



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Updated 1st April, 2010



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Formed in 1997 and restructured in 2002

convened by

**European Society for Clinical Microbiology and Infectious
Diseases (ESCMID)**

National Breakpoint Committees in Europe

financed by

ESCMID

National Breakpoint Committees in Europe

DG-SANCO of the European Union (3 year grant from May 2004)

European Centre for Disease Prevention & Control (ECDC)

(1 year interim funding from May 2007 and 3 year grant from Sept 2008)

The objectives of EUCAST are

- to form in EUCAST, under the auspices of the European Society of Clinical Microbiology and Infectious Diseases", a **professional network of**
 - the **national breakpoint committees and experts** on antimicrobial susceptibility testing and
 - **industry** involved in the production and marketing of antimicrobial agents or of in-vitro diagnostic medical devices used in antimicrobial susceptibility testing;
- to set **common European breakpoints for surveillance** of antimicrobial resistance;
- to identify national differences in clinical breakpoints and **to harmonise breakpoints for existing and new antimicrobial drugs**;
- to produce, disseminate and update a series of documents on the technology of in-vitro antimicrobial susceptibility testing, **promoting standardisation of methods** used in different parts of Europe and comparability of results obtained by different technologies;
- to encourage **internal and external national and international quality assessment** schemes;
- to collaborate with European and international groups concerned with **antimicrobial susceptibility testing** and/or the **epidemiology of antimicrobial resistance**;
- to **advise** European Community Institutions on the technology and interpretation of antimicrobial susceptibility testing;
- to work with groups outside Europe (eg CLSI) **to achieve international consensus** on susceptibility testing;
- to devise and participate in educational and **training programmes** for antimicrobial susceptibility testing.

EUCAST organisation

EUCAST General Committee:

- one representative, appointed by the appropriate medical associations, from each European country
- one representative each from ISC and FESCI
- Chairperson, Scientific secretary and Clinical Data Coordinator (appointed by ESCMID)
- meets once a year at ECCMID
- all Steering Committee proposals are referred to the General Committee for comments before decision

EUCAST Steering Committee:

- Chairperson, Scientific Secretary and Clinical Data Coordinator (appointed by ESCMID)
- one representative each from the European national breakpoint committees (presently 6)
- two representatives from the EUCAST General Committee
 - Czech Republic and Greece 2002-2004
 - Russia and Spain 2004-2006
 - Italy and Poland 2006-2008
 - Norway and ISC 2008-2010
 - Estonia and Austria 2010-2012

EUCAST industry email network

- Manufacturers of pharmaceuticals and susceptibility testing devices are invited to join the EUCAST network. Apply by contacting the chairman of EUCAST.
- Steering Committee proposals are referred to the industry network for comments before decision

EUCAST General Committee

**An updated list of EUCAST General Committee members
is available at www.eucast.org**

EUCAST Steering Committee Membership

- **Chairperson** **Gunnar Kahlmeter** **2008 - 11**
- **Scientific secretary** **Derek Brown** **2008 - 11**
- **Clinical data coordinator** **Rafael Canton** **2008 - 11**

- **BSAC (The UK)** **Alasdair MacGowan** **2008 - 11**
- **CA-SFM (France)** **C-J Soussy/Luc Dubreuil** **2008 - 11**
- **CRG (The Netherlands)** **Johan W. Mouton** **2008 - 11**
- **DIN (Germany)** **Arne Rodloff** **2008 - 11**
- **NWGA (Norway)** **A.Sundsfjord/M.Steinbakk** **2008 - 11**
- **SRGA (Sweden)** **Christian Giske** **2008 - 11**

- **General Committee rep** **Marina Ivanova (Estonia)** **2010 - 12**
- **General Committee rep** **Helmut Mittermeyer (Austria)** **2010 - 12**

- **Finishing a two-year term in 2010 are Antti Hakanen (Finland) and Paul Tulkens (ISC)**

EUCAST Subcommittees

- EUCAST Subcommittee on Antifungal Susceptibility Testing (EUCAST AFST)
- EUCAST Subcommittee on Expert Rules
- EUCAST Subcommittee on Anaerobes

EUCAST subcommittee on antifungal susceptibility testing (EUCAST AFST)

Objectives

- To develop reference methods for antifungal susceptibility testing
- Set breakpoints for antifungal drugs using EUCAST processes for breakpoint setting, consultation and decisions

Achievements

- Reference MIC methods for fermentative yeasts and filamentous fungi
- MIC breakpoints for fluconazole and voriconazole

EUCAST subcommittee on expert rules

Objectives

- To develop expert rules for antimicrobial susceptibility testing

Achievements

- Version 1 of EUCAST expert rules published (freely available at www.EUCAST.org)
- Computer program for application of expert rules developed

EUCAST subcommittee on anaerobes

Objectives

- To advise on breakpoints for anaerobic organisms
- To define methods for antimicrobial susceptibility testing of anaerobes

Achievements

- Breakpoints for anaerobes included in EUCAST breakpoint tables (www.eucast.org)
- Review of antimicrobial susceptibility testing methods for anaerobes is underway

EUCAST publications

All EUCAST publications and other documents are available from the EUCAST website in the section entitled “Documents”. These include:

- Publications in journals
- Rationale documents summarising the basis of EUCAST breakpoints for each agent
- Posters presented at international meetings
- Discussion documents posted on the EUCAST website for comments. After a period of consultation they are submitted for publication in CMI or posted on the EUCAST website (www.eucast.org). as Definitive Documents.
- Reports in ESCMID Newsletters
- Miscellaneous documents

EUCAST websites are found at www.eucast.org

This is a section of the official ESCMID website giving details of all EUCAST activities including

- organisation
- constitution
- committee member lists
- meetings
- EUCAST documents
- clinical MIC breakpoint tables
- MIC distributions for wild type bacteria and fungi
- epidemiological MIC cut-off values (ECOFFs)

Organization

Clinical breakpoints

Expert rules

MIC distributions

Zone diameter distributions

EUCAST disk diffusion test

Meetings

EUCAST Presentations

Documents

Information for industry

Links



The European Committee on Antimicrobial Susceptibility Testing - EUCAST

EUCAST is a standing committee jointly organized by ESCMID, ECDC and European national breakpoint committees. EUCAST deals with breakpoints and technical aspects of phenotypic in vitro antimicrobial susceptibility testing and functions as the breakpoint committee of EMEA and ECDC.

EUCAST does not deal with antibiotic policies, surveillance or containment of resistance or infection control.

The Steering Committee is the decision making body. It is supported by a General Committee with representatives from European countries, FESCI and ISC. The Steering Committee also consults experts within the fields of Infectious Diseases and Microbiology, pharmaceutical companies and susceptibility testing device manufacturers on EUCAST proposals.

This is the first screen of the EUCAST general website found at www.eucast.org.


Most antimicrobial MIC breakpoints in Europe have been harmonised by EUCAST by 2009. Breakpoints for new agents are set as part of the licensing process for new agents through EMEA. EUCAST breakpoints will be available in devices for automated susceptibility testing during 2009 and 2010. A disk diffusion test calibrated to EUCAST MIC breakpoints was launched at the end of 2009.

EUCAST invites anyone with an interest in antimicrobial agents in general and

search term Search

QUICK NAVIGATION

New rationale Documents from EUCAST.


 [metronidazole](#)

 [nitrofurantoin](#)

EUCAST presentation now available



This presentation gives an overview of EUCAST and its activities.

 [download](#)

 **ESCMID** EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES


European Medicines Agency


EUROPEAN CENTRE FOR DISEASE PREVENTION

EUCAST definitions of clinical breakpoints

Clinically Susceptible (S)

- a microorganism is defined as susceptible if inhibited in-vitro by a concentration of an antimicrobial agent that is associated with a high likelihood of therapeutic success
- a microorganism is **categorized** as susceptible (S) by applying the appropriate breakpoint in a defined phenotypic test system.

Clinically Intermediate (I)

- a microorganism is defined as intermediate by a level of antimicrobial agent activity associated

EUCAST has re-defined susceptible, intermediate and resistant and defined the terms "wild type" and "non-wild type" microorganism.

- **The national breakpoint committees have also agreed on a common format for susceptible ($S \leq$) and resistant ($R >$).**
-

defined phenotypic test system.

Clinical breakpoints may be altered with legitimate changes in circumstances

Clinical breakpoints are presented as $S \leq x$ mg/L; $I > x, \leq y$ mg/L; $R > y$ mg/L

EUCAST definitions of epidemiological cut off values

Wild type (WT)

- a microorganism is defined as wild type (WT) for a species by the absence of acquired and mutational resistance mechanisms to the drug in question.
- a microorganism is categorized as wild type (WT) for a species by applying the appropriate cut-off value in a defined phenotypic test system.
- wild type microorganisms may or may not respond clinically to antimicrobial treatment.

