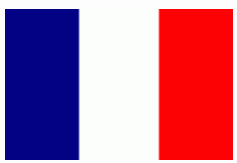
Antimicrobial susceptibility testing in human medicine in Europe – - breakpoint committees

NCCLS is now CLSI

CLSI (USA)

eucast (EUROPE)



BSAC wp	CA-SFM	CRG	DIN	NWGA	SRGA
The UK	France	Netherlands	Germany	Norway	Sweden

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Many European countries subscribe to CLSI….

Breakpoints and methods used by lab:s in EARSS 2001

	UK	Sweden	Spain	Slovenia	Portugal	Poland	Netherlands	Malta	Luxembourg	Italy	Israel	Ireland	Iceland	Hungary	Greece	Germany	France	Finland	Denmark	Czech R.	Bulgaria	Belgium	Austria	Total
BSAC	12											5												17
CRG							6																	6
Czech 98																				15				15
DIN																15								15
FIRE																		9						9
Mensura			1																					1
CLSI			25	7	11	18	8	1	5	50	3	1	3	1	14	6		12		4	20	31	9	229
SFM																	1							1
SRGA		25																	1					26
Stokes	6											9												15
>1 method	3		5	3	1	1	9			2		2				9		4	1	11		10		61
Not specified	3				4		2			1		1			3	1			3	3		16	1	38

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National breakpoint committees in Europe – what do they do?

- **breakpoint** committees
- guidelines on **methodology** (France, Sweden, the UK)
- internal and external **quality assurance**
- **education** of medical staff and laboratory personnel
- **surveillance** of antimicrobial resistance (national and international programs)
- **liaison** with regulatory authorities, the medical profession and pharmaceutical industry.

... maybe all countries should have one?!

Last updated 20-02-2005

EUCAST

European Committee on Antimicrobial Susceptibility Testing
formed in 1997 and restructured in 2002

convened by
European Society for Clinical Microbiology and Infectious Diseases (ESCMID)
National Breakpoint Committees in Europe

and financed by
ESCMID
National Breakpoint Committees in Europe
DG-SANCO of the European Union (3 year grant from May 2004)

Last updated 20-02-2005

EUCAST

- a **network** of **national breakpoint committees, experts** and **industry** involved in antimicrobial susceptibility testing
- **breakpoints for existing** and **new** antimicrobial drugs
- **epidemiological cut off values** for surveillance of antimicrobial resistance
- promote **standardisation** and **quality assessment** of AST methods in Europe
- promote **consensus** on susceptibility testing
- collaborate with groups involved in **antimicrobial susceptibility testing** (CLSI) and the **epidemiology of antimicrobial resistance** (EARSS, ESGARS, ESAC).
- **advise** European Community Institutions
- devise and participate in programmes for **education and training** in antimicrobial susceptibility testing

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EUCAST

General Committee

- One representative from each European country and ISC and FESCI
- Meets once a year in conjunction with the ECCMID meeting
- All tentative decisions referred to GC for comments

Steering Committee

- One representative from each national breakpoint committee in Europe
- Two representatives from the General Committee (2 years turnover)
- Meets 4 times a year

Industry email network

- All pharmaceutical and AST manufacturers are invited to comment on EUCAST tentative decisions.

Subcommittee on Antifungal Susceptibility Testing

- Standardised methods for susceptibility testing
- Define wild type MIC distributions
- Define breakpoints

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EUCAST steering committee

Appointments 2005

• Gunnar Kahlmeter, chairman	2008
• Derek Brown, scientific secretary	2008
• BSAC (The UK) - Alasdair MacGowan	2008
• CA-SFM (France) - F Goldstein/C-J Soussy	2008
• CRG (The Netherlands) - Johan W. Mouton	2008
• DIN (Germany) - Arne Rodloff	2008
• NWGA (Norway) - Martin Steinbakk	2008
• SRGA (Sweden) - A Österlund/I Nilsson-Ehle	2008
• EUCAST rep 1 – Olga Stetsiouk (Russia)	2004 - 06
• EUCAST rep 2 – Francisco Soriano (Spain)	2004 - 06

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EUCAST General Committee 2004-5

Austria Prof Helmut Mittermayer
Belgium Prof Jan Verhaegen
Bosnia Dr Selma Uzunovic-Kamberovic
Bulgaria Prof Krassimir Metodiev
Croatia Dr Arjana Tambic-Andrasevic
Czech Republic Dr Pavla Urbaskova
Denmark Dr Niels Frimodt-Møller
Estonia Dr Paul Naaber
Finland Dr Antti Nissinen
France Prof Claude-James Soussy
Germany Prof Bernd Wiedemann
Greece Prof Alkiviadis Vatopoulos
Hungary Dr Éva Bán
Iceland Dr Karl Gustaf Kristinsson
Ireland Dr Martin Cormican
Italy Prof Pietro Emanuele Varaldo
Lithuania Prof Arvydsa Ambrozaitis
Netherlands Prof John Degener
Norway Dr Martin Steinbakk
Poland Prof Waleria Hryniewicz
Portugal Prof Jose Melo Cristino
Romania no representative
Russia Dr Olga Stetsiouk
Serbia Dr Lazar Ranin
Slovak Republic Prof. Milan Niks
Slovenia Dr Jana Kolman
Spain Dr Francisco Soriano
Sweden Dr Barbro Olsson-Liljequist
Switzerland Prof Jaques Bille
Turkey Dr Deniz Gür
UK Prof Alasdair MacGowan
Yugoslavia no representative

ISC – Paul Tulkens
FESCI – David Livermore

Network of industry with an interest in antimicrobials

Chairman Gunnar Kahlmeter, Sweden
Scientific secretary Derek Brown, UK

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Authority of breakpoint committees?

- Breakpoint committees have **no legal authority** – only a ”scientific mandate”. This is shared by EUCAST, CLSI, BSAC, CA-SFM, CRG, DIN, NWGA, SRGA.

  The authority rests with National medicine´s agencies, EMEA and FDA.

- However, a working relationship between EMEA and EUCAST is being developing.

European Medicines Agency
Standard Operating Procedure

The SOP allows EUCAST to interact with the EMEA rapporteur and expert and the pharmaceutical company at the earliest stage of the registration process and to suggest to EMEA breakpoints for the new drug to be formally included in the SPC (summary of product characteristics) of the drug.

The purpose is to avoid discrepancies between ”regulatory” breakpoints and those of the profession.

Until now EMEA SPCs (”summary of product characteristics”) have contained breakpoints from ”all” the national European breakpoint committees and NCCLS.

In 2004 the CHMP decided that future SPCs will contain EUCAST breakpoints instead of other breakpoints

European Medicines Agency
Standard Operating Procedure

Title: Harmonisation of European Breakpoints set by EMEA/CHMP and EUCAST		Document no.: SOP/H/3043
Applies to: Product Team Leaders in the Human Pre-Authorisation Unit, (Co)Rapporteurs, External Experts, EUCAST		Effective Date: 14 February 2005
PUBLIC		Review Date: 14 February 2007 Supersedes: N/A
Prepared by	Approved by	Authorised for issue by
Name: Bo Aronsson	Name: Agnès Saint Raymond	Name: Patrick Le Courtois
Signature: On file	Signature: On file	Signature: On file
Date: 10 Feb 05	Date: 10 Feb 05	Date: 10 Feb 05

1. Purpose

To describe the interaction between EMEA/CHMP and EUCAST in the process of harmonisation of European breakpoints.

