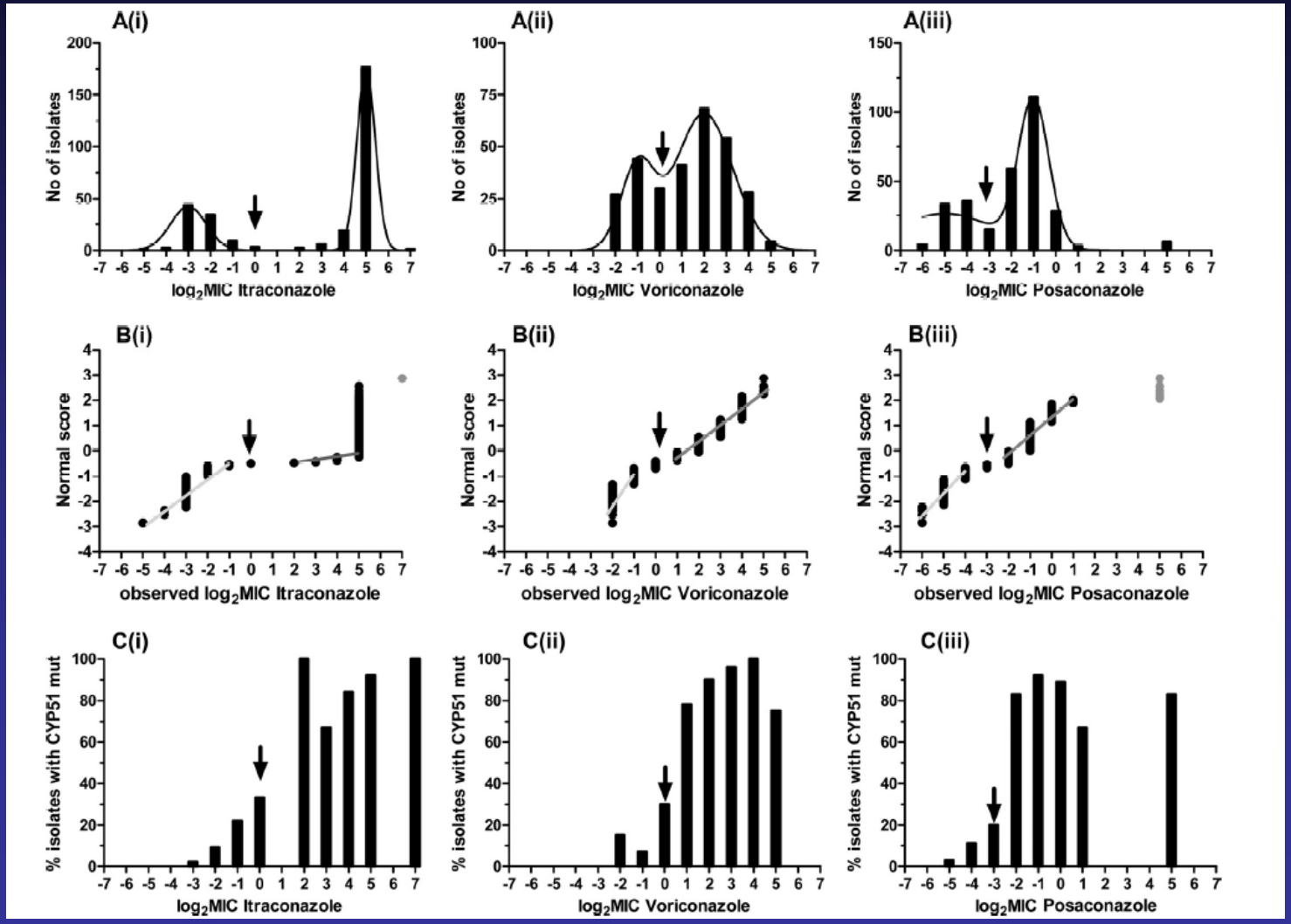
Multimodal Analysis



Multimodal Analysis

- Issues
  - Requires enrichment of the non-wild-type population to work properly

