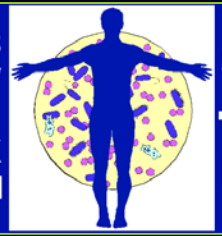


Société belge d'infectiologie et de microbiologie clinique

Belgische vereniging voor infectiologie en klinische microbiologie

30th Symposium : What will change in your daily practice with the new
Elewijt, 26-05-2008 EUCAST breakpoints for antibiotic susceptibility testing

European breakpoints and EUCAST – what next?

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

www.eucast.org

Gunnar Kahlmeter

Chairman of EUCAST 2001 -

Clinical microbiology
Central Hospital
351 85 Växjö

EUCAST

- Organisation, subcommittees and finances
- Clinical breakpoints
- Epidemiological cutoffs
- EUCAST vs. CLSI
- Future
  - Implementation - disk testing
    - Current disk tests (BSAC, CA-SFM, SRGA)
    - EUCAST Disk Test
  - Implementation - automated AST systems
  - EUCAST and the future

Organisation, subcommittees and finances

Structure of EUCAST

Steering Committee

Representatives from National breakpoint committees and the general committee

General Committee

Representatives from all European countries

Expert consultation network

Neisseria gonorrhoeae, Neisseria meningititids, Anaerobe bacteria etc

Subcommittees on Antifungals, Anaerobes, Expert rules, (Mycobacteria)

Industry consultation network

Pharmaceutical and AST-industry

EUCAST Steering Committee Membership

• Chairperson	Gunnar Kahlmeter	2008 -
• Scientific Secretary	Derek Brown	2008 -
• Clinical data coordinator	Rafael Canton	2008 -
BSAC (The UK)	Alasdair MacGowan	2008 -
CA-SFM (France)	F Goldstein, CJ Soussy	2008 -
CRG (The Netherlands)	Johan W. Mouton	2008 -
DIN (Germany)	Arne Rodloff	2008 -
NWGA (Norway)	Martin Steinbakk	2008 -
SRGA (Sweden)	I Odenholt, C Giske	2008 -
• General Committee rep*	Paul Tulkens (ISC)	2008 - 10
• General Committee rep*	Antti Hakkanen (Finland)	2008 - 10

Previously: Czech republic, Greece, Spain, Russia. Poland & Italy

EUCAST General Committee 2006

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 M Ivanova
Finland Dr Antti Hakkanen
France Dr Luc Dubreuil
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
Latvia Dr Arta Balode
Lithuania Prof Arvydsa Ambrozaitis
Netherlands Prof John Degener
Norway Dr Martin Steinbakk
Poland Prof Waleria Hryniewicz
Portugal Prof Jose Melo Cristino
Romania no official 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 official representative

ISC – Prof Paul Tulkens
FESCI – Dr David Livermore

Email network of industry with interest in antimicrobials

Chairperson Gunnar Kahlmeter, Sweden
Scientific Secretary Derek Brown, UK
Clinical coordinator Rafael Canton, ES

EUCAST Subcommittees

- EUCAST AFST
  - GC and SC
  - Breakpoints for Candida spp in EMEA SPC (fluconazole finalised, itra- and voriconazole, caspofungin 2008)
- EUCAST Anaerobe Subcommittee
- Expert Rules Subcommittee (final report 2008)
- …

EUCAST finances

- ESCMID: 40 – 100 %
- EU: Grant 60 % for 3 years (from 2004)
- ECDC – 7 months 2007
- ECDC* – long contract (2008 -)

*ECDC has been asked by European heads of national institutes to prioritise European harmonised breakpoints as No 2.

EUCAST compared with CLSI

- Committee representing the Profession and Science with input from Regulatory.

- Proactive
- Industry consultative role

- Consensus process with the profession as drivers

- Five meetings per year
- EUCAST functions as the breakpoint committee of EMEA
- Transparent, rationale documents provided

- Documents for free!

- Clinical breakpoints and epidemiological cut-offs

- Committee representing Industry, Professionals and Regulatory

- Reactive
- Industry major influence on decision process
- Voting by committee members; several from industry; process stalled by FDA regulations.
- Two meetings per year
- No agreement between CLSI and FDA
- No published rationale for decisions

- Documents for sale

- Clinical breakpoints

EUCAST
Clinical breakpoints

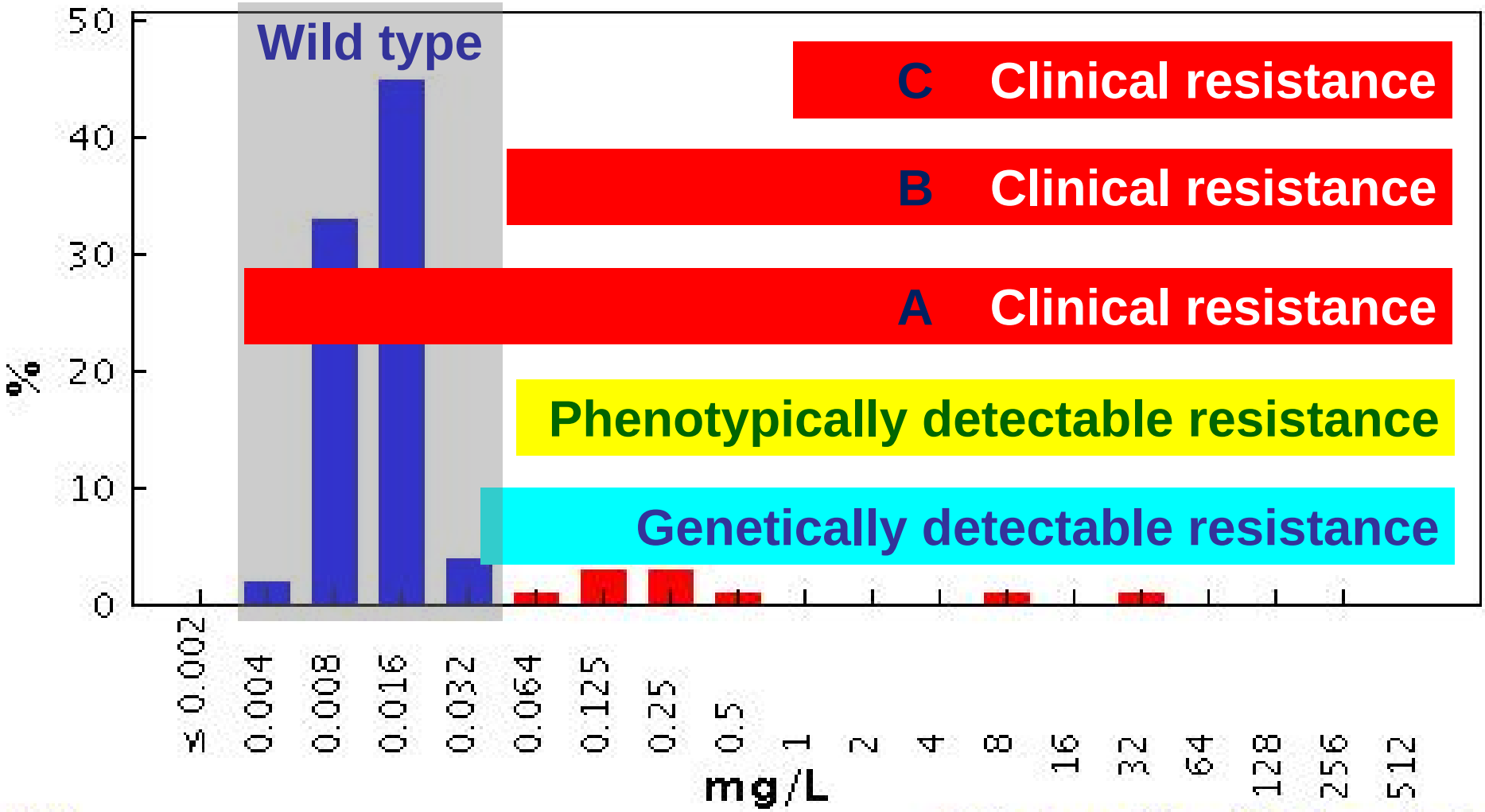
EUCAST has tried to device a system of clinically relevant breakpoints which shall not need supplementary testing* to categorise bacteria S, I or R for relevant antibiotics.