The SOP can be downloaded from the EUCAST homepage (www.eucast.org) and from the EMEA homepage

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Collaboration between EUCAST and the Clinical Laboratory Standards Institute (CLSI; formerly NCCLS)

- Cephalosporin breakpoints for Enterobacteriaceae
- Carbapenems and Monobactams (!?)

CEN and ISO (EUCAST and CLSI) – international reference method for determination of MICs for non-fastidious bacteria.

Collaboration

EUCAST AFST – will use EUCAST terminology, wild MIC distribution concept, procedure for breakpoint setting and connections with EMEA.

Expert groups on Neisseria gonorrhoeae, Neisseria meningitidis, Anaerobes, VetCAST and others have accepted our invitation to join The consultation process.

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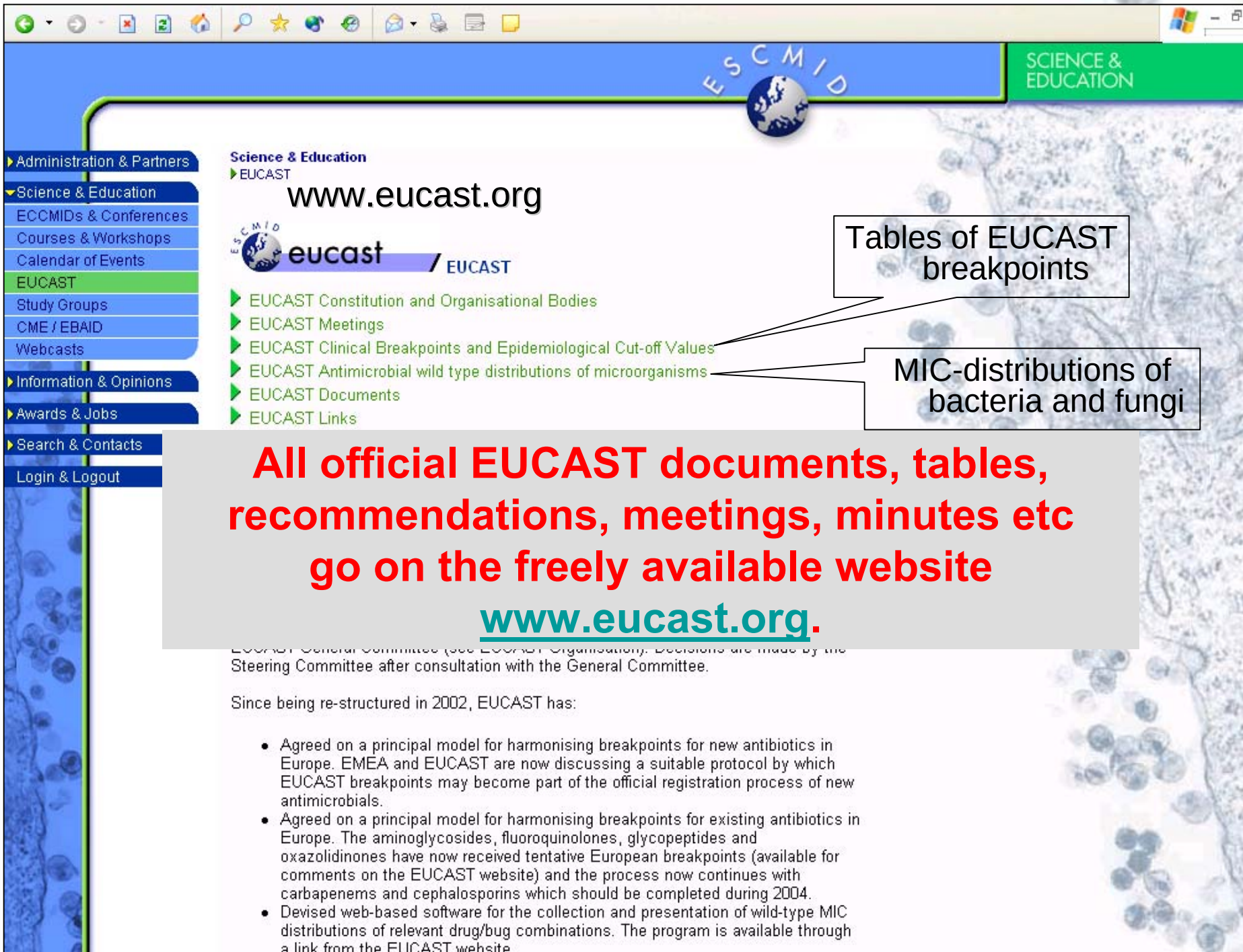
SCIENCE & EDUCATION
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Science & Education
ECCMIDs & Conferences
Courses & Workshops
Calendar of Events
EUCAST
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EUCAST Constitution and Organisational Bodies
EUCAST Meetings
EUCAST Clinical Breakpoints and Epidemiological Cut-off Values
EUCAST Antimicrobial wild type distributions of microorganisms
EUCAST Documents
EUCAST Links
Tables of EUCAST breakpoints
MIC-distributions of bacteria and fungi
All official EUCAST documents, tables, recommendations, meetings, minutes etc go on the freely available website www.eucast.org.
Steering Committee after consultation with the General Committee.
Since being re-structured in 2002, EUCAST has:
Agreed on a principal model for harmonising breakpoints for new antibiotics in Europe. EMEA and EUCAST are now discussing a suitable protocol by which EUCAST breakpoints may become part of the official registration process of new antimicrobials.
Agreed on a principal model for harmonising breakpoints for existing antibiotics in Europe. The aminoglycosides, fluoroquinolones, glycopeptides and oxazolidinones have now received tentative European breakpoints (available for comments on the EUCAST website) and the process now continues with carbapenems and cephalosporins which should be completed during 2004.
Devised web-based software for the collection and presentation of wild-type MIC distributions of relevant drug/bug combinations. The program is available through

Antimicrobial wild type distributions of microorganisms

- Search database

The EUCAST (European Committee on Antimicrobial Susceptibility Testing) under the auspices of the ESCMID (European Society for Clinical Microbiology and Infectious Diseases) offers this free website of distributions of MIC-values of wild type bacteria and fungi.
Each MIC-distribution is defined by the micro-organism, the antimicrobial drug and the method. It is the compound result of a number of separate distributions submitted to EUCAST from organisations such as national breakpoint committees, industry, antimicrobial resistance surveillance programs and research projects. Each distribution has been released by the EUCAST steering committee and thereby also by the national breakpoint committees which help form the EUCAST steering committee. The distributions are used by the committee for defining epidemiological cut-off values to for surveillance of resistance development, and for the harmonisation of European clinical breakpoints.

Each graph contains information on the number of sources of data, the total number of organisms, and when defined by EUCAST, clinical breakpoints (S≤ Y mg/L and R> Z mg/L) and/or the epidemiological cut-off value. The epidemiological cut-off value is related to the MIC distribution.of the wild type organism and categorized as WT≤Z mg/L.