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Cluster Analysis

JCM
Journals.ASM.org

Comparison of Three Statistical Methods for Establishing Tentative Wild-Type Population and Epidemiological Cutoff Values for Echinocandins, Amphotericin B, Flucytosine, and Six *Candida* Species as Determined by the Colorimetric Sensititre YeastOne Method

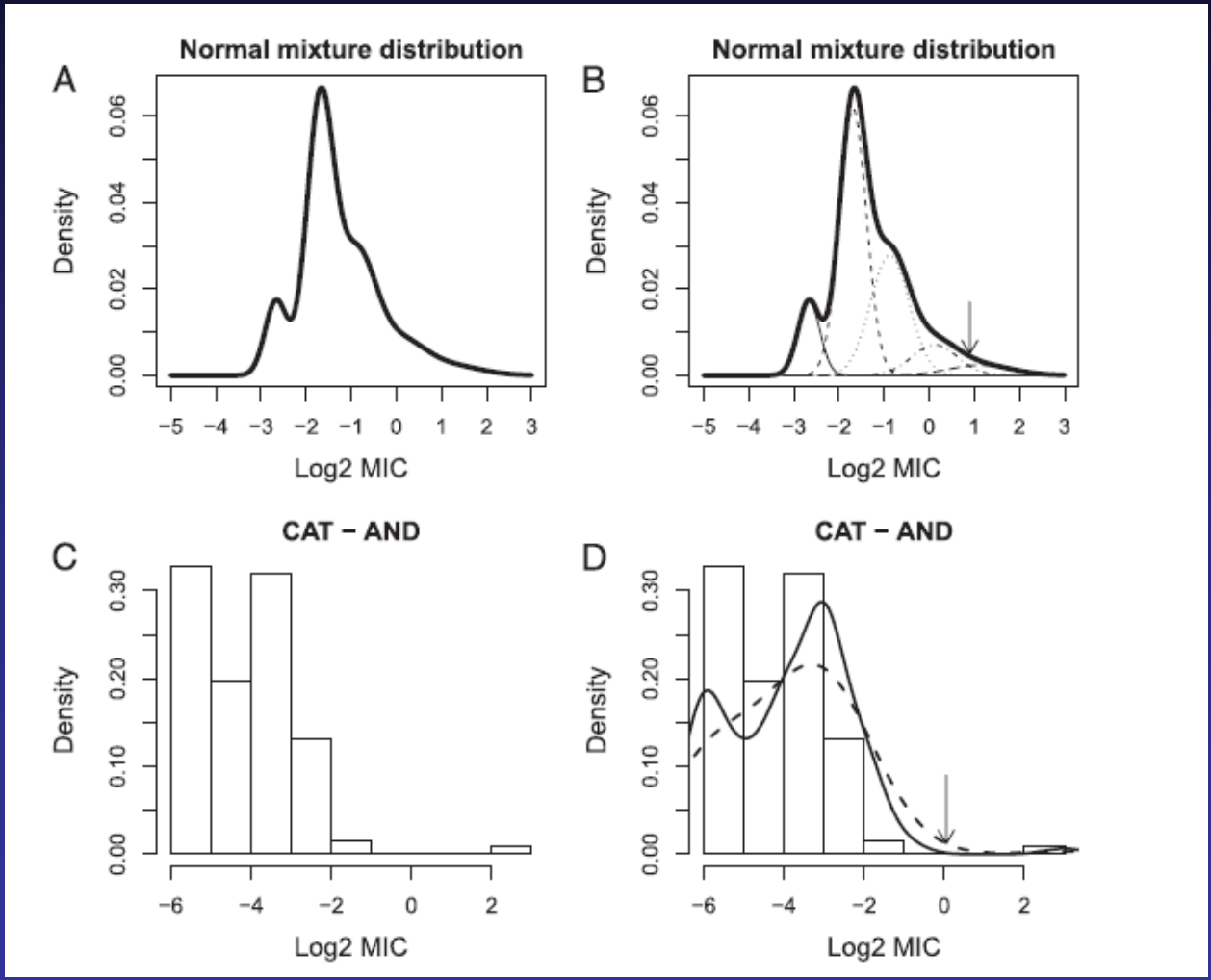
Emilia Cantón,[a] Javier Pemán,[b] David Hervás,[c] Carmen Iñiguez,[d,e] David Navarro,[f] Julia Echeverría,[g] José Martínez-Alarcón,[h] Dionisia Fontanals,[i] Bárbara Gomila-Sard,[j] Buenaventura Buendía,[k] Luis Torroba,[l] Josefina Ayats,[m] Angel Bratos,[n] Ferran Sánchez-Reus,[o] Isabel Fernández-Natal,[p] and the FUNGEMYCA Study Group