Microbiological resistance - non-wild type (NWT)

- a microorganism is defined as non-wild type (NWT) for a species by the presence of an acquired or mutational resistance mechanism to the drug in question.
- a microorganism is categorized as non-wild type (NWT) for a species by applying the appropriate cut-off value in a defined phenotypic test system.
- non-wild type microorganisms may or may not respond clinically to antimicrobial treatment.

Epidemiological cut-off values will not be altered by changing circumstances.

The wild type is presented as $WT \leq z$ mg/L and non-wild type as $NWT > z$ mg/L

EUCAST wild type MIC distributions and epidemiological cut-off values – the concept

EUCAST developed the concept of antimicrobial wild type MIC distributions and epidemiological cut-off values (JAC 52:145-148, 2003).

Software was created to receive and display large volumes of MIC data for bacteria and fungi over the internet.

It is freely available at <http://www.eucast.org>.

Distributions are displayed in an aggregated format. Tables and graphs show the part of the MIC distribution which, when EUCAST has defined the "epidemiological cut-off value", is considered the "wild type distribution".

The **epidemiological cut-off value** separating microorganisms without (wild type) and with acquired or mutational resistance (non-wild type) and **clinical breakpoints** are shown on the bottom line of the graph.

The epidemiological cut-off value (left lower corner) is shown as $WT \leq X$ mg/L.
The clinical breakpoints (right lower corner) are shown as $S \leq Y$ mg/L and $R > Z$ mg/L.

When graphs or other information is used in publications, the website should be referred to as "EUCAST MIC-distributions at <http://www.eucast.org>, last accessed <date>"



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

This is the first screen of the EUCAST program for the display of wild type MIC distributions in microorganisms. Choose to display in English, French or German. The link to the programme is found on www.eucast.org

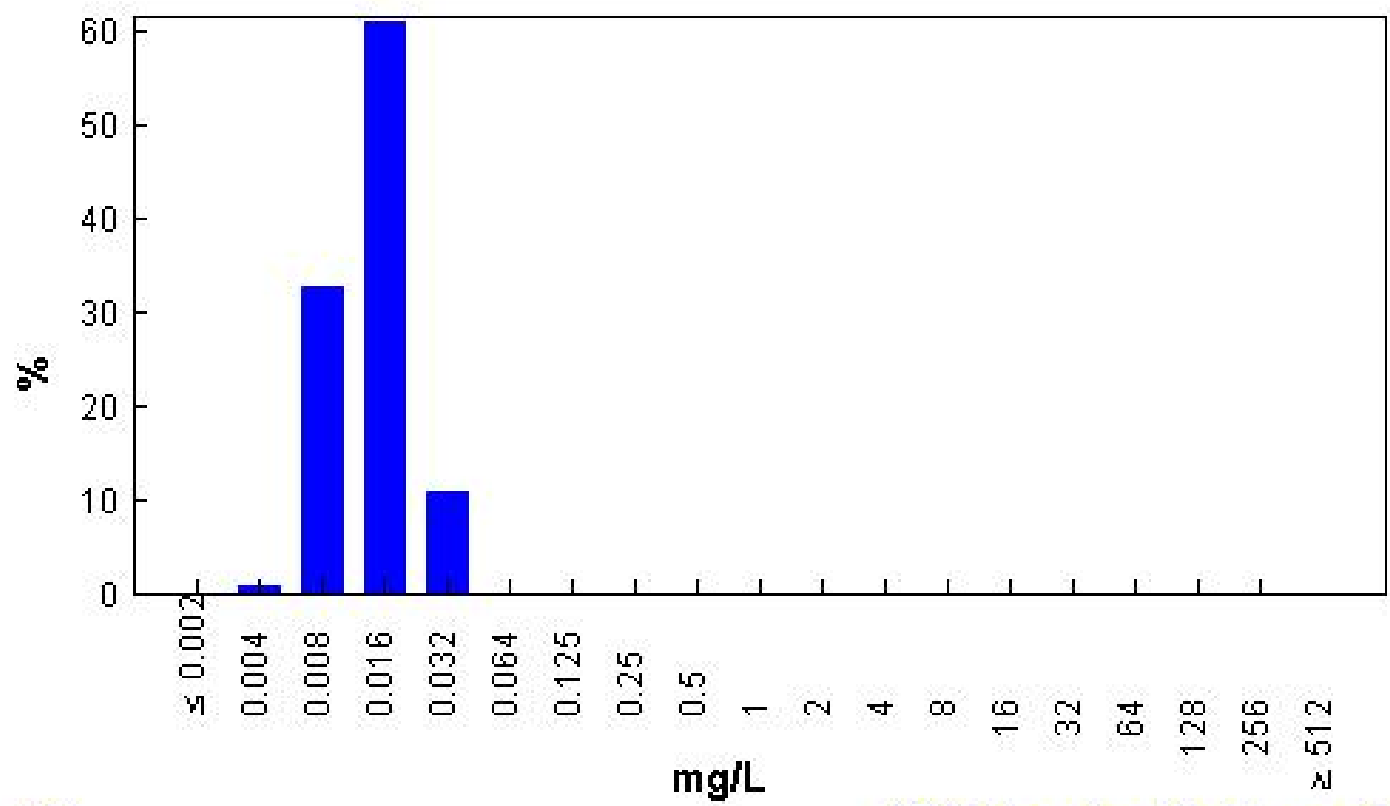
when defined by EUCAST, clinical breakpoints ($S \leq Y$ mg/L and $R > Z$ mg/L) and/or the epidemiological cut-off value. The epidemiological cut-off value is related to the MIC distribution of the wild type organism and categorized as $WT \leq Z$ mg/L.

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

www.eucast.org

Specify the drug or the bug (never both) - after a few seconds a table of MIC distributions is shown. Click on any spe...

Ciprofloxacin / Escherichia coli
Antimicrobial wild type distributions of microorganisms - reference database
EUCAST MIC Distribution



MIC 12836 observations (81 data sources)
 Epidemiological cut-off: WT ≤ 0.032 mg/L Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L

- Antimic
- Search
- Method: Antimicrobia
- Antimicrobial: Ciprofloxacin
- Acinetobacter anitratis
- Acinetobacter baumannii
- Acinetobacter calcoaceticus
- Acinetobacter lwoffii
- Acinetobacter spp
- Alcaligenes xylosoxidans
- Bacteroides fragilis
- Burkholderia cepacia
- Campylobacter coli
- Campylobacter jejuni
- Chryseobacterium meningi
- Chryseobacterium spp
- Citrobacter spp
- Clostridium difficile
- Enterobacter aerogenes
- Enterobacter agglomerans
- Enterobacter cloacae

Elements per page: 10
 Disc content: []

All Graphs

256	512	Ss
0	0	1.0
23	3	1.0
0	0	1.0
0	0	1.0
2	20	1.0
0	0	0.5
0	0	NC
0	0	NC
0	0	0.5
0	0	0.5
0	0	NC
0	0	NC
0	0	0.5
0	0	NC
1	0	0.5
256	512	Ss
0	0	NC
1	1	NC

0	0	41	106	195	83	14	23	29	28	14	18	8	4	4	2	5
---	---	----	-----	-----	----	----	----	----	----	----	----	---	---	---	---	---

EUCAST wild type distributions

- Reference material for epidemiological cut-off values for antimicrobial resistance surveillance
- Reference material for committees involved in decisions on clinical breakpoints
- Reference MIC ranges of wild type organisms for a wide spectrum of species and antimicrobials
- An international reference for calibration of antimicrobial susceptibility testing methods

EUCAST wild type MIC distributions and epidemiological cut-off values (ECOFFs) – methods and data

Origin of MIC data

Each distribution is comprised of aggregated MIC data including individual MIC distributions from

- publications in international journals
- breakpoint committees
- antimicrobial surveillance systems such as EARSS, SENTRY, the Alexander Project
- pharmaceutical companies and susceptibility testing device manufacturers.

Thus, unless otherwise specifically stated, distributions include results obtained with different methods. These methods do not give exactly the same results but the results rarely vary by more than one doubling dilution step. In this way the aggregated EUCAST MIC distributions contain the random variation between different investigators and the systematic variation seen between different methods.

Origin of the organisms included in the MIC distributions

The data are from tests on bacteria and fungi collected from man and animals, of any geographic origin and over a wide time frame.