Questions can be adressed to gunnar.kahlmeter@ltkronoberg.se

www.eucast.org

Antimicrobial wild type distributions of microorganisms

Search

Method: MIC Disc diffusion

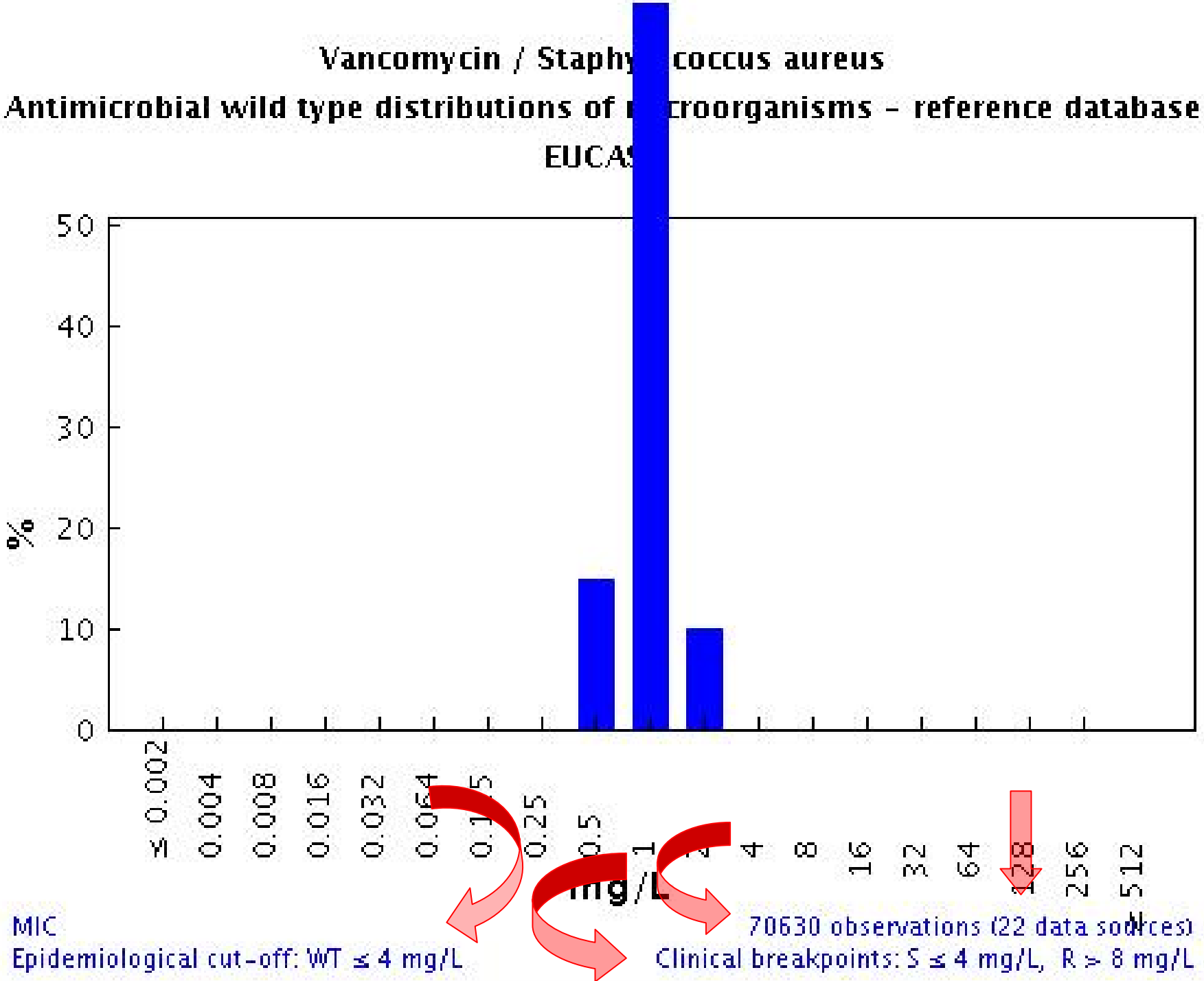
Elements per page: 50

Antimicrobial: Vancomycin Species: Species...

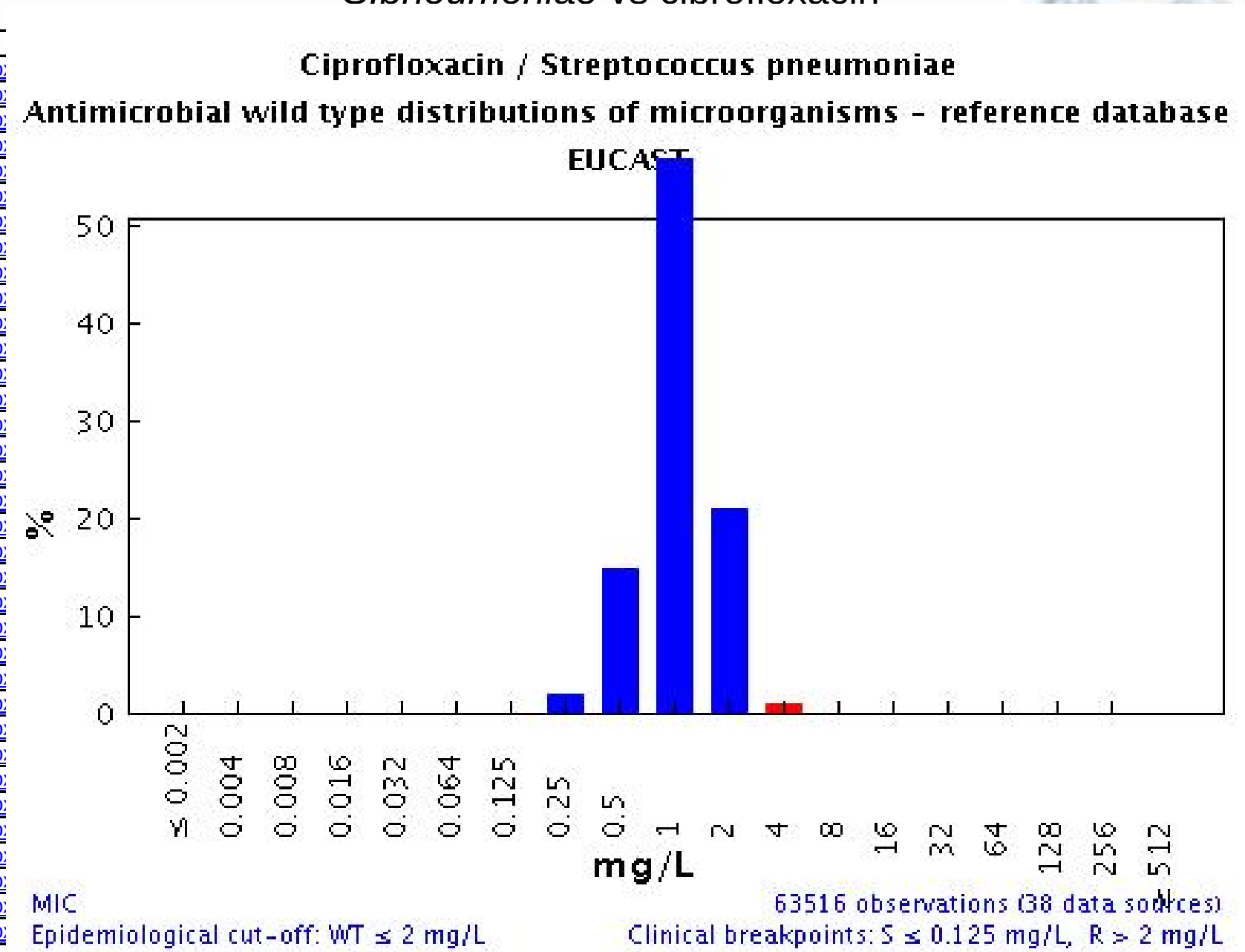
Antimicrobial: Vancomycin **(Method:** MIC **)**