(version 3.4.11) (8, 9). To assess the ECVs of the different species for the different antifungals, instead of each species being considered a homogeneous group with a normal distribution, it was treated as a mixture of different subpopulations, each with its own normal distribution. A Gaussian mixture model is given by the following equation:

$$p(x|\lambda) - \sum_{t-1}^{M} w_1 g(x|u_i, \Sigma_i)$$

where x is a continuous variable, λ stands for the mean vectors, covariance matrices, and mixture weights from all components, w_i is the probability that an observation belongs to the ith subpopulation, and $g(x|\mu_i, \Sigma_i)$ shows the component Gaussian densities. In order to approach a normal mixture distribution, the $\log_2$ MIC values were smoothed by a kernel density algorithm (26). The clustering technique selects the number of normal components in the mixture by estimation of the most parsimonious model by use of the Bayesian information criterion (BIC). It is then able to discern the different normal distributions in the mixture, producing a probabilistic clustering that quantifies the uncertainty of observations belonging to the different subpopulations. Consequently, the ECV was set at the point of maximal uncertainty between the most resistant subpopulation and the others (Fig. 1). Since the ECVs estimated by the clustering method are on a continuous scale, values were rounded to the nearest higher dilution after reconversion to concentration units.

Cluster Analysis



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Cluster Analysis

TABLE 3 Comparison of ECVs obtained for five antifungal agents by use of different methods