MIC methods represented

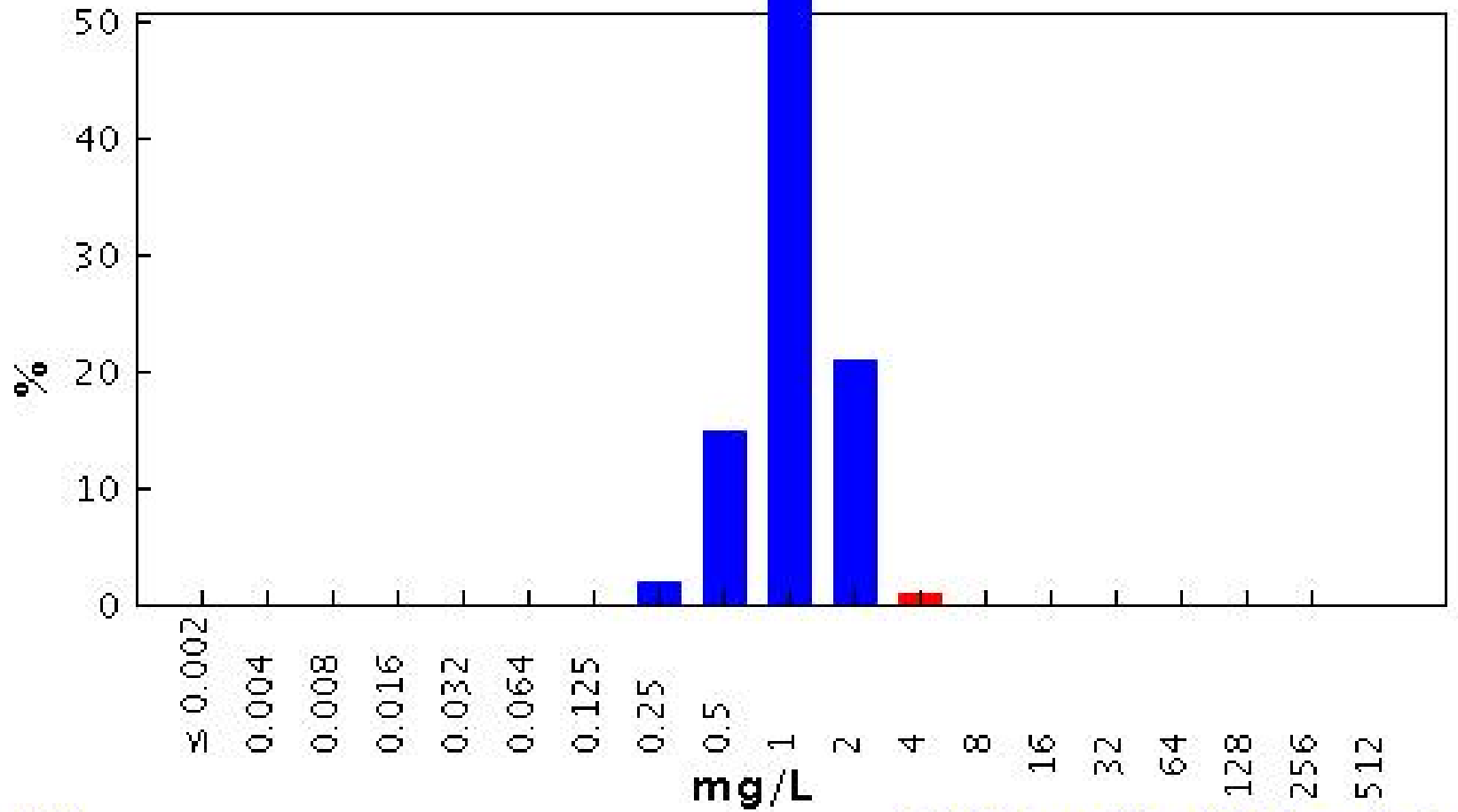
Species-specific distributions of MIC values collected from all over the world are included in the database. The distributions collected represent full range MIC values determined with methods described by EUCAST, BSAC (UK), CA-SFM (France), CRG (The Netherlands), DIN (Germany), CLSI (USA), NWGA (Norway), and SRGA (Sweden) or systems calibrated to these methods (eg. commercial methods which give full range MIC values).

S.pneumoniae vs ciprofloxacin

Ciprofloxacin / *Streptococcus pneumoniae*

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST



MIC

63516 observations (38 data sources)

Epidemiological cut-off: WT ≤ 2 mg/L

Clinical breakpoints: S ≤ 0.125 mg/L, R > 2 mg/L

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

EUCAST wild type MIC distributions

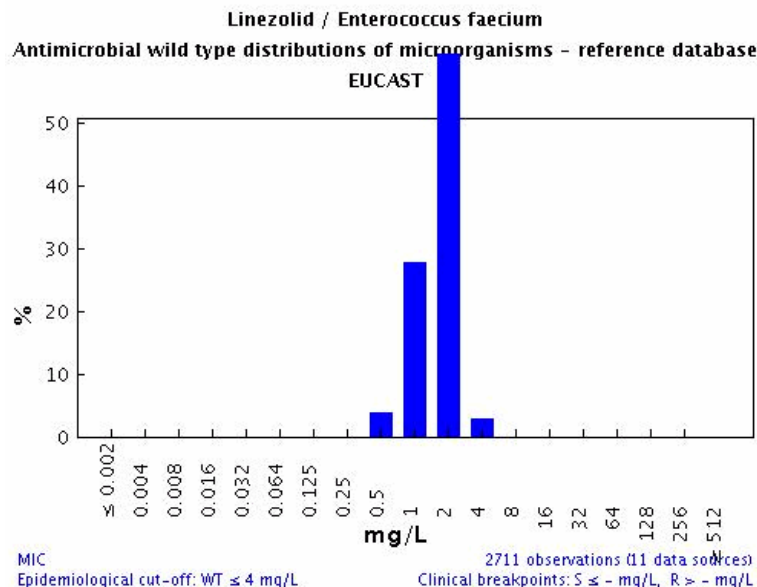
– templates for calibration of MIC determinations

Exclusion of data

All submitted full-range MIC distributions have been accepted. There has been no systematic exclusion of data from one contributor or from one method. The contributions are screened by the EUCAST Steering Committee and less than 10% have been excluded from the aggregated distributions. However, all data are held in the database and are accessible to the Steering Committee. The most common reason for exclusion has been that the data were not full-range MICs so that a significant proportion of MICs were outside the tested range.

Laboratories that cannot fit their own MIC data to the the EUCAST reference distribution should look into the following possibilities:

- The method used for MIC determination in the local set of data is not adequately calibrated,
- The species identification is incomplete,
- There are too few determinations to allow identification of the part of the distribution that constitutes the wild type microorganisms. This usually corresponds to the four lowest dilution steps.

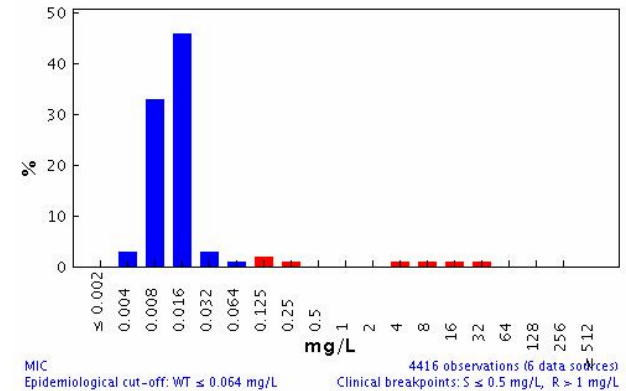


EUCAST wild type MIC distributions

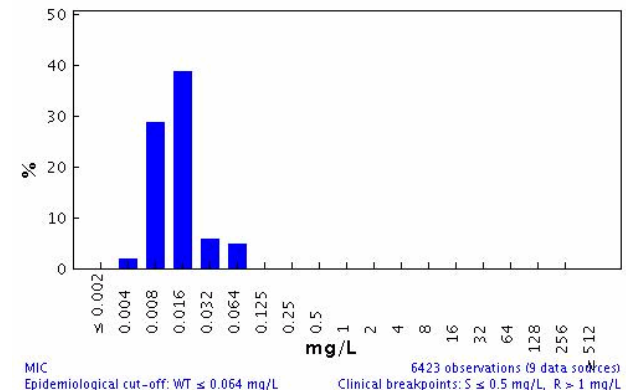
– why are only the MICs of wild type microorganisms displayed?

The distributions consist of MIC-values determined over 30 years or more. While the wild type distribution does not change there may be major differences in resistance over time and between sources. Resistance frequencies obtained through the aggregated MIC distributions would not be representative of current antimicrobial resistance frequencies and would be both confusing and misleading. Thus once the epidemiological cut-off value has been determined by the EUCAST Steering Committee it blocks display of the non-wild type microorganisms (red bars, upper figure) and shows only the part representing the wild type (lower fig).