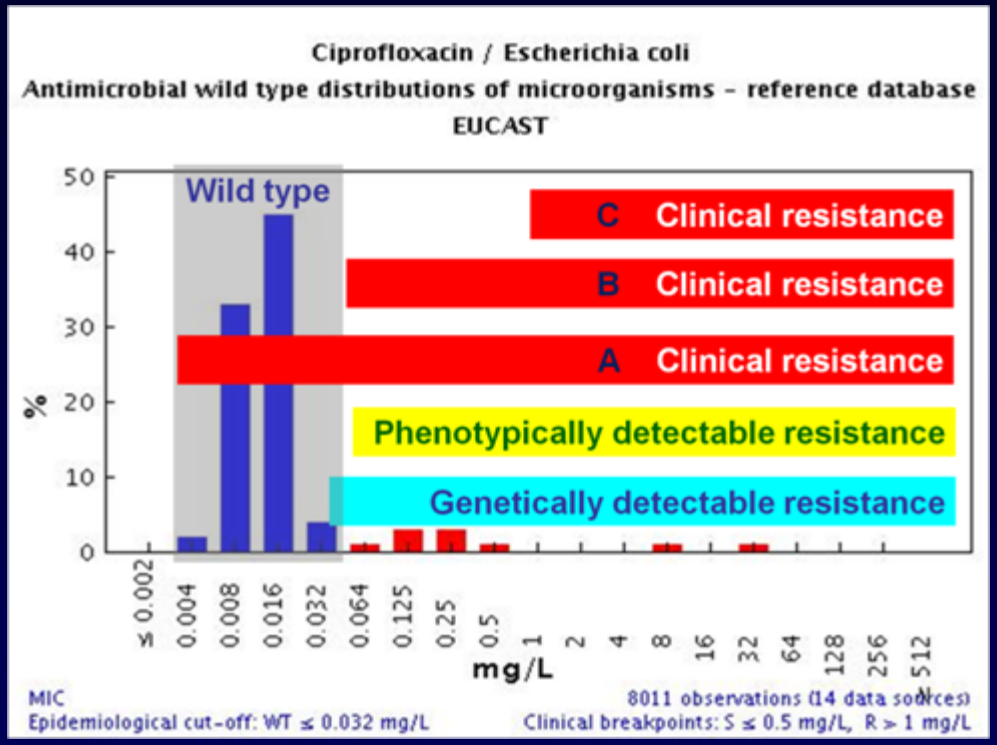
*supplementary testing – special tests needed when breakpoints fail to detect resistance mechanisms of clinical importance.

Breakpoint setting in a nutshell.....

Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms – reference database EUCAST



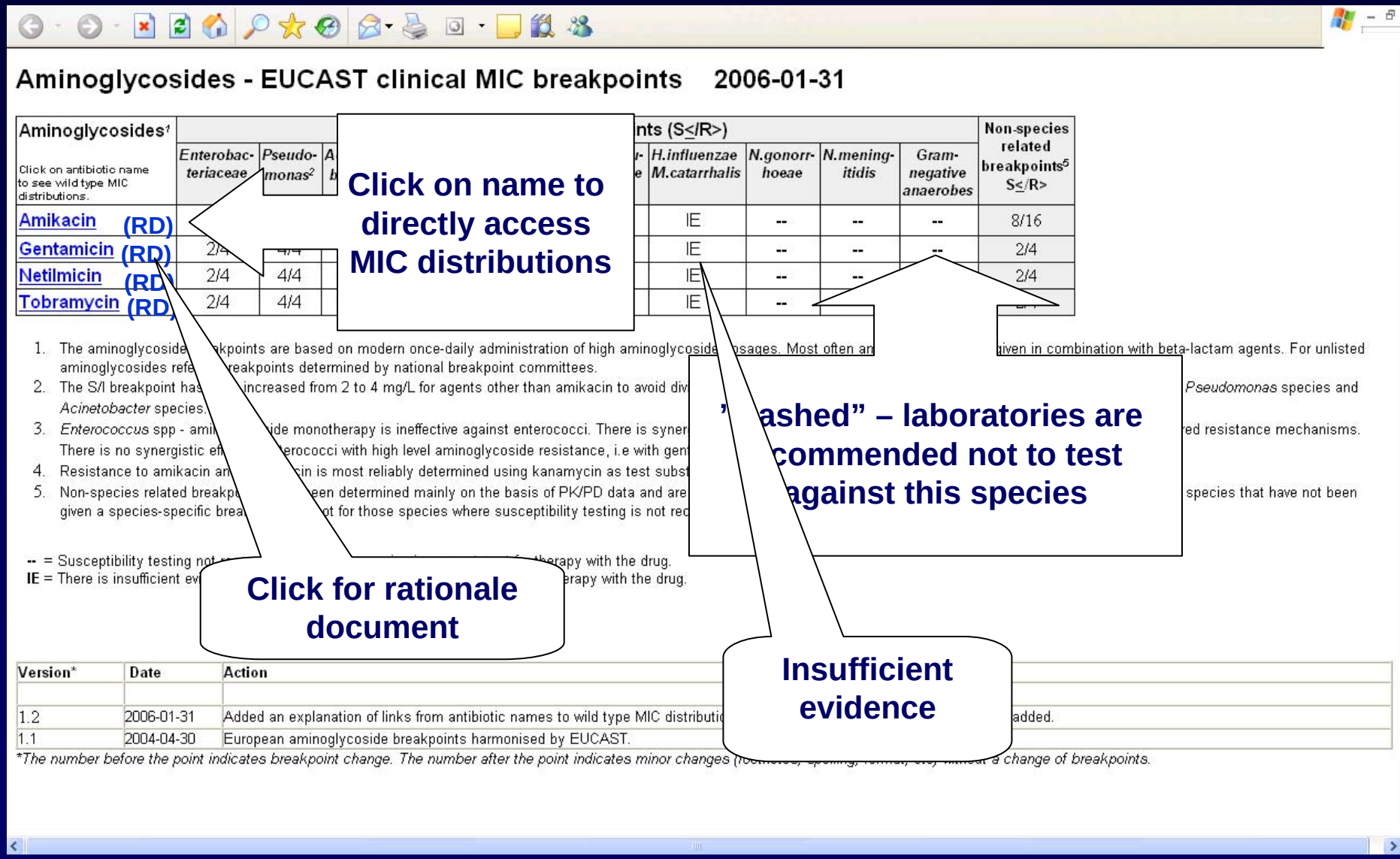


A. Gentamicin and Enterococcus spp (WT=R, no S- or I-category possible)
B. Ciprofloxacin and Salmonella spp (WT=S)
   Ciprofloxacin and S.pneumoniae (WT=I)
C. Ciprofloxacin and Enterobcteriaceae (WT=S)

To determine clinical breakpoints

- Dose or doses
- Target organisms
- MIC-distributions for target organisms
- Resistance mechanisms in target organisms
  - Mechanism rules: S.aureus and betalactamase
  - MIC rules: Enterobacteriaceae and ESBL
  - Uncertain: K.pneumoniae carbapenemase
- Target infections (approved indications)
- Pharmacokinetics (Cmax, T½, Protein binding, Vd etc)
- Pharmacodynamic properties (peak/MIC, AUC/MIC) for target organisms
- Toxicity
- Clinical outcome (clinical outcome/MIC)

EUCAST breakpoint tables available at http://www.eucast.org



Aminoglycosides - EUCAST clinical MIC breakpoints 2006-01-31

Aminoglycosides[1] Click on antibiotic name to see wild type MIC distributions.	Enterobacteriaceae	Pseudomonas[2]	A b	H.influenzae M.catarrhalis	N.gonorrhoeae	N.meningitidis	Gram-negative anaerobes	Non-species related breakpoints[5] S≤/R>
	nts (S≤/R>)							
Amikacin (RD)				IE	--	--	--	8/16
Gentamicin (RD)	2/4	4/4		IE	--	--	--	2/4
Netilmicin (RD)	2/4	4/4		IE	--	--		2/4
Tobramycin (RD)	2/4	4/4		IE	--			

1. The aminoglycoside kpoints are based on modern once-daily administration of high aminoglycoside osages. Most often an given in combination with beta-lactam agents. For unlisted aminoglycosides refe reakpoints determined by national breakpoint committees.
2. The S/I breakpoint has increased from 2 to 4 mg/L for agents other than amikacin to avoid div *Pseudomonas* species and *Acinetobacter* species.
3. *Enterococcus* spp - ami ide monotherapy is ineffective against enterococci. There is syner ed resistance mechanisms. There is no synergistic ef erococci with high level aminoglycoside resistance, i.e with gent
4. Resistance to amikacin ar cin is most reliably determined using kanamycin as test subst
5. Non-species related breakp een determined mainly on the basis of PK/PD data and are species that have not been given a species-specific brea ot for those species where susceptibility testing is not rec

-- = Susceptibility testing not r herapy with the drug.
IE = There is insufficient ev erapy with the drug.

Version*	Date	Action
1.2	2006-01-31	Added an explanation of links from antibiotic names to wild type MIC distributi added.
1.1	2004-04-30	European aminoglycoside breakpoints harmonised by EUCAST.