Species	No. of isolates tested	Agent[a]	ECV obtained by indicated method (%)[b]						
			MIC_{50} + 2 dilutions	Modal MIC + 2 dilutions	Method of Turnidge et al.	Method of Kronvall[c]	Clustering method[c]	Median for all 5 studied methods	CLSI method[d]
C. albicans	656	AND	0.12 (99.7)	0.06 (84.45)	0.25 (98.5)	0.25 (95.65)	0.25 (98.63)	0.25 (98.5)	0.12 (99.7)
	659	MCF	0.06 (95.1)	0.06 (95.1)	0.06 (95.1)	0.12 (94.95)	0.06 (94.99)	0.06 (95.1)	0.03 (97.7)
	747	CAS	0.25 (98.7)	0.25 (98.7)	0.25 (98.7)	0.5 (98.99)	0.25 (98.66)	0.25 (98.7)	0.12 (99.8)
	923	AMB	1 (100)	2 00)	2 (100)	2 (100)	1 (100)	2 (100)	2 (99.8)
	915	FLC	0.25 (90.27)	0.25 (90.27)	1 (96.4)	1 (96.99)	2 (98.8)	1 (98.5)	0.5 (94.2)
C. parapsilosis	352	AND	4 (99.71)	8 (100)	8 (100)	8 (99.87)	4 (99.75)	8 (100)	4 (100)[e]
	392	MCF	4 (99.23)	4 (99.23)	8 (100)	8 (99.36)	4 (99.24)	4 (99.2)	4 (100)[e]
	490	CAS	2 (99.2)	2 (99.2)	4 (99.8)	4 (99.39)	2 (99.19)	2 (99.2)	1(98.6)[e]
	603	AMB	1 (99.83)	1 (99.83)	2 (100)	2 (99.92)	1 (100)	1 (99.8)	2 (99.7)
	635	FLC	0.25 (93.7)	0.25 (93.7)	0.5 (97.9)	1 (98.48)	2 (99.52)	0.5 (97.9)	0.5 (98.7)
C. tropicalis	123	AND	0.25 (96.75)	0.5 (99.2)	1 (99.2)	1 (99.59)	1 (99.18)	1 (99.2)	0.12 (98.9)
	121	MCF	0.12 (99.2)	0.12 (99.2)	0.12 (99.2)	0.25 (99.58)	0.5 (99.17)	0.12 (99.2)	0.12 (99.1)
	138	CAS	0.25 (99.3)	0.25 (99.3)	0.5 (100)	0.5 (99.64)	0.25 (99.28)	0.25 (99.2)	0.12 (99.4)
	171	AMB	2 (100)	2 (100)	2 (100)	2 (99.11)	1 (98.82)	2 (100)	2 (99.8)
	175	FLC	0.25 (96.57)	0.25 (96.57)	0.5 (97.1)	0.5 (97.31)	0.5 (97.65)	0.5 (97.2)	0.5 (93.0)
C. glabrata	174	AND	0.12 (96.55)	0.12 (96.55)	0.12 (96.55)	0.25 (97.1)	0.25 (96.55)	0.12 (96.6)	0.25 (99.4)
	174	MCF	0.06 (95.97)	0.06 (95.97)	0.06 (95.97)	0.25 (96.33)	0.06 (95.98)	0.06 (96.0)	0.03 (98.2)
	188	CAS	0.25 (98.4)	0.25 (98.4)	0.25 (98.4)	0.5 (98.65)	0.12 (93.62)	0.25 (98.4)	0.12 (98.5)
	209	AMB	2 (100)	2 (100)	2 (100)	2 (99.76)	1 (99.52)	2 (100)	2 (99.6
	208	FLC	0.25 (97.6)	0.25 (97.6)	0.25 (97.6)	0.5 (97.83)	0.12 (95.67)	0.25 (97.6)	0.5 (9800)
C. krusei	33	AND	0.25 (96.97)	0.25 (96.97)	0.25 (97.0)	0.5 (98.44)	1 (96.97)	0.25 (97.0)	0.12 (99.3)
	33	MCF	0.5 (93.94)	0.5 (93.94)	0.25 (94.0)	1 (96.83)	0.25 (93.94)	0.5 (93.9)	0.12 (97.8)
	37	CAS	1 (91.89)	1 (91.89)	2 (94.6)	4 (95.77)	1 (91.89)	1 (91.9)	0.25 (96.3)
	51	AMB	2 (100)	4 (100)	4 (100)	4 (100)	2 (100)	4 (100)	2 (99.3)
	53	FLC	32 (100)	32 (100)	64 (100)	64 (100)	16 (98.11)	32 (100)	32 (94.4)
C. orthopsilosis	33	AND	2 (100)	4 (100)	4 (100)	4 (98.46)	2 (97.06)	4 (100)	2 (100)
	33	MCF	2 (100)	2 (100)	4 (100)	4 (100)	2 (100)	2 (100)	1 (100)
	54	CAS	2 (100)	2 (100)	4 (100)	4 (100)	2 (100)	2 (100)	0.5 (100)
	90	AMB	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	ND
	91	FLC	0.25 (93.41)	0.25 (93.41)	1 (97.8)	0.5 (96.07)	0.25 (94.44)	0.25 (93.4)	ND

Cluster Analysis

TABLE 3 Comparison of ECVs obtained for five antifungal agents by use of different methods

Species	No. of isolates tested	Agent[a]	ECV obtained by indicated method (%)[b]						
			MIC_{50} + 2 dilutions	Modal MIC + 2 dilutions	Method of Turnidge et al.	Method of Kronvall[c]	Clustering method[c]	Median for all 5 studied methods	CLSI method[d]
C. albicans	656	AND	0.12 (99.7)	0.06 (84.45)	0.25 (98.5)	0.25 (95.65)	0.25 (98.63)	0.25 (98.5)	0.12 (99.7)
	659	MCF	0.06 (95.1)	0.06 (95.1)	0.06 (95.1)	0.12 (94.95)	0.06 (94.99)	0.06 (95.1)	0.03 (97.7)
	747	CAS	0.25 (98.7)	0.25 (98.7)	0.25 (98.7)	0.5 (98.99)	0.25 (98.66)	0.25 (98.7)	0.12 (99.8)
	923	AMB	1 (100)	2 00)	2 (100)	2 (100)	1 (100)	2 (100)	2 (99.8)
	915	FLC	0.25 (90.27)	0.25 (90.27)	1 (96.4)	1 (96.99)	2 (98.8)	1 (98.5)	0.5 (94.2)