Show All Graphs

	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
Enterococcus faecalis	0	0	0	0	0	0	2	15	250	1552	1539	214	8	3	1	3	17	15	4
Enterococcus faecium	0	0	0	0	0	0	1	35	676	1275	168	39	16	2	3	5	1	52	3
Propionibacterium acne	0	0	0	0	0	0	0	13	158	131	1	0	0	0	0	0	0	0	0
Staphylococcus aureus	0	0	0	0	0	0	62	440	8813	35433	3215	67	3	0	1	1	1	0	0
Staphylococcus capitis	0	0	0	0	0	0	0	5	28	110	25	1	0	0	0	0	0	0	0
Staphylococcus coagulase negative	0	0	0	0	0	0	9	52	352	2978	3554	155	6	2	0	0	0	0	0
Staphylococcus cohnii	0	0	0	0	0	0	0	0	0	18	2	0	0	0	0	0	0	0	0
Staphylococcus epidermidis	0	0	0	0	0	0	2	21	180	2699	3914	145	2	0	0	0	0	0	0
Staphylococcus haemolyticus	0	0	0	0	0	0	0	7	72	503	332	34	0	0	0	0	0	0	0
Staphylococcus hominis	0	0	0	0	0	0	0	6	52	256	88	1	0	0	0	0	0	0	0
Staphylococcus intermedius	0	0	0	0	0	0	1	0	10	13	6	0	0	0	0	0	0	0	0
Staphylococcus lugdunensis	0	0	0	0	0	0	0	2	16	44	7	0	0	0	0	0	0	0	0
Staphylococcus saprophyticus	0	0	0	0	0	0	0	0	14	138	59	2	0	0	0	0	0	0	0
Staphylococcus simulans	0	0	0	0	0	0	0	0	9	53	24	0	0	0	0	0	0	0	0
Staphylococcus warnerii	0	0	0	0	0	0	0	0	10	71	35	2	0	0	0	0	0	0	0
Streptococcus agalactiae	0	0	0	0	0	0	1	174	1818	176	5	1	0	0	0	0	0	0	0
Streptococcus anginosus	0	0	0	0	0	0	2	3	42	39	0	0	0	0	0	0	0	0	0
Streptococcus bovis	0	0	0	0	0	0	0	54	144	12	1	0	0	0	0	0	0	0	0


Vancomycin / Staphy coccus aureus
Antimicrobial wild type distributions of r croorganisms - reference database
EUCAS
%
50
40
30
20
10
0
≤ 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
mg/L
N
MIC
Epidemiological cut-off: WT ≤ 4 mg/L
70630 observations (22 data sources)
Clinical breakpoints: S ≤ 4 mg/L, R > 8 mg/L

S.pneumoniae vs ciprofloxacin



Ciprofloxacin	0	0	0	0	0	0	1	2	41	99	55	11	1	0	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	0	422	2706	13072	3987	320	68	31	82	62	0	0	0	0

”Wild type” MIC distributions

1. reference for **calibration of antimicrobial susceptibility testing methods**
2. to define **epidemiological cut-off values**
3. reference material for committees involved in decisions on **clinical breakpoints**
4. reference **MIC ranges** for a wide spectrum of species and antimicrobials
5. an opportunity to **measure** and **compare resistance** development in bacteria that lack breakpoints or are classified as naturally resistant (Enterococci vs. Gentamicin)

EUCAST procedure for setting breakpoints

Last updated 20-02-2005

1. Data on dosing, formulations, clinical indications and target organisms are reviewed and differences which might influence breakpoints are highlighted

National breakpoint committees

Dosage	BSAC UK	CA-SFM France	CRG Netherlands	DIN Germany	NWGA Norway	SRGA Sweden	
Most common dose	500 x 2 oral 400 x 2 iv	500 x 2 oral 200 x 2 iv	250 x 2 oral 200 x 2 iv	500 x 2 oral 200 x 2 iv	2-400 x 2 oral 400 x 2 iv	500 x 2 oral 400 x 2 iv	
Maximum dose schedule	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 2 iv	data pending	750 x 2 oral 400 x 3 iv	
Available formulations	oral, iv	oral, iv	oral, iv	oral, iv	oral, iv	oral, iv	