**The number before the point indicates breakpoint change. The number after the point indicates minor changes (footnotes, spelling, format, etc) without a change of breakpoints.*

Click on name to directly access MIC distributions

"ashed" – laboratories are commended not to test against this species

Click for rationale document

Insufficient evidence

Finalised 2004-2005

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*
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[6] 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 recomm - 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

Finalised 2006

EUCAST clinical MIC breakpoints - cephalosporins - Microsoft Internet Explorer erhållet av Landstinget Kronoberg

Arkiv Redigera Visa Favoriter Verktyg Hjälp

Adress http://www.srga.org/eucastwt/MICTAB/MICcephalosporins.html

Cephalosporins - EUCAST clinical MIC breakpoints 2006-03-31 (v 1.1)

Cephalosporins Click on antibiotic name to see wild type MIC distributions.		Species-related breakpoints (S≤/R>)											Non-species related breakpoints[1] S≤/R>
		Enterobacteriaceae[2]	*Pseudomonas*[3]	*Acinetobacter*	*Staphylococcus*[4]	*Enterococcus*	*Streptococcus A,B,C,G*	*S.pneumoniae*	*H.influenzae M.catarrhalis*	*N.gonorrhoeae*	*N.meningitidis*	*Gram-negative, anaerobes*	
Cefazolin	RD	--	--	--	note[4]	--	--	--	--	--	--	--	1/2
Cefepime	RD	1/8	8/8	--	note[4]	--	0.5/0.5[6]	1/2	0.25/0.25[6]	--	--	--	4/8
Cefotaxime	RD	1/2	--	--	note[4]	--	0.5/0.5[6]	0.5/2[6]	0.12/0.12[6]	0.12/0.12[6]	0.12/0.12[6]	--	1/2
Ceftazidime	RD	1/8	8/8	--	--	--	--	--	--	--	--	--	4/8
Ceftriaxone	RD	1/2	--	--	note[4]	--	0.5/0.5[6]	0.5/2[6]	0.12/0.12[6]	0.12/0.12[6]	0.12/0.12[6]	--	1/2
Cefuroxime	RD	8/8[5]	--	--	note[4]	--	0.5/0.5[6]	0.5/1	1/2	--	--	--	4/8

1. Non-species related breakp
species where susceptibili
2. The cephalosporin breakpo
these breakpoints. Laborat
3. For cefepime and ceftazidi
4. Susceptibility of staphyluc
5. The non-species related S/
only.
6. Strains with MIC values ab
evidence regarding clinical

-- = Susceptibility testing not
IE = There is insufficient evider
RD = rationale document listin

Version*	Date	A
1.1	2006-05-17	
1.0	2006-03-31	

*The number before the point ind

Klar

Start

EUCAST clinical MIC breakpoints - carbapenems - Microsoft Internet Explorer erhållet av Landstinget Kronoberg

Arkiv Redigera Visa Favoriter Verktyg Hjälp

Adress http://www.srga.org/eucastwt/MICTAB/MICcarbapenems.html

Carbapenems - EUCAST clinical MIC breakpoints 2006-06-20 (v 1.1)

Carbapenem Click on antibiotic name to see wild type MIC distributions		Species-related breakpoints (S≤/R>)											Non-species related breakpoints[1] S≤/R>
		Enterobacteriaceae	*Pseudomonas*	*Acinetobacter*	*Staphylococcus*	*Enterococcus*	*Streptococcus A,B,C,G*	*S.pneumoniae*	*H.influenzae M.catarrhalis*	*N.gonorrhoeae*	*N.meningitidis*	*Gram-negative anaerobes*	
Ertapenem	RD	0.5/1	--	--	note[3]	--	0.5/0.5[4,7]	0.5/0.5[4,7]	0.5/0.5[4,7]	IE	--	1/1[8]	0.5/1
Imipenem	RD	2/8[2]	4/8[6]	2/8	note[3]	4/8[6]	2/2[4,7]	2/2[4,7]	2/2[4,7]	IE	--	2/8	2/8
Meropenem	RD	2/8	2/8	2/8	note[3]	--	2/2[4,7]	2/2[4,7]	2/2[4,7]	IE	0.25/0.25[6,7]	2/8	2/8

1. Non-species related b
species where suscep
2. *Proteus* and *Morganell*
3. Susceptibility of staph
4. Imipenem and ertapen
5. Meropenem breakpoin
6. The imipenem S/I brea
7. Strains with MIC value
regarding clinical resp
8. The ertapenem S/I bre

-- = Susceptibility testing
IE = There is insufficient e
RD =Rationale document li

Version*	Date
1.1	2006-06-2
1.0	2006-03-3

*The number before the point

Klar

Start

EUCAST clinical MIC breakpoints - aztreonam - Microsoft Internet Explorer erhållet av Landstinget Kronoberg

Arkiv Redigera Visa Favoriter Verktyg Hjälp

Adress http://www.srga.org/eucastwt/MICTAB/MICaztreonam.html

Aztreonam - EUCAST clinical MIC breakpoints 2006-06-20 (v 1.2)

Aztreonam Click on antibiotic name to see wild type MIC distributions		Species-related breakpoints (S≤/R>)										Non-species related breakpoints[1] S≤/R>
		Enterobacteriaceae[2]	*Pseudomonas*	*Acinetobacter*	*Staphylococcus*	*Enterococcus*	*Streptococcus A,B,C,G*	*S.pneumoniae*	*H.influenzae M.catarrhalis*	*N.gonorrhoeae*	*N.meningitidis*	*Gram-negative anaerobes*	
Aztreonam	RD	1/8	1/16[3]	--	--	--	--	--	IE	IE	--	--	4/8

1. 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).
2. The aztreonam breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some strains that produce ESBLs appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.
3. The I/R-breakpoint for aztreonam in Pseudomonas aeruginosa was increased to avoid dividing the MIC wild type distribution. The I/R-breakpoint relates to high dose therapy.

-- = 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.
RD = rationale document listing data used by EUCAST for determining breakpoints.

Version*	Date	Action
1.2	2006-06-20	*This table rearranged in reversed chronological order*
1.1	2006-06-12	*Footnote 2, amended to include intermediate.*
1.0	2006-03-31	*Released by EUCAST*

**The number before the point indicates breakpoint change. The number after the point indicates minor changes (footnotes, spelling, format, etc) without a change of breakpoints.*

Finalised 2007

Adress Q:\Raf\Eucast\MICTAB\MICpenicillins.html

Penicillins - EUCAST clinical MIC breakpoints 2007-03-02 (version 0.6)

Penicillins (iv) Click on antibiotic name to see wild type MIC distributions.	Species-related breakpoints (S≤/R>)												Non-species related breakpoints[18] S≤/R>
	Enterobacteriaceae[3]	*Pseudomonas*	*Acinetobacter*[7]	*Staphylococcus*[8]	*Enterococcus*	*Streptococcus A,B,C,G*[12]	*S.pneumoniae*	*H.influenzae M.catarrhalis*	*N.gonorrhoeae*	*N.meningitidis*	*Gram-negative, anaerobes*	*Gram-positive, anaerobes*	
Benzylpenicillin	--	--	--	0.12/0.12[8]	Note[10]	0.25/*0.25*[13]	0.06/1[A]	IE[16]	0.06/1[16]	0.06/0.25	0.25/0.5	0.25/0.25	0.25/1
Ampicillin[D]													
Ampicillin oral													
Ampicillin/sulbactam[1]													
Amoxicillin													
Amoxicillin oral													
Amoxicillin/clavulanate[1]													
Amoxicillin/clavulanate oral													
Piperacillin													
Piperacillin/tazobactam[1]													
Ticarcillin													
Ticarcillin/clavulanate[1]													
Phenoxymethylpenicillin													
Pivmecillinam													
Oxacillin[2]													
Cloxacillin													
Dicloxacillin													
Flucloxacillin													

[A] It was agreed to discus
one hand and ampicillin a
[B] Penicillin susceptible is
[C] Ampicillin/amoxicillin su
[D] Ampicillin is active agai

1. For susceptibility t
2. For susceptibility t
3. *Klebsiella* spp and
4. For systemic infec
and some isolates
5. Pivmecillinam brea
6. Piperacillin and tic
7. Penicillin susceptil
8. Most staphylococ
producers.
9. Susceptibility of st
10. For *Enterococcus*
11. Aminopenicillin br
international endoc
12. For viridans strept
13. Strains with MIC v
evidence regarding

EUCAST clinical MIC breakpoints - macrolides - Microsoft Internet Explorer erhållet av Landstinget Kronoberg

Arkiv Redigera Visa Favoriter Verktyg Hjälp

Adress Q:\Raf\Eucast\MICTAB\MICmacrolides.html

Macrolides, lincosamides, streptogramins - EUCAST clinical MIC breakpoints 2007-01-31 (v 0.4)