Ciprofloxacin / *Escherichia coli*
Antimicrobial wild type distributions of microorganisms – reference database
EUCAST



Ciprofloxacin / *Escherichia coli*
Antimicrobial wild type distributions of microorganisms – reference database
EUCAST

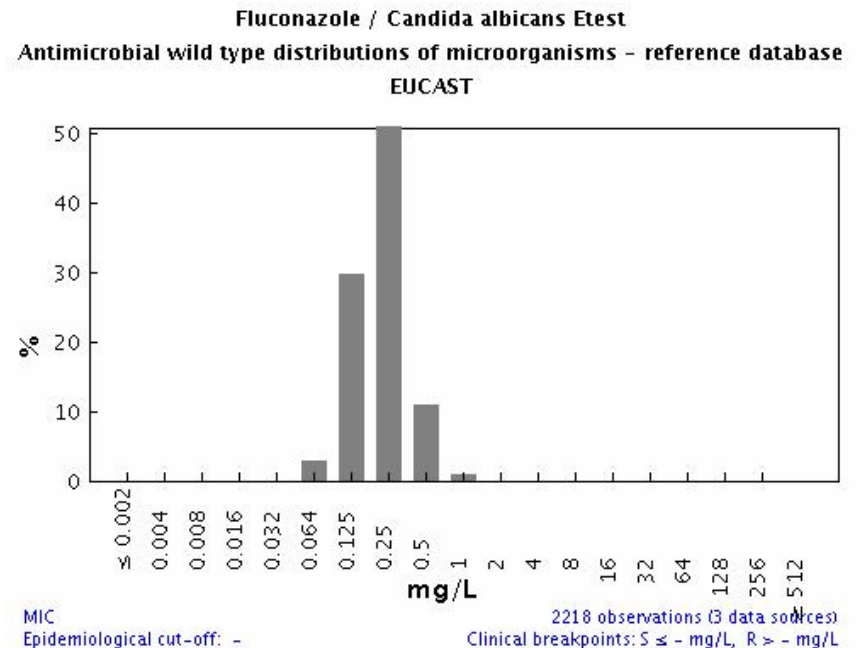


EUCAST wild type MIC distributions

- what does "Data not released for public use" in pull-down lists imply

When selecting antimicrobials in the pull-down list, many agents are followed by the text "data not released for public use". This implies that data for the drug in question are present (fig) but are incomplete and require more data contributions.

As EUCAST decisions on epidemiological cut-off values and clinical breakpoints are made for each group of agents, the tables and graphs are released for general use.



EUCAST wild type MIC distributions – how to contribute data

Everyone is invited to contribute data

All who have full-range MIC data for bacteria or fungi are invited to contribute data as long as MICs are determined with an accepted standardised method, which should be named. Once entered on the database the data will not be identifiable as separate distributions but will help build the aggregate reference distributions. The biologically resistant (non-wild type) part of the distribution will be seen only by the EUCAST Steering Committee.

Submitting data to the EUCAST database does not interfere with publication of data.

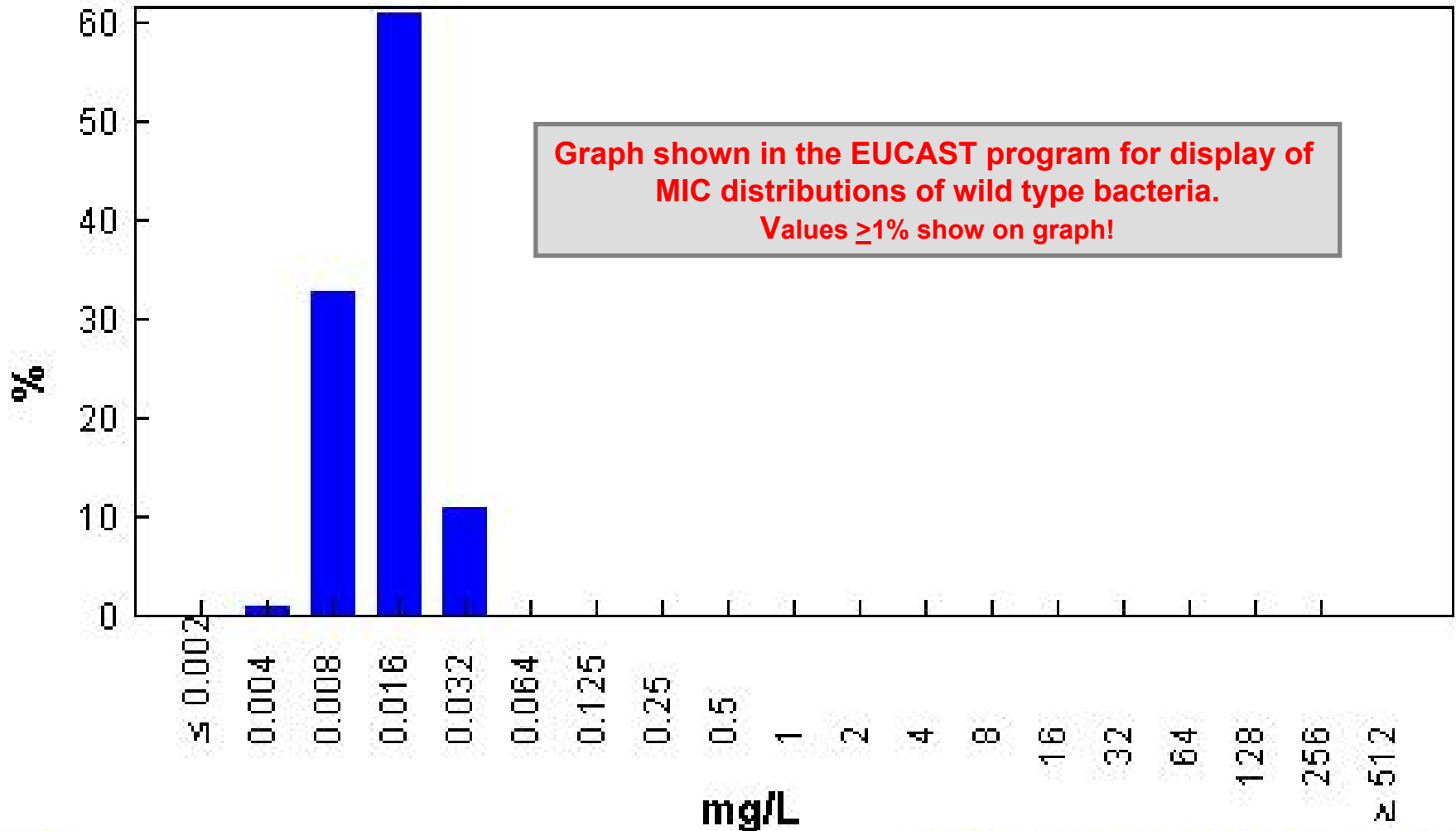
Where can I get more information?

Contact EUCAST – email addresses and information can be obtained through the EUCAST website at <http://www.eucast.org>

Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST MIC Distribution



MIC 12836 observations (81 data sources)

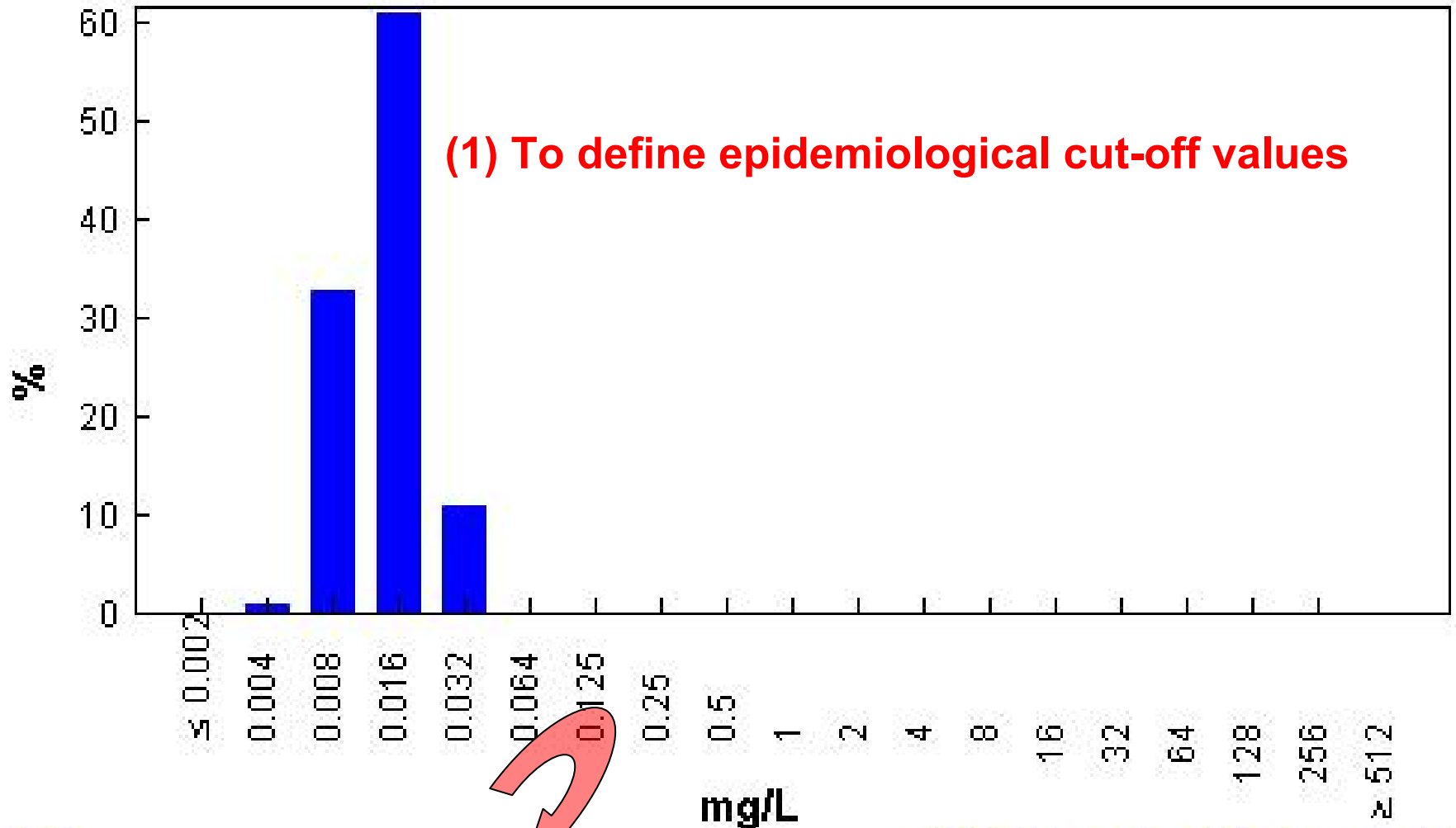
Epidemiological cut-off: WT ≤ 0.032 mg/L

Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L

Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST MIC Distribution



MIC

Epidemiological cut-off: WT ≤ 0.032 mg/L

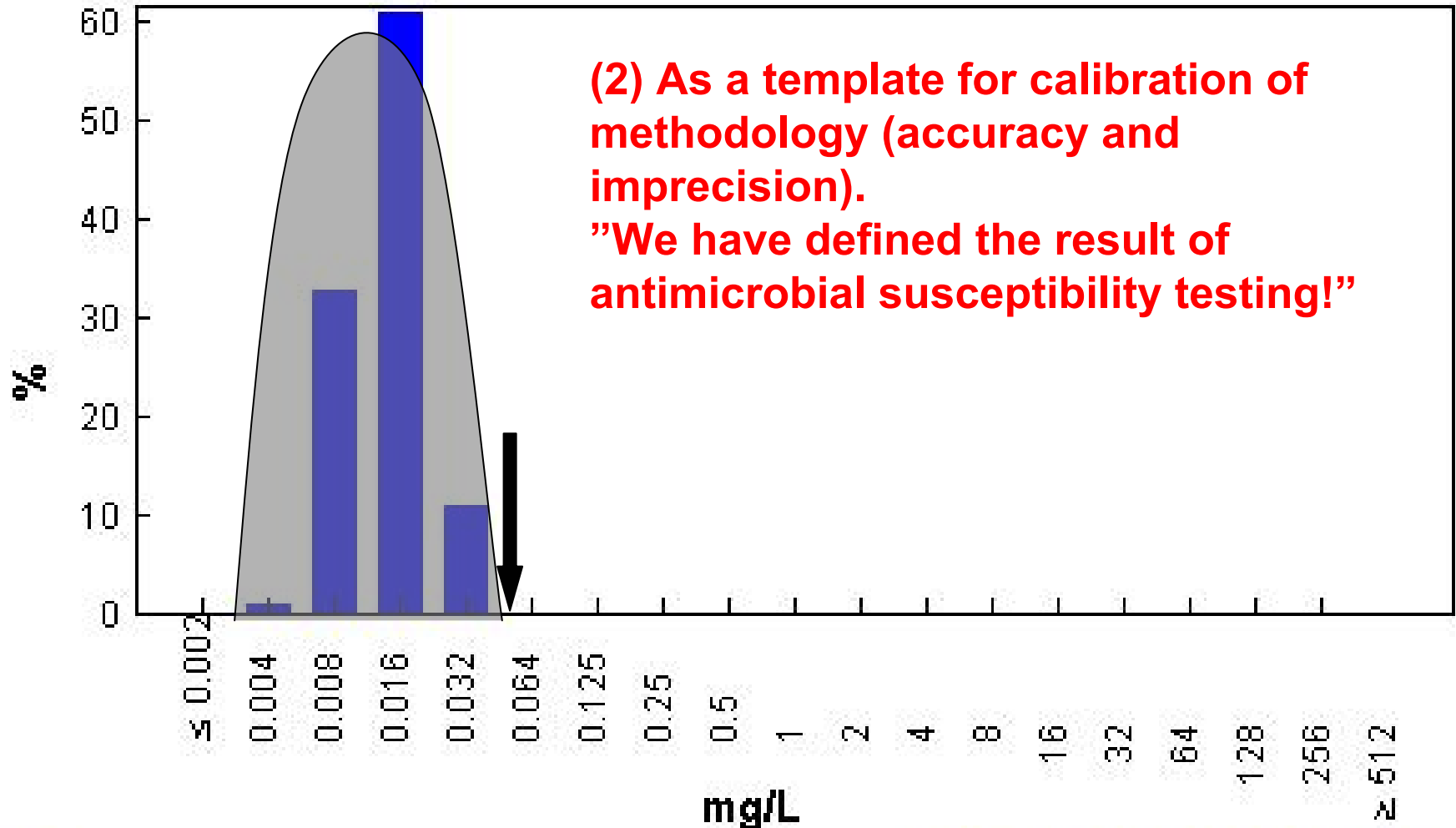
12836 observations (81 data sources)

Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L

Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST MIC Distribution



MIC

Epidemiological cut-off: WT ≤ 0.032 mg/L

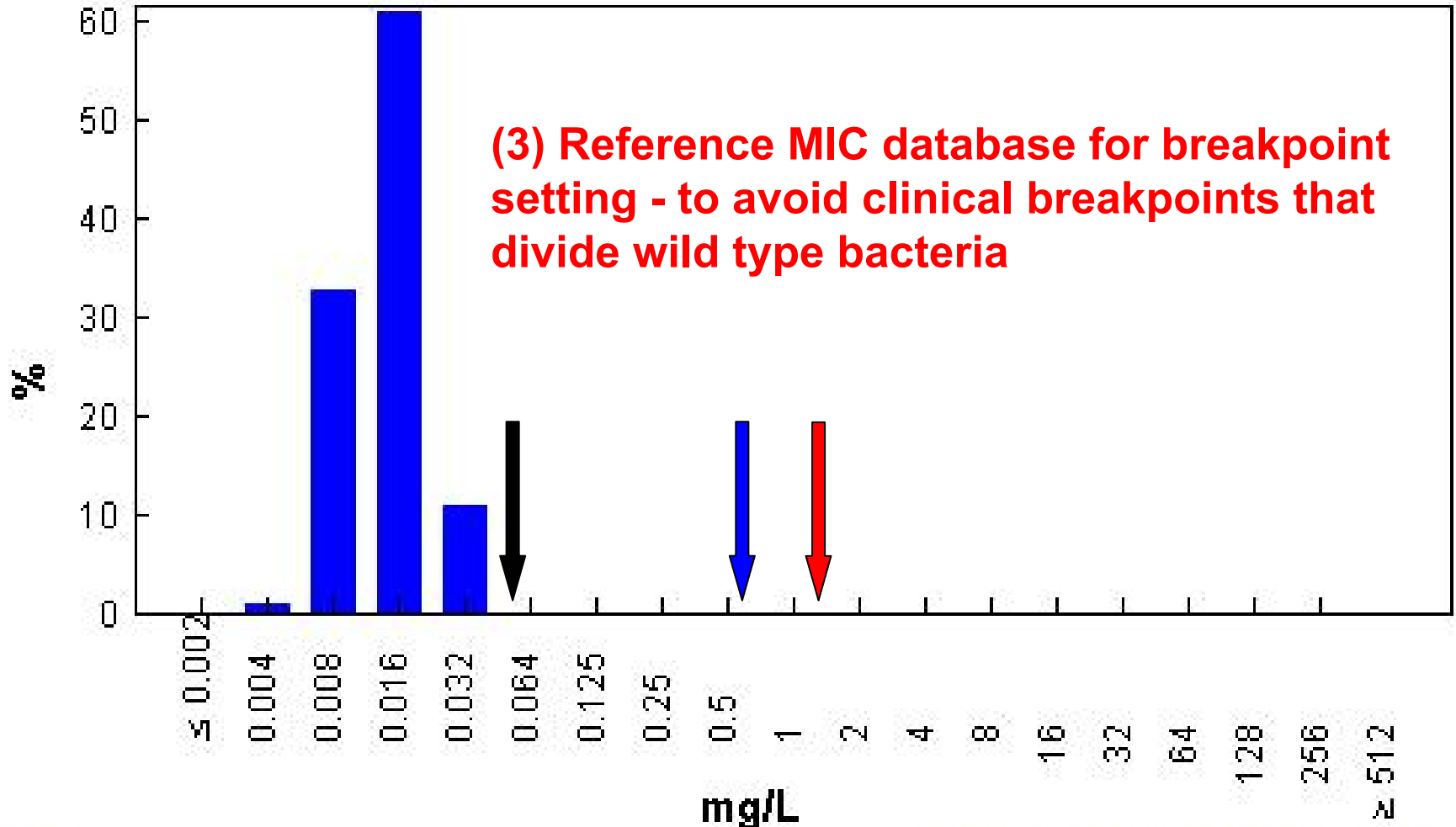
12836 observations (81 data sources)

Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L

Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST MIC Distribution



MIC

Epidemiological cut-off: WT ≤ 0.032 mg/L

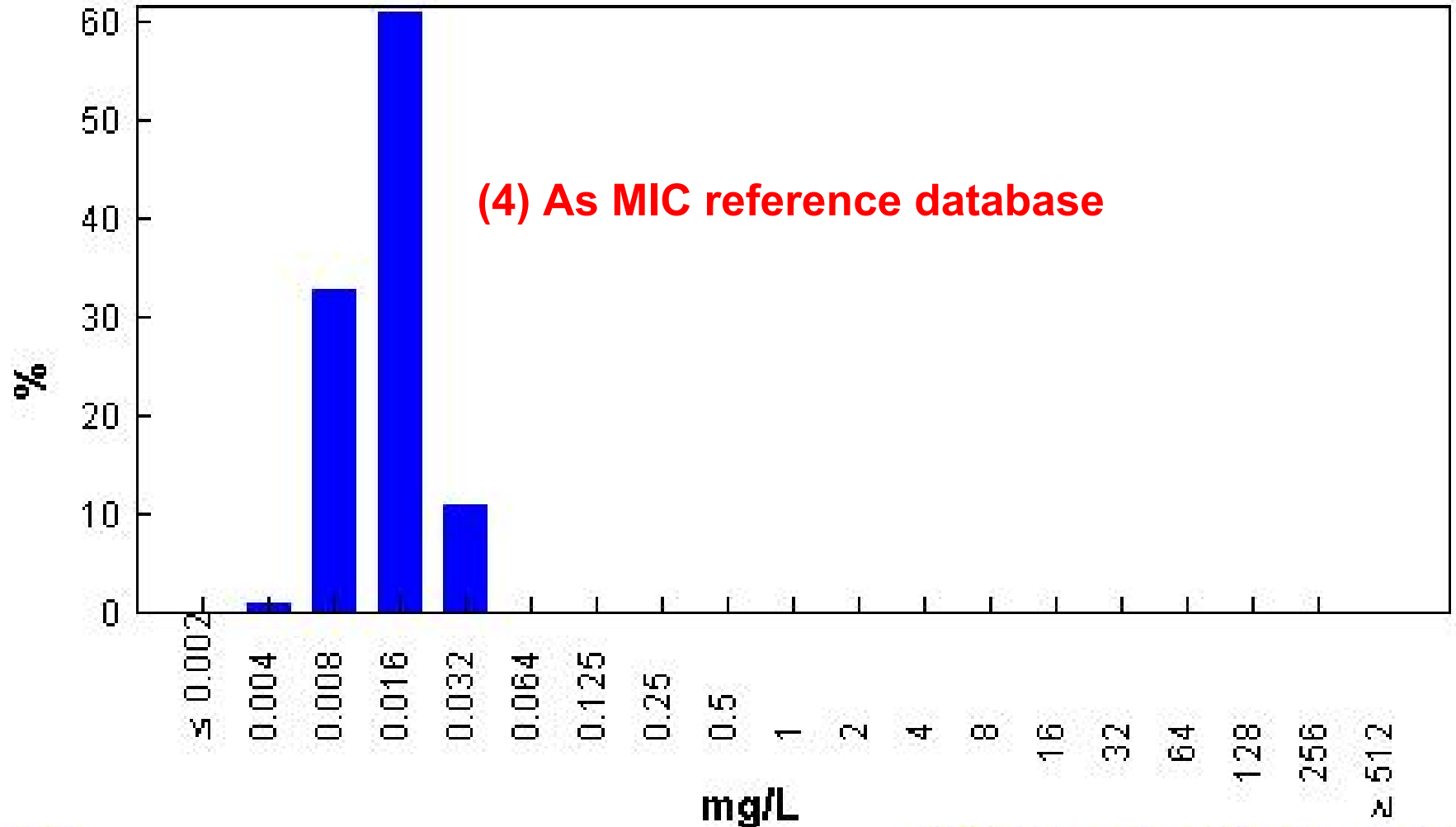
12836 observations (81 data sources)

Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L

Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST MIC Distribution



MIC

12836 observations (81 data sources)

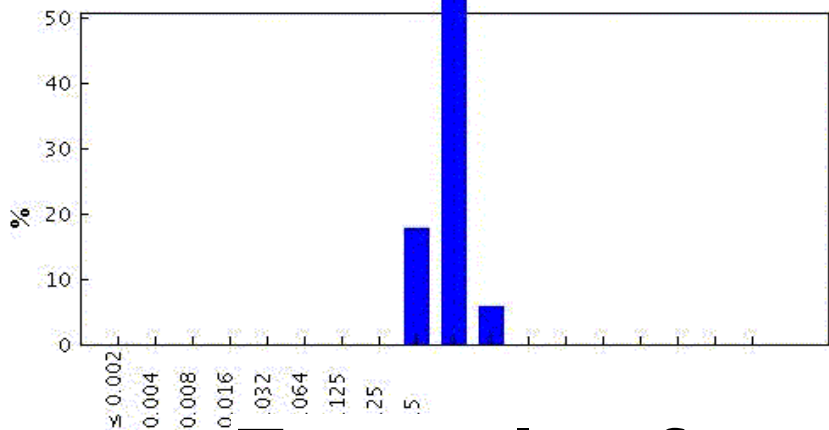
Epidemiological cut-off: WT ≤ 0.032 mg/L

Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L

Vancomycin / *Staphylococcus aureus*

Antimicrobial wild type distributions of microorganisms - reference database

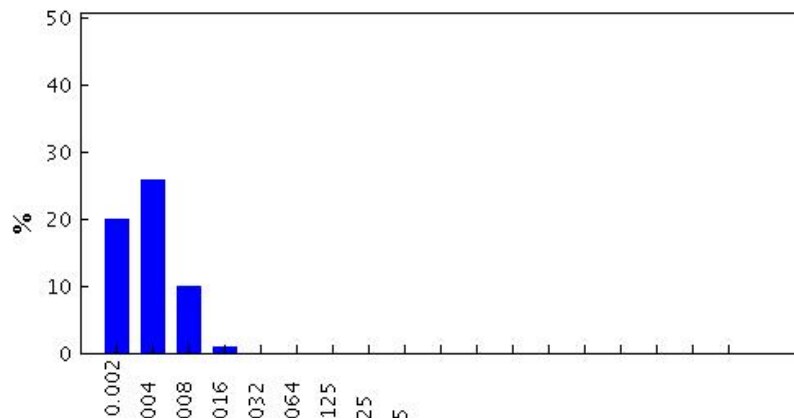
EUCAST



Ciprofloxacin / *Neisseria gonorrhoeae*

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST

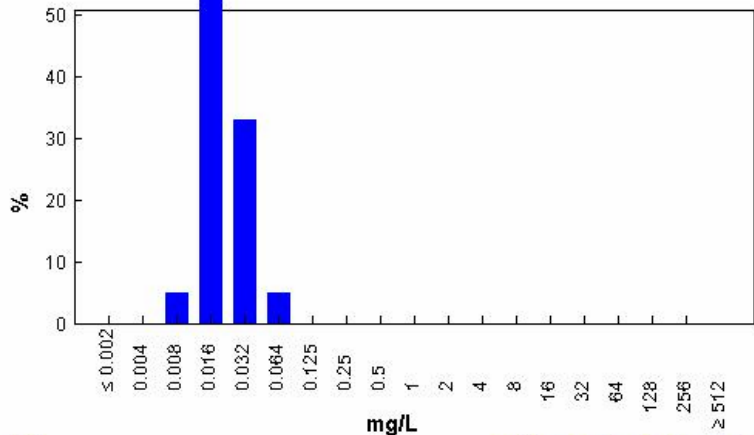


Examples from the EUCAST wild type MIC distribution program.