- Issues
  - Assumes that the wild-type population is a true mixture of sub-populations, rather than assay variation
  - Could be re-interpreted as site-to-site mixture

Limitations

- Little work has been done to 'validate' the ECOFFs with molecular analyses (e.g. resistance gene detection)
  - Meletiadis et al. AAC 2012
  - Pfaller et al. Drug Resist Updates 2011
  - AFST and AST Agenda papers!
- The 2-fold dilution scale that we use for MIC measurements, while the simplest of the integer log scales, is in reality TOO COURSE, limiting the predictive power of estimations

Limitations

- It remains unclear whether the wild-type populations of MICs are due to true biological variation, only assay variation, or a combination of both
  - if it's just assay variation then all we need is a QC study!
- When pooling data for analysis, should data be weighted?
  - Weighting by "n" can change results
- Is it possible to identify 'statistical outlier' labs
  - Outlier strategy for QC studies doesn't seem to work?

Data Pooling – Weighted vs Unweighted

- 9 laboratories – 77% from one laboratory - unweighted

Step 1. Population Data

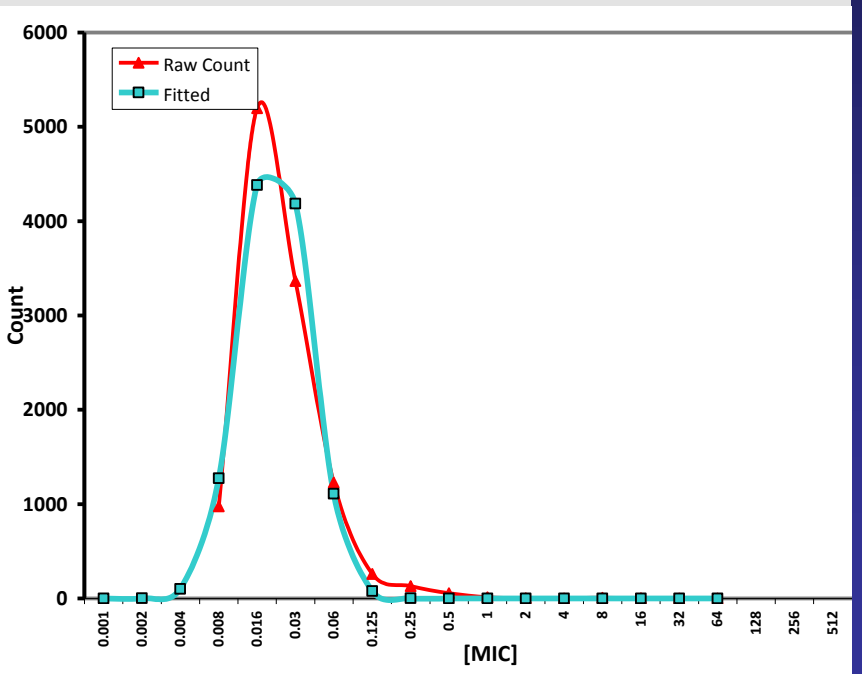
MIC	Log_2MIC	Raw Count	Cum. Count	Fitted
0.001	-10		0	0.0
0.002	-9		0	2.1
0.004	-8		0	100.3
0.008	-7	976	976	1273.6
0.016	-6	5197	6173	4382.9
0.03	-5	3365	9538	4186.7
0.06	-4	1230	10768	1108.9
0.125	-3	259	11027	79.4
0.25	-2	132	11159	1.5
0.5	-1	55	11214	0.0
1	0	13	11227	0.0
2	1	3	11230	0.0
4	2	1	11231	0.0
8	3	7	11238	0.0
16	4	2	11240	0.0
32	5	0	11240	0.0
64	6	1	11241	0.0
128	7		11241	
256	8		11241	
512	9		11241	
1024	10		11241	

?
Enter/paste data in this column

Modal MIC	0.0156
Log_2MIC Mode	-6
Max Log_2MIC	6
Selected Log2 Mean	-6.036 =0.02
Selected Log2 SD	0.8331