Macrolide Click on antibiotic name to see wild type MIC distributions		Species-related breakpoints (S≤/R>)												Non-species related breakpoints[1]
		Enterobacteriaceae	*Pseudomonas*	*Acinetobacter*	*Staphylococcus*	*Enterococcus*	*Streptococcus*	*S.pneumoniae*	*H.influenzae*	*M.catarrhalis*	*N.gonorrhoeae*	*N.meningitidis*	*Gram-negative*	*Gram-positive*	
Azithromycin	RD	Note[4]	--	--											
Clarithromycin[2]	RD	--	--	--											
Erythromycin[3]	RD	Note[4]	--	--											
Josamycin	RD	--	--	--											
Roxithromycin	RD	--	--	--											
Telithromycin	RD	--	--	--											
Clindamycin	RD	--	--	--											
Quinupristin/Dalfopristin	RD	--	--	--											

1. Non-species related breakpoints have been determined not been given a species-specific breakpoint and not for
2. Clarithromycin is used for the eradication of *H. pylori* an
3. Erythromycin administered intravenously is active again mg/L).
4. Azithromycin is used in the treatment of *S. typhi* (S≤1 respective wild type distributions (strains without any re
5. Inducible clindamycin resistance can only be detected i
6. Erythromycin MIC values of 1-16 mg/L are typical for wi are not given.
7. Erythromycin is no longer used in the therapy of *N. gon*
8. Quinopristin/dalfopristin breakpoints for *Enterococcus* s
9. Pharmacodynamic data for calculation of non-species r

-- = Susceptibility testing not recommended as the species
IE = There is insufficient evidence that the species in questi
RD = Rationale document listing data used for setting EUCA

Version*	Date	Action
0.5	2007-03-01	Preliminary table followin introduction of epidemiol
0.4	2007-01-30	Preliminary table after the EU
0.3	2006-11-21	Preliminary table after the EU
0.2	2006-09-09	Preliminary table for discussic
0.1	2006-04-06	Preliminary table for discussic

*The number before the point indicates breakpoint change. The

Miscellaneous antimicrobials - EUCAST clinical MIC breakpoints 2007-05-14 (v 0.2)

Wild type MIC distributions of bacteria and epidemiological cut-off values for measurement of resistance development.

Antimicrobial	Species-related breakpoints (S≤/R>)												Non-species related breakpoints
	Enterobacteriaceae	*Pseudomonas*	*Acinetobacter*	*Staphylococcus*	*Enterococcus*	*Streptococcus*	*S.pneumoniae*	*H.influenzae M.catarrhalis*	*N.gonorrhoeae*	*N.meningitidis*	Gram+ *anaerobe bacteria*	*Gram-anaerobe bacteria*	
Doxycycline	note[2]	--	--	1/2	--	1/2	1/2	1/2	1/2	--	?	?	IE
Tetracycline[4]	0.25/4	--	--	1/2	--	1/2	1/2	1/2	1/2	--	?	?	IE
Minocycline	0.25/4[3]	--	IE	0.5/0.5	--	0.5/0.5	0.5/0.5	?	?	1/2[5]	?	?	IE
Fusidic acid	--	--	--	0.5/1	--	--	--	--	--	--	--	--	IE
Chloramphenicol	8/8	--	--	8/8	--	8/8	8/8	1/2	--	2/4	?	?	IE
Rifampicin	--	--	--	0.06/1	--	0.06/1	0.06/1	1/1[5]	--	0.5/1[5]	--	--	IE
Nitrofurantoin[7]	64/64	--	--	64/64	64/64	64/64	--	--	--	--	--	--	IE
Trimethoprim[7]	2/4	--	--	2/4	0.032/1[8]	--	--	--	--	--	--	--	IE
Trimethoprim-sulfamethoxazole (co-trimoxazole)[9]	2/4[9]	-- *Note*[10]	2/4[9]	2/4[9]	0.032/1[8,9]	1/2[9]	1/2[9]	0.5/1[9]	--	--	--	--	IE
Fosfomycin iv	?		--				IE	IE	--	--	--	--	IE
Fosfomycin-trometamol	8/128	--	--	--	--	--	--	--	--	--	--	--	IE
Colistin	2/4	4/4	2/4	-	-	-	-	-	-	-	-	-	IE
Metronidazole[11]	-	-	-	-	-	-	-	-	-	-	4/4	4/4	--

1. Non-species related breakpoints are 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 susceptibility testing is not recommended (marked with -- or IE in the table).
2. Doxycycline susceptibility is best determined using tetracycline.
3. Microorganisms susceptible to tetracycline are also susceptible to doxycycline and minocycline. Some staphylococci, streptococci and H.influenzae resistant to tetracycline may be susceptible to minocycline.
4. Tetracyclines are used in the treatment of brucellosis (MIC of wild type distributions:), *Pasteurella multocida* breakpoints for tetracycline is 2/4 mg/L. *Yersinia pestis* ( ), *Yersinia enterocolitica* ( ) and *Burkholderia pseudomallei*.
5. For prophylaxis only. Refer to national guidelines for prophylaxis of bacterial meningitis.
7. For urinary tract infections only.
8. Enterococcus - find some more MIC-distributions.
9. Trimethoprim concentration in the presence of sulfamethoxazole in the ratio 1:19.
10. Trimethoprim-sulfamethoxazole (co-trimoxazole) breakpoint 4/4 mg/L for *Stenotrophomonas maltophilia* only (see 9).
11. Metronidazole is used for the treatment of Helicobacter pylori infections. The breakpoint is 4/4 mg/L.

Klar

Start 6 Microsoft Outlook

Den här datorn

Penicillins - EUCAST clinical MIC breakpoints 2008-05-12 (ve

Finalised 2008

Penicillins Click on antibiotic name to see wild type MIC distributions.		Species-relate														Non-species related breakpoints[M] S≤/R>
		Enterobac-teriaceae[A]	*Pseudo-monas*[B]	*Acineto-bacter*[C]	*Staphylo-coccus*[D]	*Entero-coccus*[E]	*Strepto-coccus A,B,C,G*[F]	*Viridans-strepto-cocci*[G]	*S.pneu-moniae*[H]	*H.influ-enzae*[I]	*M.catarr-halis*[J]	*N.gonor-hoeae*[K]	*N.mening-itidis*	*Gram-negative anaerobes*[L]	*Gram-positive anaerobes*	
Benzylpenicillin	RD	–	–	–	0.12/0.12	Note[E]	0.25/0.25	0.25/2	0.06/2	IE	–	0.06/1	0.06/0.25	0.25/0.5	0.25/0.5	0.25/2
Ampicillin[N]	RD	Note[A]/8	–	–	Note[D]	4/8	Note[F]	0.5/2	0.5/2	1/1	1/1	Note[K]	0.12/1	0.5/2	4/8	2/8
Ampicillin/sulbactam[O]	RD	Note[A]/8	–	IE	Note[D]	4/8	Note[F]	Note[G]	Note[H]	1/1	1/1	IE	IE	4/8	4/8	2/8
Amoxicillin	RD	Note[A]/8	–	–	Note[D]	4/8	Note[F]	0.5/2	0.5/2	1/1	1/1	Note[K]	(0.12/1)	0.5/2	4/8	2/8
Amoxicillin/clavulanate[O]	RD	Note[A]/8	–	–	Note[D]	4/8	Note[F]	Note[G]	Note[H]	1/1	1/1	Note[K]	–	4/8	4/8	2/8
Piperacillin	RD	8/16	16/16	IE	Note[D]	Note[E]	Note[F]	IE	Note[H]	Note[I]	Note[J]	–	–	16/16	8/16	4/16
Piperacillin/tazobactam[O]	RD	8/16	16/16	IE	Note[D]	Note[E]	Note[F]	IE	Note[H]	Note[I]	Note[J]	–	–	8/16	8/16	4/16
Ticarcillin	RD	8/16	16/16	IE	Note[D]	Note[E]	–	IE	–	IE	IE	–	–	16/16	8/16	8/16
Ticarcillin/clavulanate[O]	RD	8/16	16/16	IE	Note[D]	Note[E]	–	IE	–	IE	IE	–	–	8/16	8/16	8/16
Phenoxymethylpenicillin	RD	–	–	–	Note[D]	–	Note[F]	–	Note[H]		–	–	–	–	–	IE
Mecillinam[P]	RD	8/8	–	–	–	–	–	–	–		–	–	–	–	–	IE
Oxacillin	RD	–	–	–	Note[D]	–	Note[F]	–	–		–	–	–	–	–	IE
Cloxacillin	RD	–	–	–	Note[D]	–	Note[F]	–	–		–	–	–	–	–	IE
Dicloxacillin	RD	–	–	–	Note[D]	–	Note[F]	–	–		–	–	–	–	–	IE
Flucloxacillin	RD	–	–	–	Note[D]	–	Note[F]	–	–		–	–	–	–	–	IE