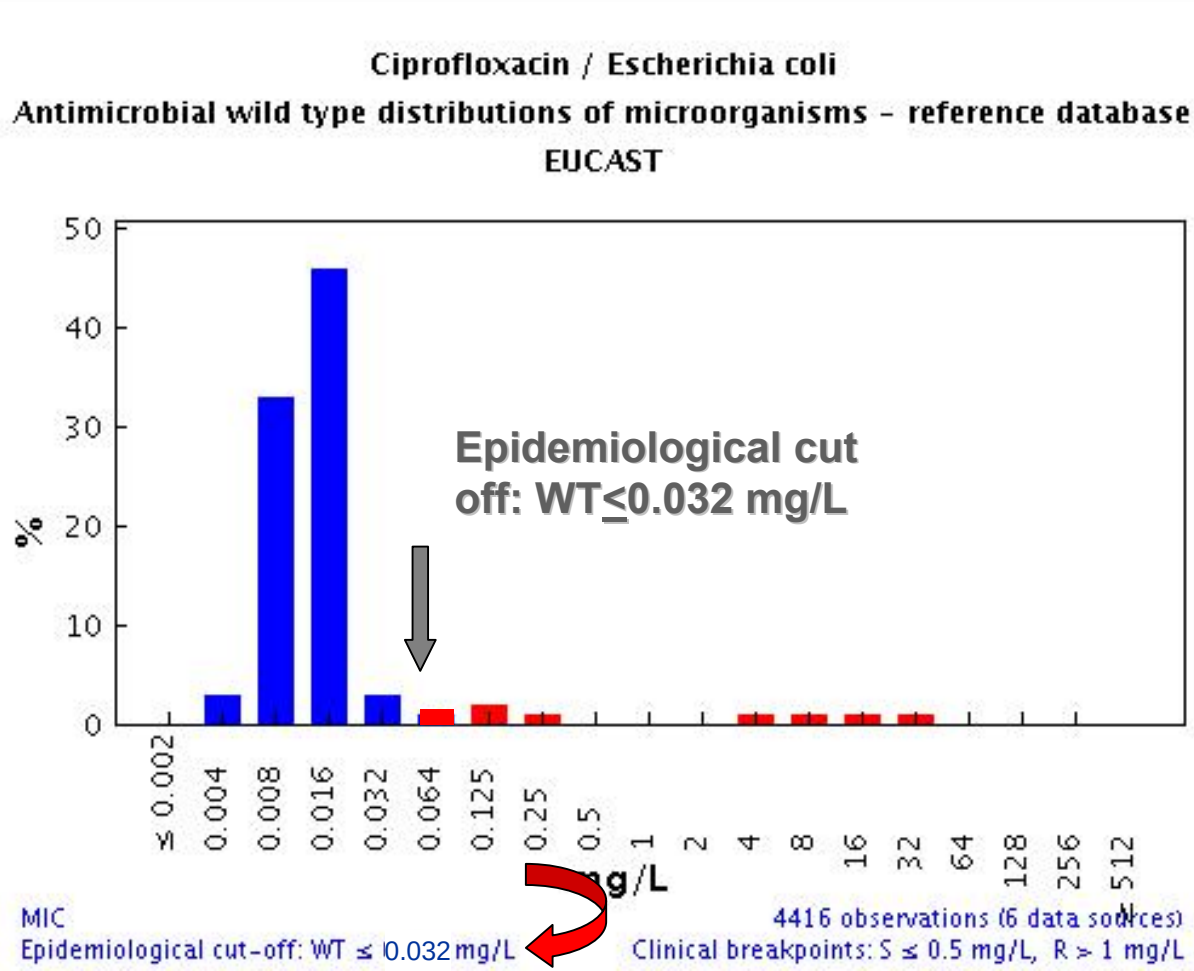
Clinical data

There is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by *Salmonellae* with low-level Fluoroquinolone resistance (MIC>0.064 mg/L) EUCAST has suggested that the epidemiological cut off value (S≤0.064/R>0.064 mg/L) be used in Salmonellae systemic infections. These strains are best found using a nalidixic acid 30 µg screen disc in routine susceptibility testing.

There is agreement in EUCAST that ciprofloxacin activity against Enterococci and Streptococci, including S.pneumoniae, is insufficient to categorize wild type bacteria “susceptible”.

Last updated 20-02-2005

2. Multiple MIC-distributions are collected, the wild type MIC distribution is defined and tentative epidemiological cut-off values determined (WT ≤X mg/L)



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3. Existing national clinical breakpoints are compared

Ciprofloxacin was used in this example:

Breakpoints prior to harmonisation (mg/L) S≤ R>							
	BSAC	**CA-SFM**	**CRG**	**DIN**	**NWGA**	**SRGA**	**NCCLS**
General breakpoints	**ND**	**1/2**	**1/2**	**1/2**	**0.125/2**	**1/2**	
Species related breakpoints		**not yet**		**no**			
Enterobacteriaceae	**1/1**				**0.12/2**	**0.12/1**	**1/2**
Pseudomonas spp.	**1/4**				**ND**	**1/1**	**1/2**
Acinetobacter spp.						**1/1**	**1/2**
Staphylococci	**1/1**				**0.12/2**	**0.06/2**	**1/2**
Streptococci	**1/1**	**excluded**			**0.12/2**	**0.12/2**	**excl**
S. pneumoniae	**2/2 (I)***	**excluded**			**0.12/2 (I)***	**0.12/2 (I)***	**excl**
Enterococci	**excluded**	**excluded**			**0.12/2**	**0.12/2**	**1/2**
Haemophilus/Moraxella spp.	**1/1**				**0.12/0.5**	**0.12/0.25**	**1/-**
Corynebacteria						**excl**	
N. Meningitidis	**1/1**				**0.06/0.12**	**0.03/0.25**	
N. Gonorrhoeae	**0.06/-**		**0.06/1**		**0.06/0.12**	**0.06/0.25**	**0.06/0.5**
P. Multocida	**ND**				**ND**	**0.12/0.25**	
Anaerobes	**excluded**				**ND**	**excluded**	
Campylobacter spp.	**1/1**						
Helicobacter pylori	**2/2**	**no**	**no**		**no**	**no**	

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4. Pharmacokinetic data are collected and evaluated

Pharmacokinetic data are collected from various sources, particularly data from patients. If the data allow it and if necessary, population pharmacokinetic models are developed.

These are necessary for pk/pd analyses, including Monte Carlo simulations

5. Pharmacodynamic data are evaluated

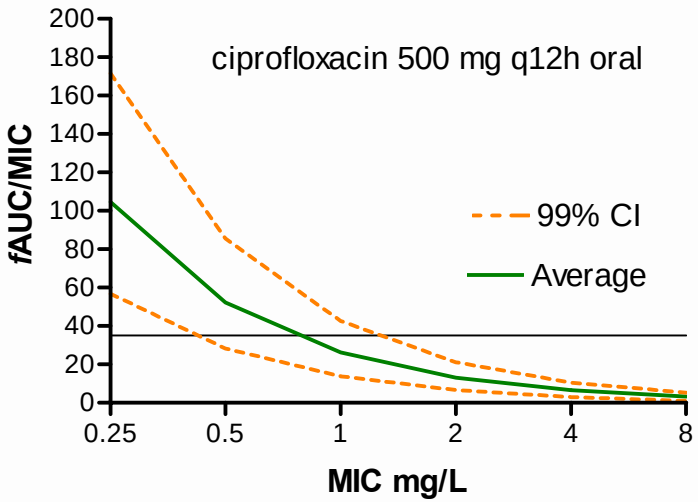
The Pk/Pd index value resulting in optimal outcome is determined from:

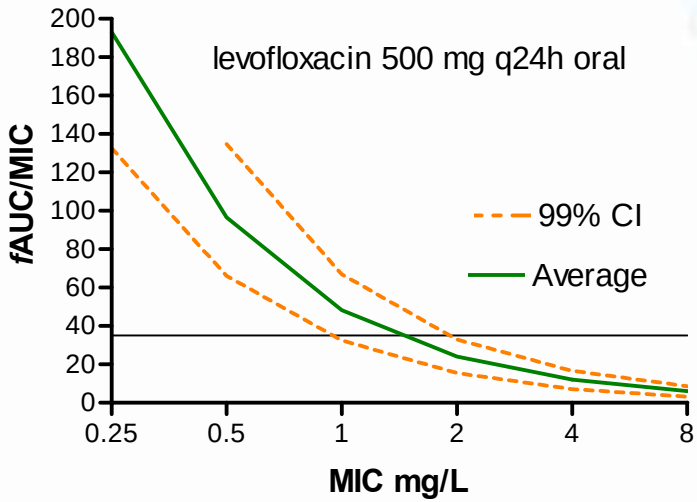
-in vitro data
-animal studies
-clinical trials

In each of the model systems, as well as results from clinical trials, Pk/Pd analyses are performed on outcome data if possible.
The efficacy of the drugs is assessed quantitatively.