Selected CO_{WT} Values		%>
CO_{WT} 95.0%	0.0625	4.2%
CO_{WT} 97.5%	0.0625	4.2%
CO_{WT} 99.0%	0.0625	4.2%
CO_{WT} 99.9%	0.125	1.9%

REVIEW AREA



Data Pooling – Weighted vs Unwweighted

- 9 laboratories – 77% from one laboratory - weighted

Step 1. Population Data

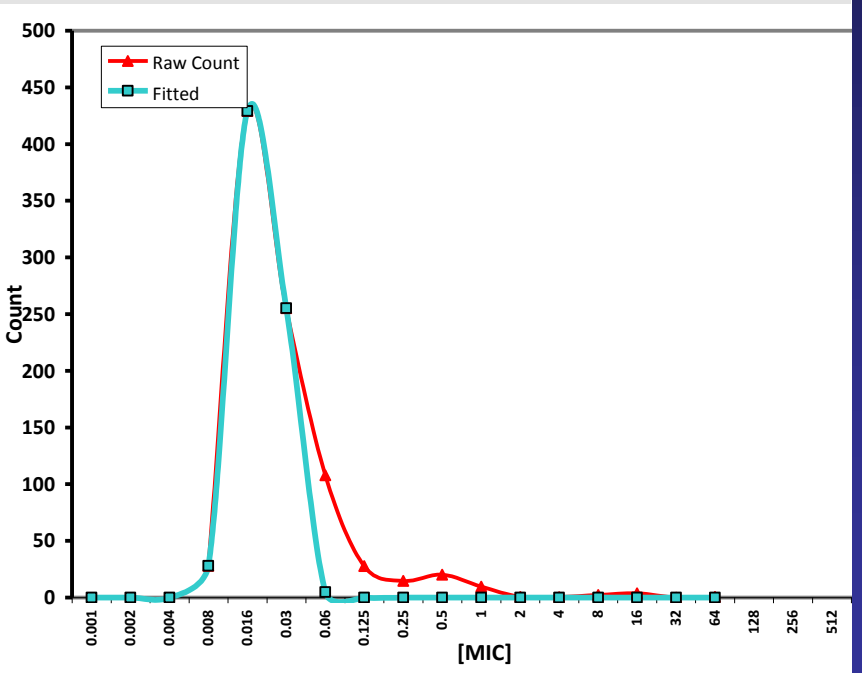
MIC	Log_2MIC	Raw Count	Cum. Count	Fitted
0.001	-10		0	0.0
0.002	-9		0	0.0
0.004	-8		0	0.0
0.008	-7	28.00636365	28.00636365	28.0
0.016	-6	429.0781349	457.0844986	429.1
0.03	-5	255.2847671	712.3692657	255.3
0.06	-4	107.8577203	820.226986	4.9
0.125	-3	27.6833742	847.9103602	0.0
0.25	-2	14.6173611	862.5277213	0.0
0.5	-1	20.28967626	882.8173976	0.0
1	0	9.729328132	892.5467257	0.0
2	1	0.566441748	893.1131675	0.0
4	2	0.331125828	893.4442933	0.0
8	3	2.210468613	895.6547619	0.0
16	4	3.75	899.4047619	0.0
32	5	0	899.4047619	0.0
64	6	0.595238095	900	0.0
128	7		900	
256	8		900	
512	9		900	
1024	10		900	

?
Enter/paste data in this column

Modal MIC	0.0156	
Log_2MIC Mode	-6	
Max Log_2MIC	6	
Selected Log2 Mean	-6.166	=0.01
Selected Log2 SD	0.4733	

Selected CO_{WT} Values		%>
CO_{WT} 95.0%	0.0313	20.8%
CO_{WT} 97.5%	0.0313	20.8%
CO_{WT} 99.0%	0.0313	20.8%
CO_{WT} 99.9%	0.0625	8.9%

REVIEW AREA



Important Questions

- If ECOFFs are to be used for interpretation of susceptibility testing results:
  - should they be reported to the clinician?
  - if so, how?

- **Suggestion** – report as "N" = "Non-wild-type" with a comment/footnote"
  - *N = non-wild-type