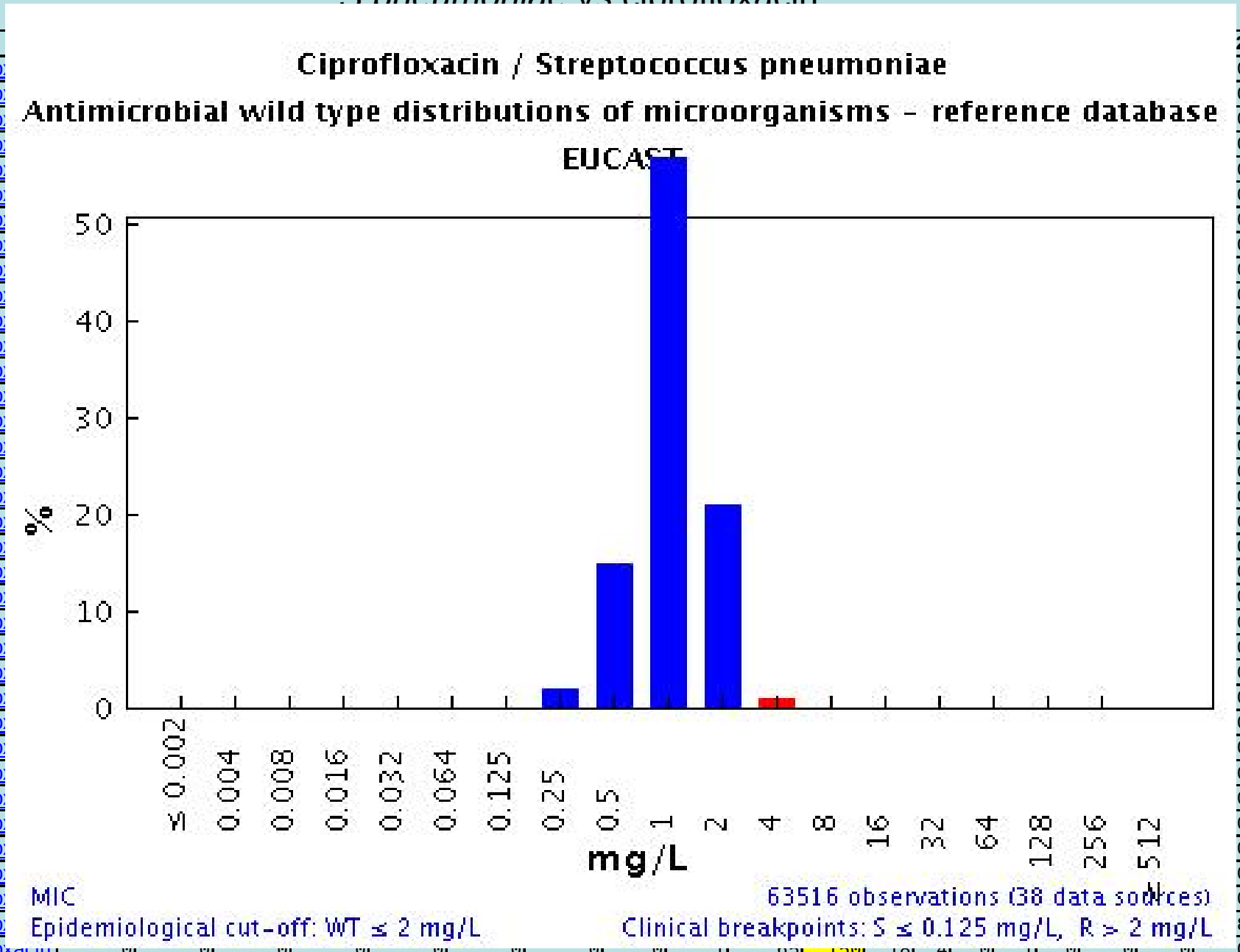
A. Enterobacteriaceae: and aminopenicillin breakpoints: The resistant breakpoi
intravenous vs. oral administration significantly affect therapeutic efficacy. The uns
This will depend on dosing, route of administration and on whether the infection is
poor targets for penicillins with or without beta-lactamase inhibitors.
B. *Pseudomonas aeruginosa*: Piperacillin and ticarcillin breakpoints for *Pseudon*
clavulanate 3 g x 4). The susceptible breakpoints were increased to avoid dividing
C. Acinetobacter: Susceptibility testing of *Acinetobacter* spp. to penicillins is un
D. Staphylococci: Most staphylococci are penicillinase-producers. Penicillinase-
benzylpenicillin breakpoint will mostly, but not unequivocally, separate beta-lactar
S. aureus and *S. lugdunensis* with oxacillin MIC values >2 mg/L and/or cefoxitin M

Oral cefalosporins

Autumn 2008

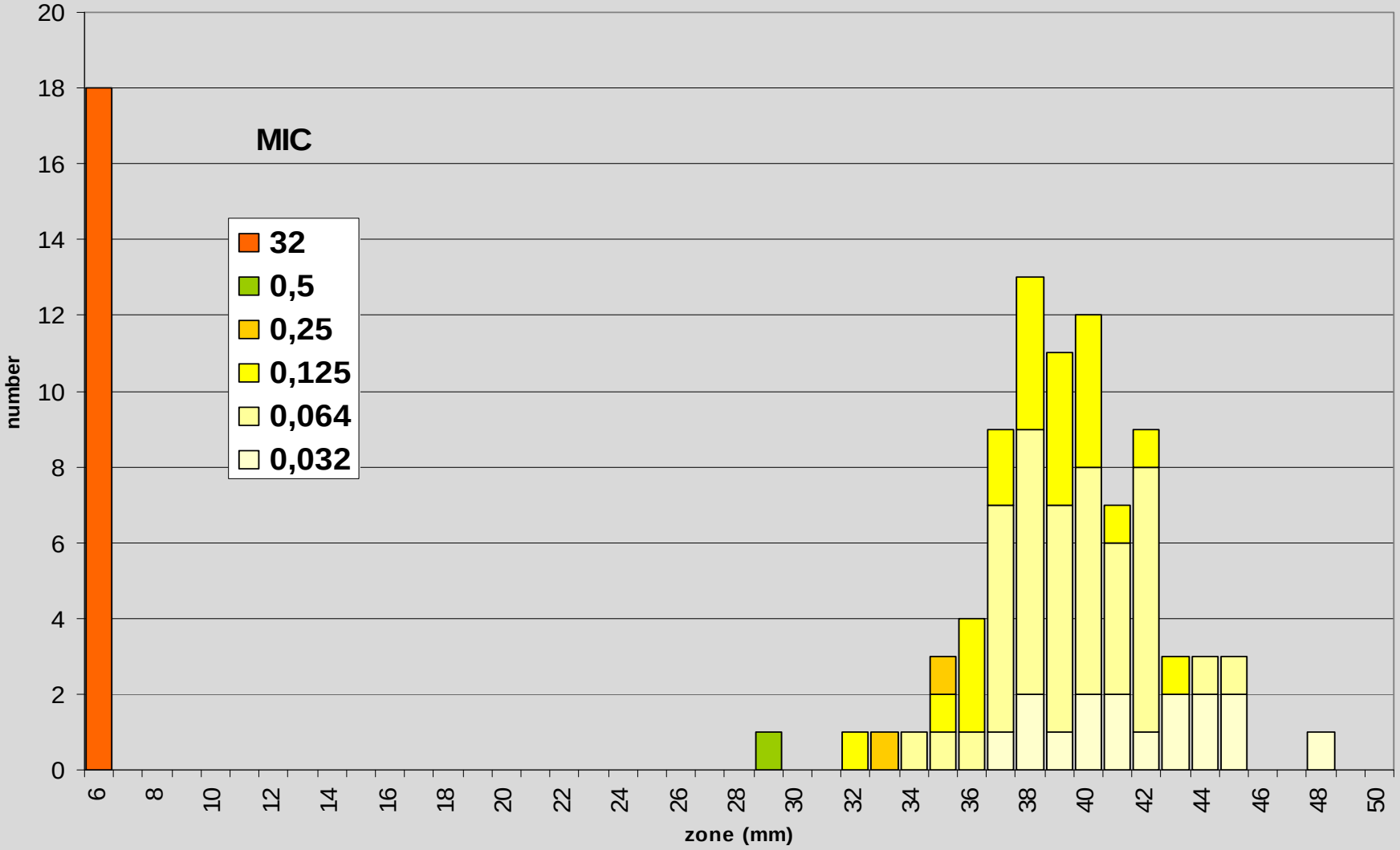
EUCAST
Wild type MIC-distributions and Epidemiological cut-offs