Relationships between concentration time profiles and emergence of resistance are evaluated

6. Using available Pk/Pd data, Monte Carlo simulations are performed and a Pk/Pd breakpoint is calculated. It is based on conventional dosing regimens.





S = 0.5 mg/L Pk/Pd S = 1 mg/L

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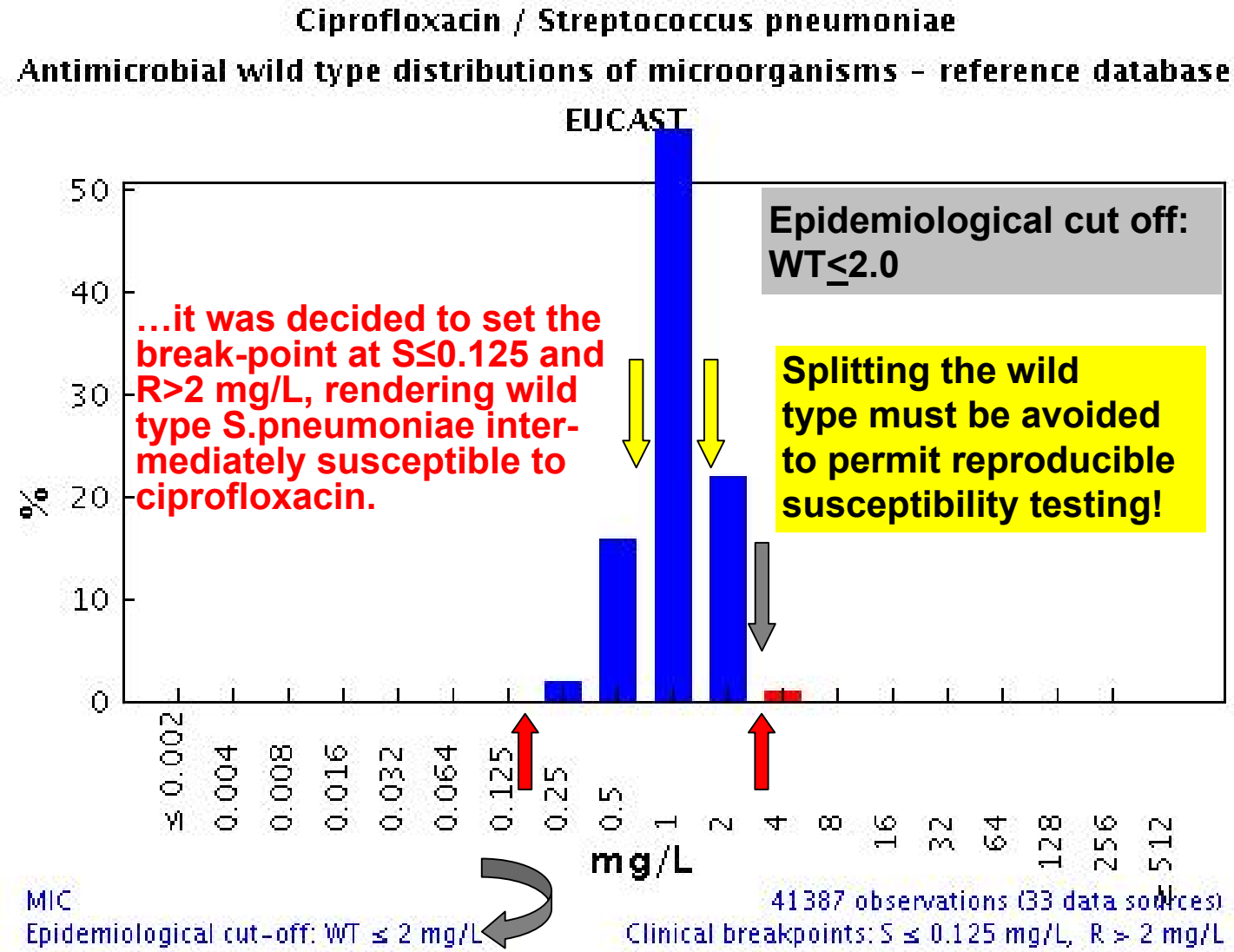
7. Clinical data relating outcome to MIC-values, wild type and resistance mechanisms are assessed in relation to the tentative breakpoint

”Minimum requirement for S-category” is that the upper value of the wild type MIC-distribution is ≤ the MIC derived from the Pk/Pd index needed for optimal efficacy based on free drug”.

8a. Pk/Pd breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type to obtain tentative breakpoints - example ciprofloxacin



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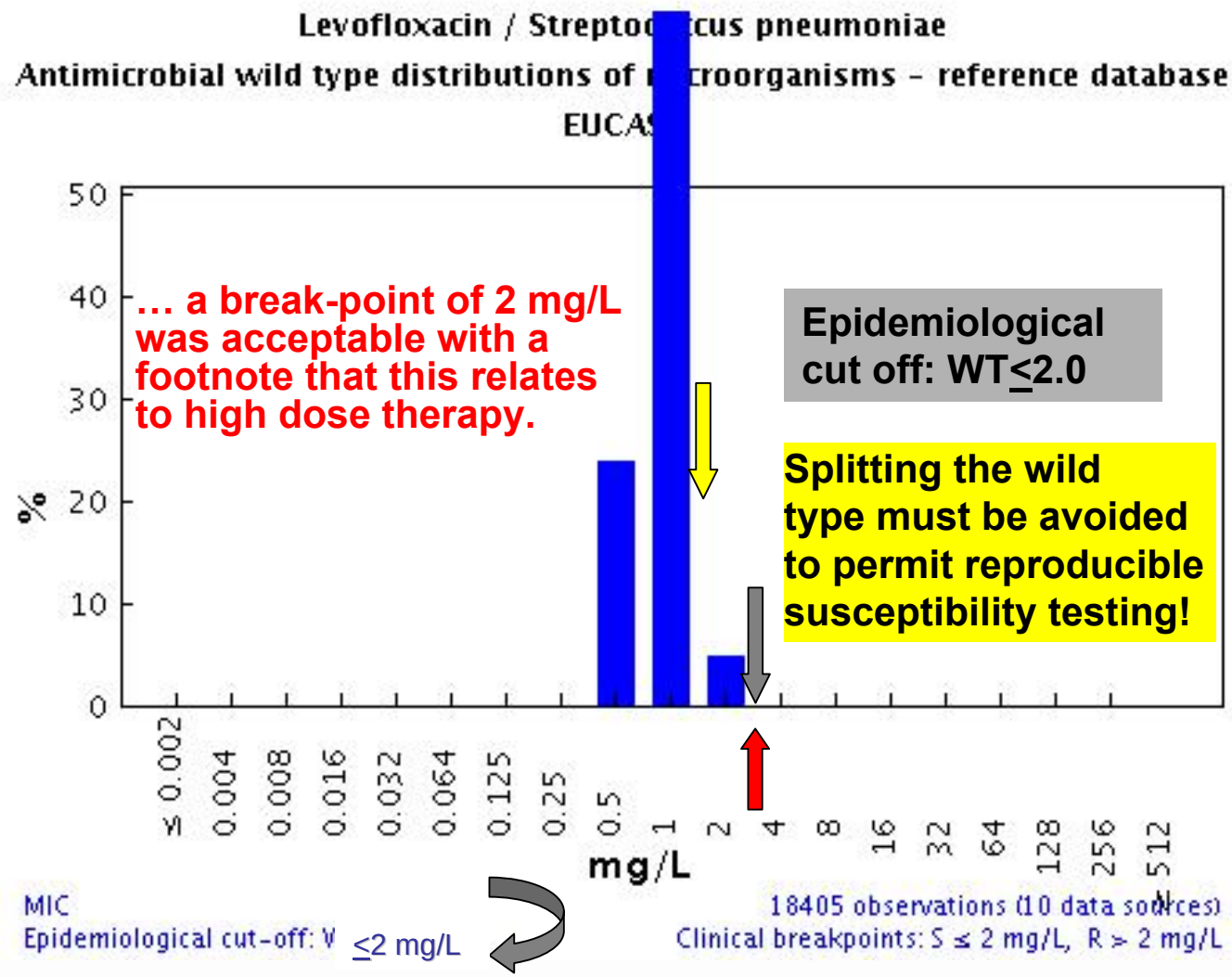
8b. Pk/Pd breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type to obtain tentative breakpoints - example levofloxacin