Moxifloxacin / *Haemophilus influenzae*

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST



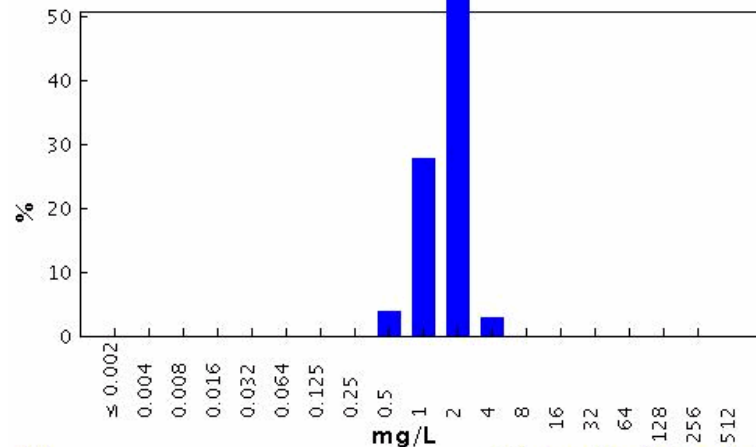
MIC Epidemiological cut-off: WT ≤ 0.125 mg/L

5715 observations (8 data sources)
Clinical breakpoints: S ≤ 1 mg/L, R > 2 mg/L

Linezolid / *Enterococcus faecium*

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST



MIC Epidemiological cut-off: WT ≤ 4 mg/L

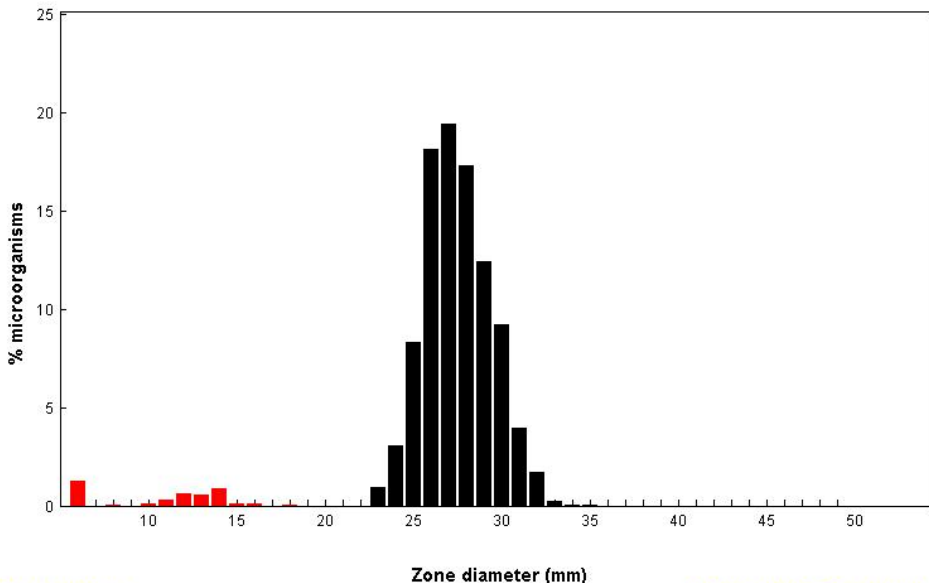
2711 observations (11 data sources)
Clinical breakpoints: S ≤ - mg/L, R > - mg/L

EUCAST Zone diameter Distributions

- During 2009/10 EUCAST has developed a European disk diffusion method based on Mueller-Hinton (MH) medium and MacFarland 0.5 inoculum. For *Haemophilus* spp and streptococci, including *S. pneumoniae*, a MH-F plate was developed, containing 5 % defibrinated horseblood and 20 mg/L of beta-NAD. More information on the EUCAST disk diffusion test is available on the website.
- The “Antimicrobial wild type distributions of microorganisms” website now contains an increasing number of inhibition zone diameter distributions and MIC-zone diameter correlations (to access these, select a Disk Diffusion distribution, click on the required organism or antimicrobial agent in the left column of the distribution table and click on the MIC/Zone Correlation button below the graph.

Cefoxitin / Staphylococcus aureus
EUCAST zone diameter distributions - Reference database
EUCAST disk diffusion method

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

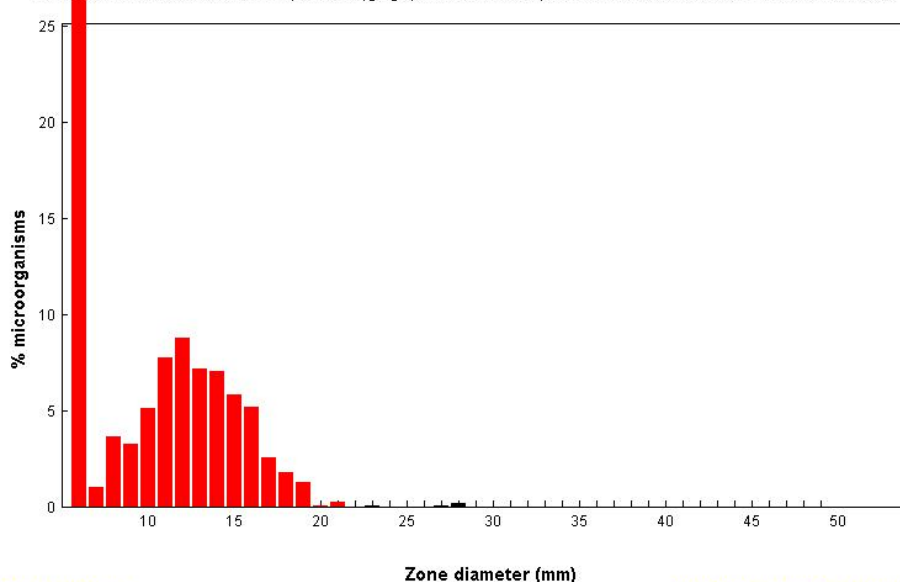


Disk content: 30
 Epidemiological cut-off: WT \geq 22 mm (MIC: \leq 4 mg/L)

2885 observations (3 data sources)
 Clinical breakpoints: S \geq 22 mm, R < 22 mm

Cefoxitin / Staphylococcus aureus MRSA
EUCAST zone diameter distributions - Reference database
EUCAST disk diffusion method

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

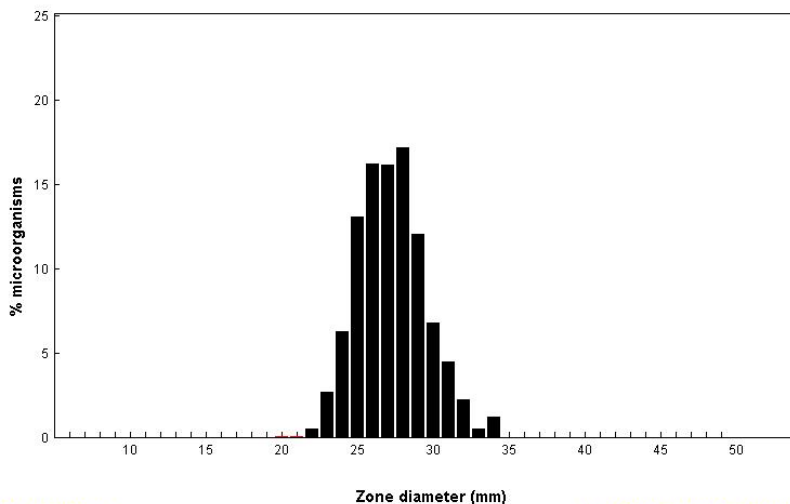


Disk content: 30
 Epidemiological cut-off: WT \geq 22 mm (MIC: \leq 4 mg/L)

973 observations (11 data sources)
 Clinical breakpoints: S \geq 22 mm, R < 22 mm

Cefoxitin / Staphylococcus aureus MSSA
EUCAST zone diameter distributions - Reference database
EUCAST disk diffusion method