S pneumoniae vs ciprofloxacin



Ciprofloxacin	0	0	0	0	0	0	1	2	41	99	55	11	1	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

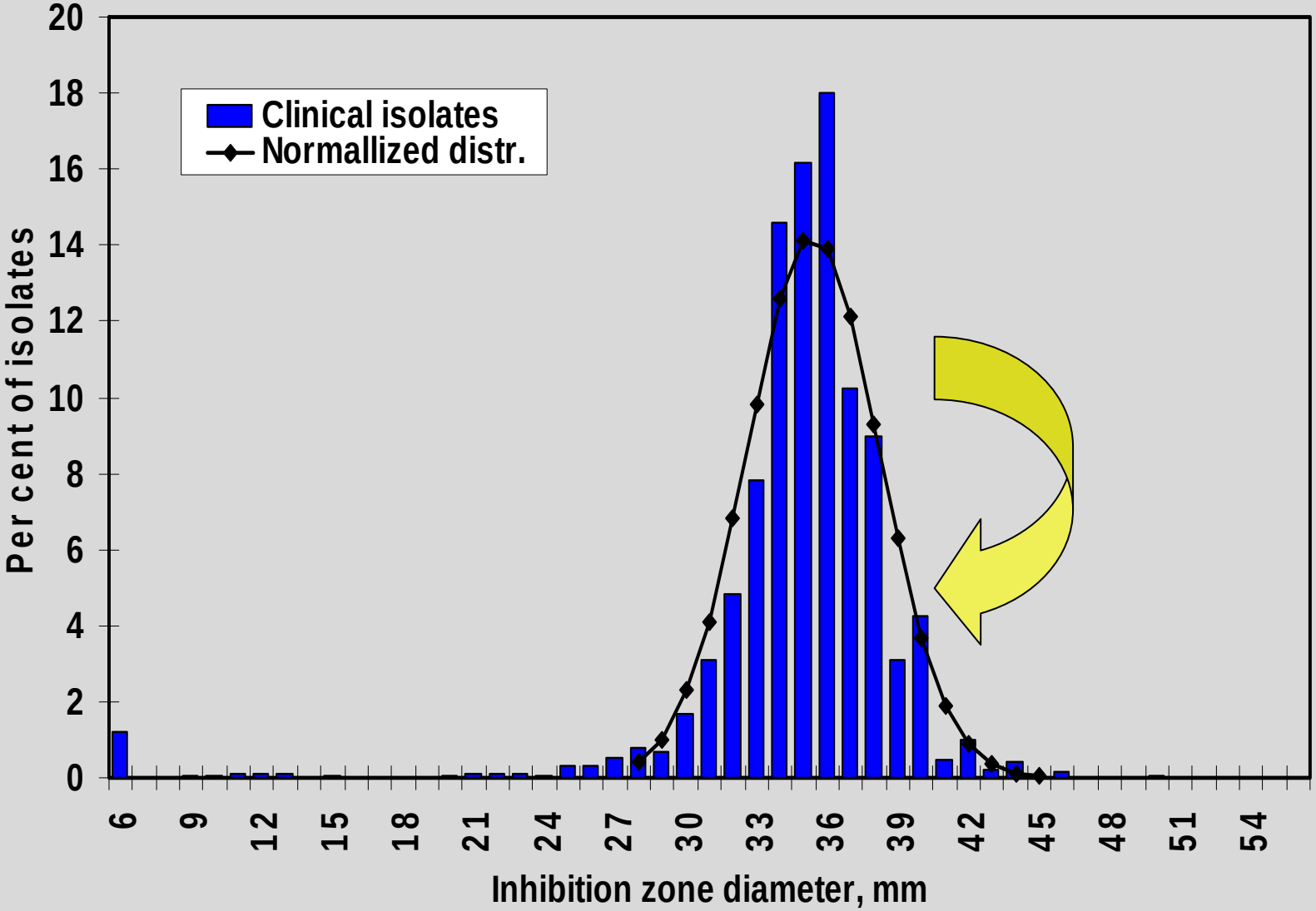
Campylobacter
Ciprofloxacin 5 µg disc vs. Ciprofloxacin MICs



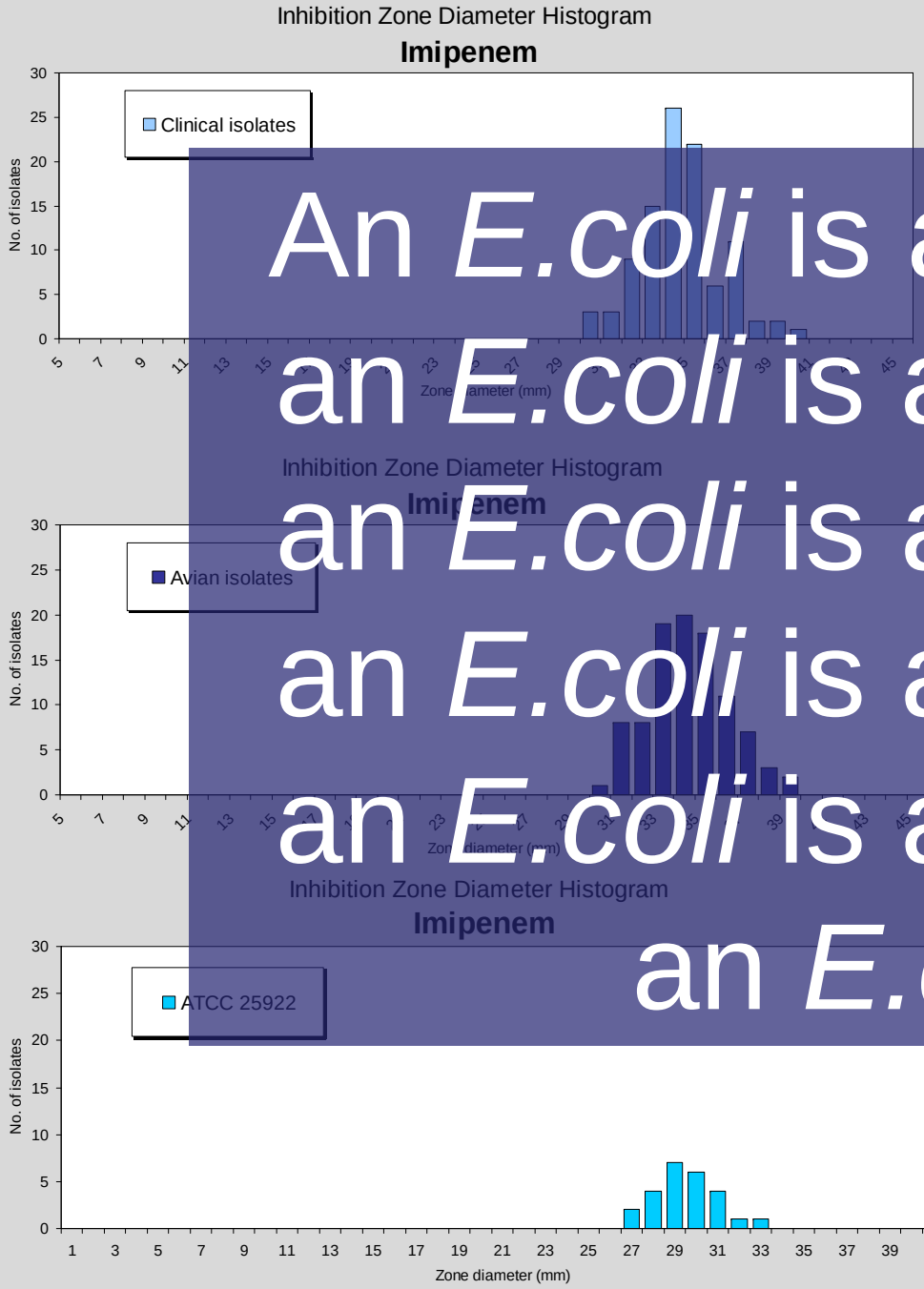
Data by Hanna Odén, Clinical microbiology, Växjö

E.coli and ciprofloxacin 5 µg disc
Växjö, Sweden

G Kronvall et al, CMI, 2003



E.coli in arctic birds and humans



Clinical isolates

(n=100)

Avian isolates

(n=97)

Reference strain ATCC 25922

(n=25)

An *E.coli* is an *E.coli* is an *E.coli* is an *E.coli* is an *E.coli* is an *E.coli* is an *E.coli* is an *E.coli* is an *E.coli* is an *E.coli*!