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9. Tentative breakpoints by the EUCAST Steering Committee are referred to the national breakpoint committees for (written) comments.
When steering committee and national committees agree the tentative breakpoints are subjected to the EUCAST consultation process:

10. Consultation process on tentative breakpoints:

- **EUCAST general committee**
- **Expert committees (Neisseria, Anaerobes, others)**
- **pharmaceutical industry, AST device manufacturers**
- **others via EUCAST website**

11 . Rationale document prepared and published on website

EUCAST breakpoint tables at www.eucast.org

Fluoroquinolones - EUCAST clinical MIC breakpoints 30 april 2004

Fluoroquinolone[1]	Species-related breakpoints (S≤/R>)											Non-species related breakpoints[7] S≤/R>
	Entero-bacteriace				*Entero-coccus*	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*[4]	*H.influenzae M.catarrhalis*[5]	*N.go hoe*			
Ciprofloxacin					--	--	0.125/2	0.5/0.5	0.03/0.06	0.06	--	0.5/1
Levofloxacin	1/2				--	1/2	2/2	1/1	IE	IE	--	1/2
Moxifloxacin	0.5/1				--	IE	0.5/0.5	0.5/0.5	IE	IE	IE	0.5/1
Norfloxacin	0.5/1				--	--	--	--	IE	--	--	0.5/1
Ofloxacin	0.5/1	--	--	1/1[3]		--	0.125/4	0.5/0.5	0.12/0.25	IE	--	0.5/1

Click on name to directly access MIC distributions

Insufficient evidence

"Dashed" – laboratories are recommended not to test against this species

1. For breakpoints for other fluoroquinolones (eg. **pefloxacin** and **e** to breakpoints determined by national breakpoint committees.
2. *Salmonella* spp - there is clinical evidence for ciprofloxacin to ind nence in systemic infections caused by *Salmonella* spp with low-level fluoroquinolone resistance (MIC>0.064 mg lso case reports of poor response with other *Salmonella* species.
3. *Staphylococcus* spp - breakpoints for cipr
4. *Streptococcus pneumoniae* - wild type *S.p* ofloxacin and are therefore categorized as intermediate. For ofloxacin the I/R breakpoint was increased rom 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints for levofloxac
5. *Haemophilus/Moraxella* - fluoroquinolone lo ay occur in *H.influenzae*. There is no evidence that low-level resistance is of clinical importance in resp egory was not defined since only few clinically resistant strains have been reported.
6. *Neisseria meningitidis* - breakpoints apply to the use of ciprofloxacin in the prophylaxis of meningococcal disease.
7. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or **IE** in the table).

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

Breakpoints finalised at EUCAST Steering committee meeting 2004 April 30.

EUCAST rationale document

Fluoroquinolones - EUCAST clinical MIC breakpoints 30 april 2004

Fluoroquinolone[1]	Species-related breakpoints (S≤/R>)								
	Entero-bacteriaceae[2]	*Pseudo-monas*[2]	*Acineto-bacter*	*Staphylo-coccus*	*Entero-coccus*	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*[4]	*H.influenzae M.catarrhalis*[5]	*N.g h*
Ciprofloxacin	0.5/1	0.5/1	1/1	1/1[3]	--	--	0.125/2	0.5/0.5	0.0
Levofloxacin	1/2	1/2	1/2	1/2	--	1/2	2/2	1/1	
Moxifloxacin	0.5/1	--	--	IE	--	IE	0.5/0.5	0.5/0.5	
Norfloxacin	0.5/1	--	--	--	--	--	--	--	
Ofloxacin	0.5/1	--	--	1/1[3]	--	--	0.125/4	0.5/0.5	0.1

1. For breakpoints for other fluoroquinolones (eg. **pefloxacin** and **enoxacin**) - refer to breakpoints determined by nation
2. *Salmonella* spp - there is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused fluoroquinolone resistance (MIC>0.064 mg/L). The available data relate mainly to *S.typhi* but there are also case repor species.
3. *Staphylococcus* spp - breakpoints for ciprofloxacin and ofloxacin relate to high dose therapy.
4. *Streptococcus pneumoniae* - wild type *S.pneumoniae* are not considered susceptible to ciprofloxacin or ofloxacin and ofloxacin the I/R breakpoint was increased from 1.0 to 4.0 mg/L and for levofloxacin the S/I-breakpoint from 1.0 to 2.0 distribution. The breakpoints for levofloxacin relate to high dose therapy.
5. *Haemophilus/Moraxella* - fluoroquinolone low-level resistance (ciprofloxacin MIC:s of 0.125 - 0.5 mg/L) may occur in *H.* resistance is of clinical importance in respiratory tract infections with *H.influenzae*. An Intermediate category was not

Aminoglycosides - EUCAST clinical MIC breakpoints 23 november 2004

Aminoglycosides[1]	Species-related breakpoints (S≤/R>)											Non-species related breakpoints[5] S≤/R>
	Enterobac-teriaceae	*Pseudo-monas*[2]	*Acineto-bacter*[2]	*Staphylo-coccus*	*Entero-coccus*[3]	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*	*H.influenzae M.catarrhalis*	*N.gonorr-hoeae*	*N.mening-itidis*	*Gram-negative anaerobes*	
Amikacin	8/16	8/16	8/16	8/16[4]	--	--	--	IE	--	--	--	8/16
Gentamicin	2/4	4/4	4/4	1/1	--	--	--	IE	--	--	--	2/4
Netilmicin	2/4	4/4	4/4	1/1	--	--	--	IE	--	--	--	2/4
Tobramycin	2/4	4/4	4/4	1/1	--	--	--	IE	--	--	--	2/4

1. The aminoglycoside breakpoints are based on modern once-daily administration of high aminoglycoside dosages. Most often aminoglycosides are given in combination with beta-lactam agents. For unlisted aminoglycosides refer to breakpoints determined by national breakpoint committees.
2. The S/I breakpoint has been increased from 2 to 4 mg/L for agents other than amikacin to avoid dividing the wild type MIC distribution. Thus there is no intermediate category for *Pseudomonas* species and *Acinetobacter* species.
3. *Enterococcus* spp - aminoglycoside monotherapy is ineffective against enterococci. There is synergism between aminoglycosides and betalactams in enterococci without acquired resistance mechanisms. There is no synergistic effect in enterococci with high level aminoglycoside resistance, i.e with gentamicin MIC>128 mg/L.
4. Resistance to amikacin and kanamycin is most reliably determined using kanamycin as test substance.
5. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -

recommended as the species is a poor target for therapy with the drug.
nce that the species in question is a good target for therapy with the drug.