Epidemiological cut-offs
MIC- and/or Inhibition Zone Diameter

- Early detection of resistance
- Sensitive detection of resistance
- When insufficient Pk/Pd–data – cinical breakpoint
- Comparison of resistance between host species (man, animals, plants etc)
  - Veterinarians use EUCAST ECOFFs for pan-European surveillance
  - Food/Feed industry to screen for resistance

Epidemiological cut-offs

Is there a clinical use for ECOFFs?
In serious infections: isolates categorised with clinical breakpoints AND epidemiological cut-offs!

S^{WT} - E.coli: CIP 0.016 mg/L

S^{NWT} - E.coli: CIP 0.5 mg/L

Method: (•) MIC ( ) Disc diffusion

Antimicrobial: Erythromycin Species: Species...

Antimicrobial: Erythromycin **(Method:** MIC **)**

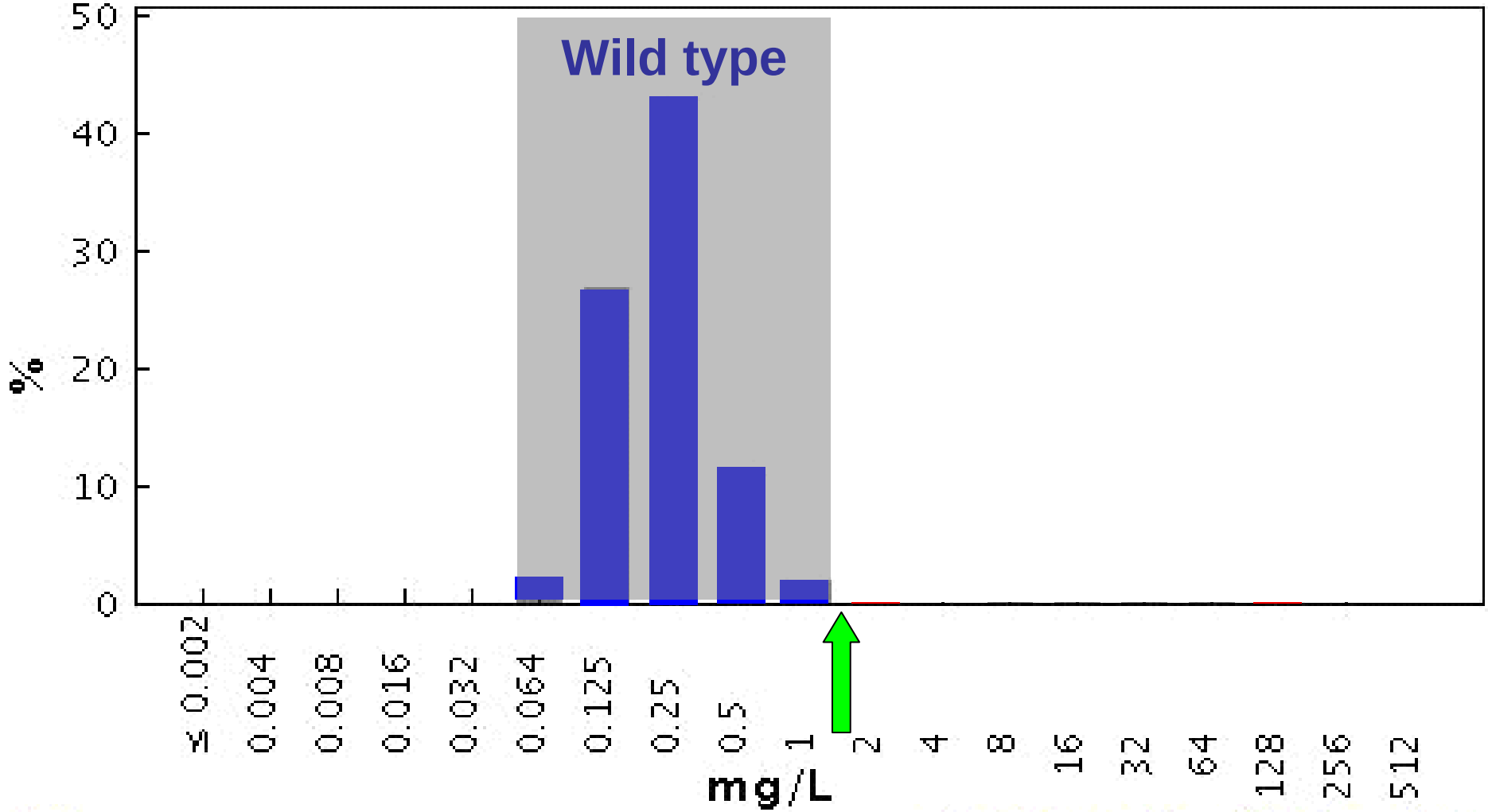
	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128
Bacteroides fragilis group	0	0	0	0	0	0	0	2	10	30	10	0	0	0	0	0	0
Campylobacter coli	0	0	0	0	0	0	2	15	111	198	405	517	277	55	31	107	469
Campylobacter jejuni	0	0	0	0	2	4	20	76	270	577	403	121	13	3	0	2	1
Clostridium difficile	0	0	0	0	0	0	0	5	1	1	0	0	0	2	0	0	0
Clostridium perfringens	0	0	0	0	0	0	0	0	4	6	0	0	0	0	0	0	0
Enterococcus faecalis	0	0	0	0	1	11	8	25	192	463	444	303	120	486	20	252	57
Enterococcus faecium	0	0	0	0	0	12	115	320	604	559	663	426	152	53	167	159	977
Enterococcus hirae	0	0	0	0	0	0	0	97	403	9	8	2	5	0	0	42	2
Haemophilus influenzae	0	0	0	0	1	2	11	100	112	529	3871	12902	6183	655	67	19	18
Haemophilus parainfluenzae	0	0	0	0	0	0	0	3	22	84	127	135	38	7	0	0	0
Legionella pneumophila	0	0	0	0	0	0	0	87	13	0	0	0	0	0	0	0	0
Listeria monocytogenes	0	0	0	0	0	0	3	24	79	0	0	0	0	0	0	0	0
Moraxella catarrhalis	0	0	10	26	131	1666	292	19	2	1	2	0	0	0	0	0	0
Neisseria gonorrhoeae	0	0	3	0	27	48	124	201	292	348	239	213	51	5	1	2	0
Neisseria meningitidis	0	0	0	0	0	0	6	3	1	0	0	0	0	0	0	0	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**
Peptostreptococcus spp	0	0	0	1	6	0	0	1	3	5	0	2	0	0	0	0	0
Staphylococcus aureus	0	0	0	17	62	967	4958	15716	5259	808	124	146	145	3550	71	1293	1649
Staphylococcus aureus MRSA	0	0	0	0	0	0	1	6	41	2	0	5	0	1	0	0	22
Staphylococcus aureus MSSA	0	0	0	0	0	0	2	45	198	6	2	41	0	0	2	1	3
Staphylococcus capitis	0	0	0	1	0	38	74	47	12	0	1	1	2	38	4	0	0
Staphylococcus coagulase negative	0	0	0	0	0	1	18	256	296	22	6	5	8	15	45	45	39
Staphylococcus coagulase negative MRSE	0	0	0	0	0	0	0	19	30	4	0	1	0	0	10	14	15

Species: Staphylococcus aureus **(Method:** MIC)

	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
Amikacin	0	0	0	0	0	0	0	17	62	209	1296	2234	883	301	76	62	0	0	0
Amoxicillin-clavulanic acid	0	0	0	7	18	113	1744	2098	3983	3865	1185	524	1092	250	509	1	0	14	200
Ampicillin	0	0	0	1	4	11	298	248	305	407	182	155	130	87	80	0	2	1	0
Avilamycin	0	0	0	0	0	0	0	0	0	0	2	11	1	0	0	0	0	0	0
Azithromycin	0	0	0	0	2	5	7	345	1865	1784	162	16	29	37	30	1218	1646	0	0
Benzylpenicillin	0	0	85	553	547	223	199	308	891	937	794	720	2968	123	554	309	246	1	0
Cefaclor	0	0	0	0	0	0	0	0	143	424	1824	1395	280	117	104	166	753	0	0
Cefalexin	0	0	0	0	0	0	0	0	1	16	34	13	10	5	5	7	5	6	0
Cefalothin	0	0	0	0	0	10	111	128	60	6	1	0	0	0	0	0	0	0	0
Cefazoline	0	0	0	0	0	18	359	3277	7870	4718	878	250	181	157	1343	0	0	0	201
Cefepime	0	0	0	11	9	3	3	12	16	150	1114	325	37	14	6	60	1	2	0
Cefoperazone	0	0	0	0	0	4	0	1	10	69	599	95	20	2	2	2	2	0	0
Cefoperazone-sulbactam	0	0	0	0	9	1	0	4	18	477	244	44	3	1	0	4	0	0	0
Cefotaxime	0	0	0	0	1	2	71	53	232	1900	2192	182	94	24	243	1	1	1	0
Cefoxitin	0	0	0	0	0	0	0	0	2	34	59	70	22	13	9	1	1	23	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**
Cefpodoxime	0	0	0	0	0	0	7	10	23	597	3340	193	96	72	900	0	1	2	0
Ceftiofur	0	0	0	0	0	0	4	13	63	43	0	0	0	0	0	0	0	0	0
Ceftriaxone	0	0	0	0	0	0	0	0	0	4	154	213	9	9	1	3	1	1	0
Cefuroxime	0	0	0	2	3	2	55	363	1265	7253	1443	234	125	890	247	1	0	8	0
Chloramphenicole	0	0	0	0	0	0	0	0	0	9	38	481	1050	27	9	31	2	0	0
Ciprofloxacin	0	0	0	4	93	700	4894	12698	13843	2663	777	209	1941	391	243	405	365	105	40
Clarithromycin	0	0	0	2	7	181	1889	1963	116	22	20	43	43	33	50	2777	0	0	0
Clinafloxacin	0	0	0	0	654	1216	542	63	49	118	100	93	1	1	0	0	0	0	203
Clindamycin	0	0	1	23	1080	7175	13531	686	70	25	16	35	1229	1192	88	9	9	66	562
Cloxacillin	0	0	0	0	4	29	395	646	106	1	0	0	0	0	0	0	0	0	0
Dalbavancin	0	0	0	226	6368	8722	372	48	16	16	2	0	0	2	0	0	0	0	0

Fluconazole / Candida albicans EUCAST

Antimicrobial wild type distributions of microorganisms - reference database EUCAST



MIC

Epidemiological cut-off: **1.0 mg/L**

3012 observations (11 data sources)

Clinical breakpoints: S ≤ - mg/L, R > - mg/L

EUCAST and the future

EUCAST Questionnaire 2008
Last question:

”The bottom line, is there a need for EUCAST in the future?”

YES: 52

NO: 0

EUCAST and the future

- Revision of breakpoints
- Breakpoints for new drugs (5-6 ongoing) as part of EMEA process
- Advisory Committee to European agencies, institutions, networks and industry (ECDC, EMEA, EFSA, EARSS, Industry)
- Subcommittees on Antifungals, Expert Rules, Anaerobes, Mycobacteria.
- Disk test to develop and sustain
- Expert rules to implement and review
- Encourage the institution of NACs and a network of NACs
- Education and implementation through workshops throughout Europe

National Antimicrobial Committees NACs and their role

- Antimicrobial susceptibility testing
  - Liaison and consultation nationally and internationally
  - Strategy on national level
  - Education through national workshops
  - QA
  - ….
- Antimicrobial Resistance Surveillance
  - Methodology
  - National and international systems
- Antimicrobial Consumption and Policies

How to implement EUCAST breakpoints

- Use BSAC, CA-SFM or SRGA disk diffusion guidelines - available for MH and ISA semiconfluent inoculum on internet in French and/or English.
- EUCAST breakpoints applied to MIC-testing
- Acquire an automated AST system with EUCAST breakpoints (from 2009).
- Wait for a European or International disk test with zone diameter/MIC correlates?

Automated Systems for AST

- Phoenix - 2009-01-01
- Vitek - 2010-01-01
- Microscan - ?

Species	No.	Characteristics
Staph.aureus (MSSA)	34	PCG, ERY, CLI, FUS^{A}, FUS^{B}, CIP/MOX, GEN
Staph.aureus (MRSA)	30	Various spa-types
Staph.lugdunensis	9	ERY, CLI, TET
Coagulase negative Staph.	31	Various R´s
Streptococcus pneumoniae	30	PCG MIC≥0.5; PCG, AMO, CTX-, CLI, ERY
Streptococcus pyogenes	31	ERY, PEL, CLI, TET, LEV
Enterococcus faecalis	10	WT, vanA, vanB; GENTAMICIN LLR & HLR;
Enterococcus faecium	15	WT, vanA, vanB; AMP, IMI, NIT.
Pseudomonas aeruginosa	26	CIP, IMI, MER, GEN, PIP.
Enterobacteriaceae ESBL	30	**CTX-M types** (1, 9, 14, 15).
Escherichia coli	31	CTX-I, CXM, CIP, TRI, TSU, GEN, PTZ-I
Enterobacter aerogenes	10	AMC, CPM-I, CXM
Enterobacter cloacae	12	AMC, AZT, CTX, CFZ, CXM, CIP, PTZ, TRI, TSU
Klebsiella pneumoniae	29	AMC, AZT, CTX, CFZ, CXM, CPM, CIP, GEN, TOB, TRI, TSU
Klebsiella oxytoca	10	AMC, AZT, CPM, CTX, CXM, GEN, TOB-I, PTZ, TRI, TSU
Proteus mirabilis	10	TRI, TSU
Morganella morganii	10	AMC, AZT, CTX, CFZ-I, CXM, CIP, TRI, TSU

Phoenix

ESBL in E.coli and K.pneumoniae:

"Crude" results prior to expert system interpretation

	PHX			DISK		
	S	**I**	**R**	**S**	**I**	**R**
AZT*	3	7	20	2	6	22
CAZ*	6	8	16	5	8	17
CTX*	0	2	28	0	1	29
CXM*	1	0	29	0	0	30
CPM*	3	5	22	1	5	24
PIP/TAZ**	**17**	**9**	**4**	**5**	**5**	**15**

* Interpretation changed to R by the expert system for all the isolates identified as ESBL+ (29/30)

**In ESBLs disk test overcalls resistance on strains with MICs 8 or 16

EUCAST Disc Testing
– choosing the way forward (decision June 2008)

MH + Confluent inoculum

- Inoculum standardisation
  - possible
- Data available: US/CLSI
  - Official query has been sent
- Implementation
  - in Europe easy
  - For countries outside easy
  - International acceptance +++
- Funding
  - ESCMID: probably
  - ECDC: ?

MH + Semi-confluent inoculum

- Inoculum standardisation
  - easy
- Data available: France (?)
  - Official query to be sent
- Implementation
  - For Europe: possible ?
  - For other countries – hopeless
  - International standing: ???
- Funding
  - ESCMID: probably
  - ECDC: ?

Country						Automated systems (%)	EUCAST Disk Test	EUCAST Disk Test
SWE	28	SRGA	Y	Y	SRGA	10 - 50	Y	MHMF
DEN	15	Y	Y	Y	SRGA	10 - 50	Y	MHMF
NOR	25	NWGA	Y	Y	NWGA	10 - 50	Y	MH**SC** ISA**SC**
FIN	25	Y	Y	Y	CLSI	10 - 50	Y	MHMF
POL	>700	N	Y	Y	CLSI	10 - 50	Y	MHMF
BUL	250	N	Y	Y	CLSI	10 - 50	Y	MHMF
UK	250	BSAC	Y	Y	BSAC	10 - 50	Y	MHMF
SCO	27	N	Y	Y	CLSI	>75	Y/N	MHMF
NET	70-80	CRG	N	N	CRG/CLSI	50 - 75	Y/N	MHMF
ITA	>300	N	N	N	CLSI	50 - 75	Y	MHMF
AUS	40	N	Y	Y/N	CLSI	10 - 50	Y	MHMF
LIT	18	N	N	N	CLSI	10 - 50	Y	MHMF
EST	15	N	Y	N	CLSI	1 - 10	Y	MHMF
GER	>2000	DIN	Y	N	DIN/CLSI	10 - 50 - 75	Y	MH**SC**
FRA	4000	CA-SFM	Y	Y	CA-SFM	10 - 50 - 75	Y/N	MHMF/**SC**
BEL	120 - 180	N	N	N	CLSI	25 - 50	Y	MHMF/**SC**
ESP	>500	N	N	Y/N	CLSI/MENSURA	50 - 75	Y	MHMF
RUS	>700	N	N	Y	CLSI	1 - 10	Y	MHMF
CRO	35	N	Y	Y	CLSI	1 - 10	Y	MHMF
CZE	114	N	Y	Y	CLSI	10 - 50	N	MHMF
SLK	20 / 57	N	Y/N	Y/N	CLSI	1-10	Y/N	MHMF
POR	?	N	N	N	CLSI	>75	Y	MHMF
HUN	80	N	N	N	CLSI	10 - 50	Y	MHMF
SLV	12	N	N	N	CLSI	50 - 75	Y	MHMF
MAL	1	N	N	N	CLSI	100	N	MHMF

NABC=breakpoint committee, NAC=antibiotic committee, MH=Mueller-Hinton, MF=MacFarland 0.5, SC=SemiConfluent

Thank you!

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