Glycopeptides - EUCAST clinical MIC breakpoints 30 april 2004

Glycopeptides	Species-related breakpoints (S≤/R>)										
	Enterobac-teriaceae	*Pseudo-monas*	*Acineto-bacter*	*Staphylo-coccus*[1]	*Entero-coccus*	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*	*H.influenzae M.catarrhalis*	*N.gonorr-hoeae*	*N.mening-itidis*	*Gram-negative anaerobe*
Vancomycin	--	--	--	4/8	4/8	4/4	4/4	--	--	--	--
Teicoplanin	--	--	--	4/8	4/8	4/4	4/4	--	--	--	--

1. *Staphylococcus aureus* may be categorized as falsely susceptible to glycopeptides as glycopeptide MICs for strains with reduced susceptibilit the test conditions, in particular the medium used.

2. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recomr - or **IE** in the table).

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

Breakpoints finalised at EUCAST Steering committee meeting 2004 April 30.

EUCAST 2003 (The European Committee on Antimicrobial Susceptibility Testing)
Updated 2004-11-23, G Kahlmeter

Oxazolidinones - EUCAST clinical MIC breakpoints 30 april 2004

Oxazolidinone	Species-related breakpoints (S≤/R>)											Non-species related breakpoints[2]
	Enterobac-teriaceae	*Pseudo-monas*	*Acineto-bacter*	*Staphylo-coccus*[1]	*Entero-coccus*[1]	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*	*H.influenzae M.catarrhalis*	*N.gonorr-hoeae*	*N.mening-itidis*	*Gram-negative anaerobes*	
Linezolid	--	--	--	4/4	4/4	2/4	2/4	--	--	--	--	2/4

1. The S/I-breakpoint has been increased from 2.0 to 4.0 mg/L to avoid dividing wild type MIC-distributions. Hence there is no intermediate category.

2. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with - - or **IE** in the table).

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

Breakpoints finalised at EUCAST Steering committee meeting 2004 April 30.

EUCAST 2003 (The European Committee on Antimicrobial Susceptibility Testing)
Updated 2004-12-11, G Kahlmeter

Last updated 20-02-2005

Carbapenems - EUCAST clinical MIC breakpoints 23 november 2004

Carbapenem	Species-related breakpoints (S≤/R>)											Non-species related breakpoints[6] S≤/R>
	Enterobac-teriaceae	*Pseudo-monas*	*Acineto-bacter*	*Staphylo-coccus*[1]	*Entero-coccus*[2]	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*	*H.influenzae M.catarrhalis*	*N.gonorr-hoeae*	*N.mening-itidis*	*Gram-negative anaerobes*	
Ertapenem												
Imipenem												
Meropenem												

1. Methicillin resis
2. Except for activ
3. *Proteus* and *Mo*
4. Ertapenem S/I- strains.
5. Meropenem bre
6. Non-species re use only for sp - or **IE** in the ta

-- = Susceptibility tes
IE = There is insufficie

Status:
Preliminary breakpo
Open for consultatio

To be finalised March

Breakpoints finalised

Cephalosporins - EUCAST clinical MIC breakpoints 18 februari 2005

Cephalosporins	Species-related breakpoints (S≤/R>)											Non-species related breakpoints[6] S≤/R>
	Enterobac-teriaceae[1]	*Pseudo-monas*	*Acineto-bacter*	*Staphylo-coccus*[2]	*Entero-coccus*	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*	*H.influenzae M.catarrhalis*	*N.gonorr-hoeae*[5]	*N.mening-itidis*	*Gram-negative, anaerobes*	
Cefuroxime												
Cefotaxime												
Ceftriaxone												
Ceftazidime												
Cefepime												
Cefalothin												
Cefalexin												
Cefoxitin												
Cefazolin												
Cefaclor												
Cefixime												
Cefuroxime-axetil												
Cefpodoxime												

1. Susceptible breakpoin
2. Methicillin resistant st
3. Isolates in this catego resistance mechanism
4. The intermediate cate
5. Neisseria gonorrhoeae
6. Non-species related b use only for species th - or **IE** in the table).

-- = Susceptibility testing no
IE = There is insufficient evid

Status: Preliminary breakp

Aztreonam - EUCAST clinical MIC breakpoints 23 november 2004

Aztreonam	Species-related breakpoints (S≤/R>)											Non-species related breakpoints[3] S≤/R>
	Enterobac-teriaceae[1]	*Pseudo-monas*[2]	*Acineto-bacter*	*Staphylo-coccus*	*Entero-coccus*	*Strepto-coccus*	*S.pneu-moniae*	*H.influenzae M.catarrhalis*	*N.gonorr-hoeae*	*N.mening-itidis*	*Gram-negative anaerobes*	
Aztreonam	1											2/8

1. Enterobacteriaceae - the S/I breakpoint was decreased to 1 mg/L so as not to miss ESBLs
2. Pseudomonas
3. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or **IE** in the table).

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

Status:
Preliminary breakpoints by EUCAST 2004-11-23;
Open for consultation with national breakpoint committees.
Breakpoints to be finalised March 2005.

Breakpoints finalised at EUCAST Steering committee meeting YEAR-MONTH-DAY.

EUCAST 2004 (The European Committee on Antimicrobial Susceptibility Testing)
Updated 2004-11-23, G Kahlmeter

Ongoing breakpoint harmonisation

Last updated 20-02-2005

How to implement EUCAST breakpoints

- The national breakpoint committees have committed themselves to implementing EUCAST breakpoints – which means that anyone using one of the European national systems will gradually adhere to the European breakpoints
- Breakpoints as presented in EUCAST tables can be directly applied to MIC distributions (local and national surveillance, EARSS, etc)
- Systems for automated susceptibility testing can be set up with EUCAST MIC breakpoints.
- Through an agreement between EMEA, EFPIA and EUCAST new antimicrobials will be given breakpoints through EUCAST as part of the registration process. The SPC for these drugs will contain only EUCAST breakpoints.

EUCAST future activity

- Cephalosporin, carbapenem and aztreonam breakpoints to be completed during 2005
- Commence work 2005 on harmonising penicillin breakpoints
- EMEA SOP for registration of new drugs implemented for 2 new antibacterial drugs
- Rationale documents for breakpoints extended and made available on the website (links from the breakpoint tables)
- Documents for update
- EUCAST/EARSS Workshop in Rome
  - 23-25th of November, 2005

EUCAST

Thank you