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

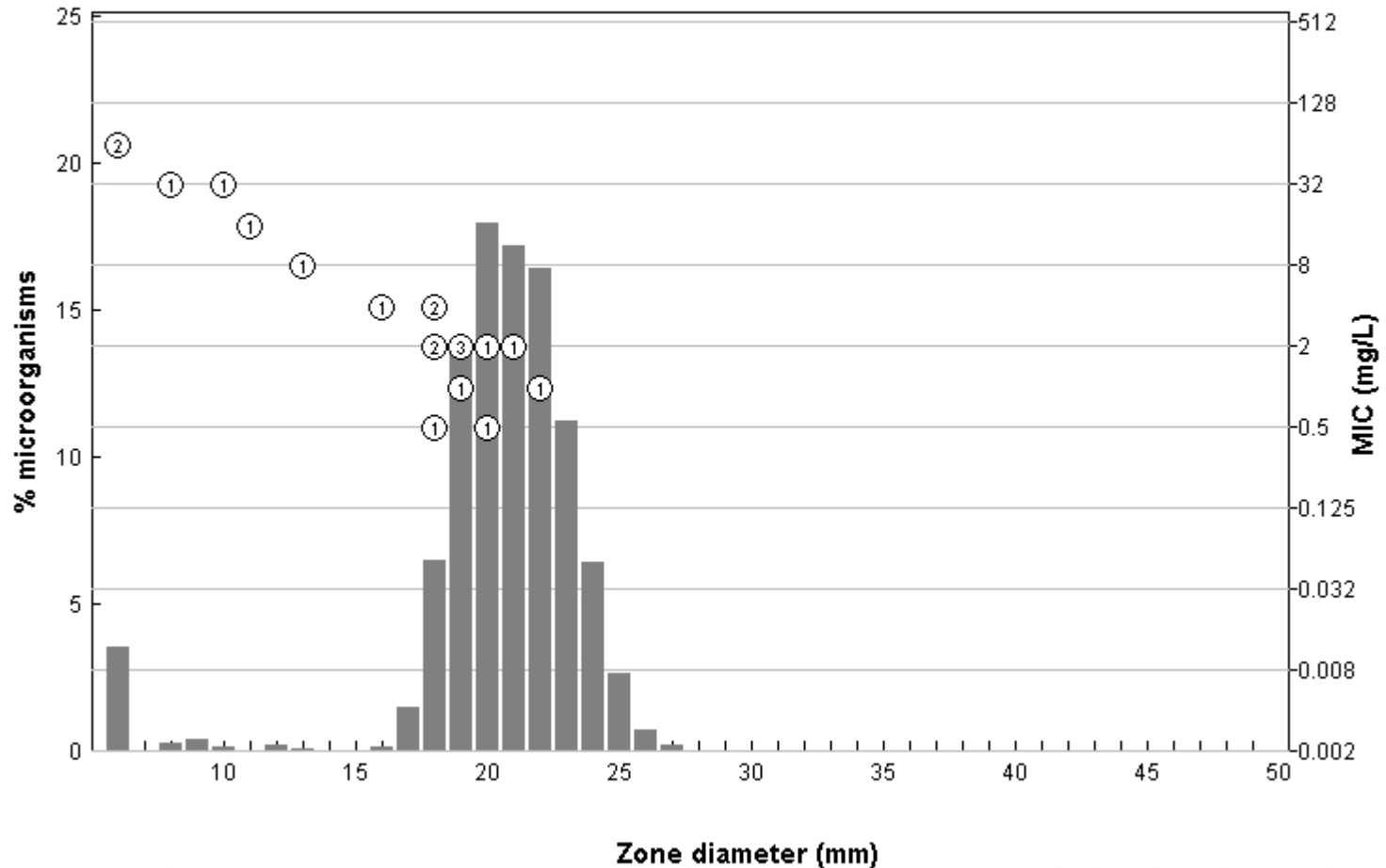


Disk content: 30
 Epidemiological cut-off: WT \geq 22 mm (MIC: \leq 4 mg/L)

1364 observations (11 data sources)
 Clinical breakpoints: S \geq 22 mm, R < 22 mm

Gentamicin / Escherichia coli
EUCAST zone diameter distribution - Reference database
EUCAST disk diffusion method

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



Disk content: 10
 Epidemiological cut-off: -

2457 observations (2 data sources)
 Clinical breakpoints: S ≥ 17 mm, R < 14 mm

Isolates included in the MIC v. zone diameter distribution (indicated by circles) were selected to increase the proportion with susceptibility close to breakpoints. Numbers within circles denote numbers of isolates (red circle if >99). The zone diameter histogram depicts a different population, with unselected isolates.

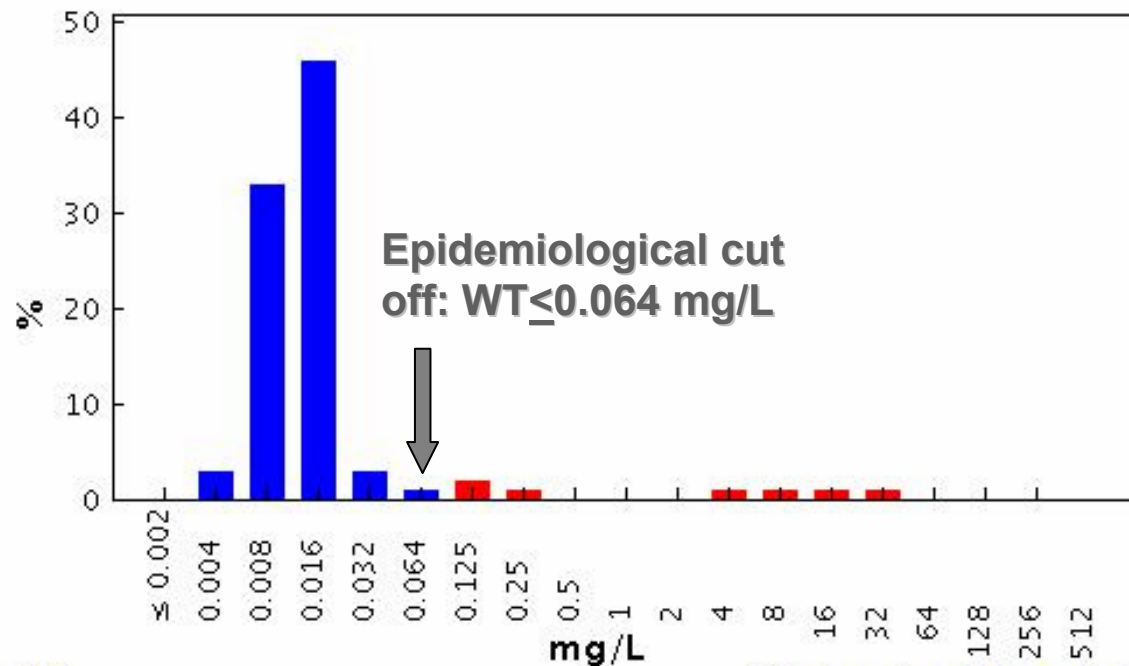
EUCAST procedure for setting breakpoints

The next 9 slides describe the EUCAST procedure for harmonising European breakpoints.

EUCAST procedure for setting breakpoints

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

Ciprofloxacin / *Escherichia coli*
Antimicrobial wild type distributions of microorganisms - reference database
EUCAST



MIC
Epidemiological cut-off: $WT \leq 0.064$ mg/L

4416 observations (6 data sources)
Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L

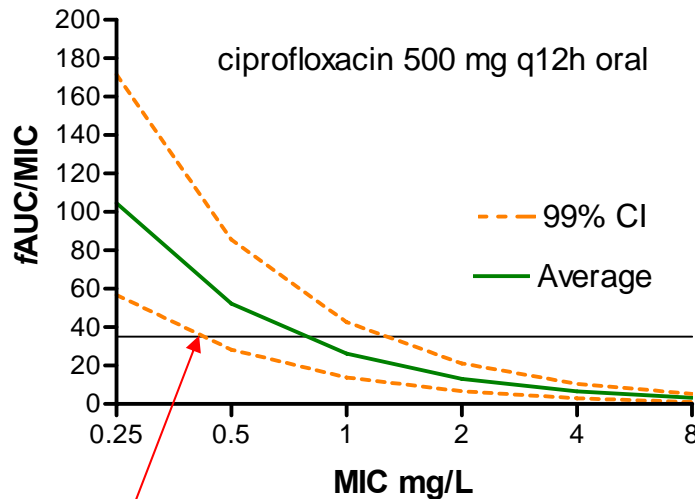
EUCAST procedure for setting breakpoints

3. Existing national clinical breakpoints are compared

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
<i>Pseudomonas</i> spp.	1/4				ND	1/1	1/2
<i>Acinetobacter</i> 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
<i>S. pneumoniae</i>	2/2 (I)*	excluded			0.12/2 (I)*	0.12/2 (I)*	excl
Enterococci	excluded	excluded			0.12/2	0.12/2	1/2
<i>Haemophilus/Moraxella</i> spp.	1/1				0.12/0.5	0.12/0.25	1/-
Corynebacteria						excl	
<i>N. Meningitidis</i>	1/1				0.06/0.12	0.03/0.25	
<i>N. Gonorrhoeae</i>	0.06/-		0.06/1		0.06/0.12	0.06/0.25	0.06/0.5
<i>P. Multocida</i>	ND				ND	0.12/0.25	
Anaerobes	excluded				ND	excluded	
<i>Campylobacter</i> spp.	1/1						
<i>Helicobacter pylori</i>	2/2	no	no		no	no	

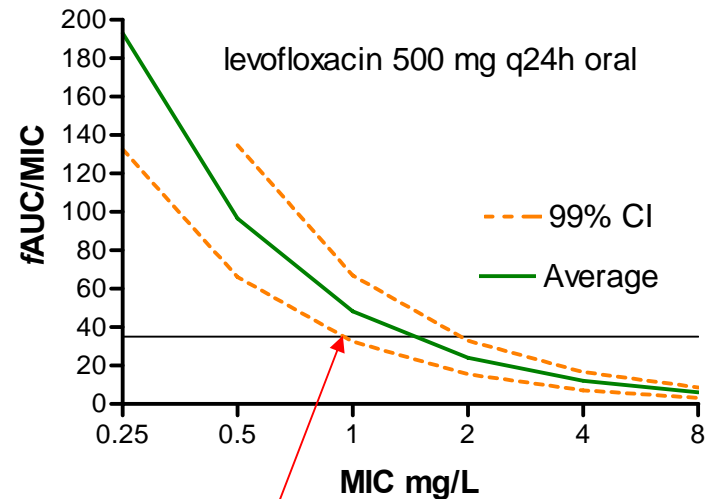
EUCAST procedure for setting breakpoints

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



S = 0.5 mg/L

Pk/Pd



S = 1 mg/L

EUCAST procedure for setting breakpoints

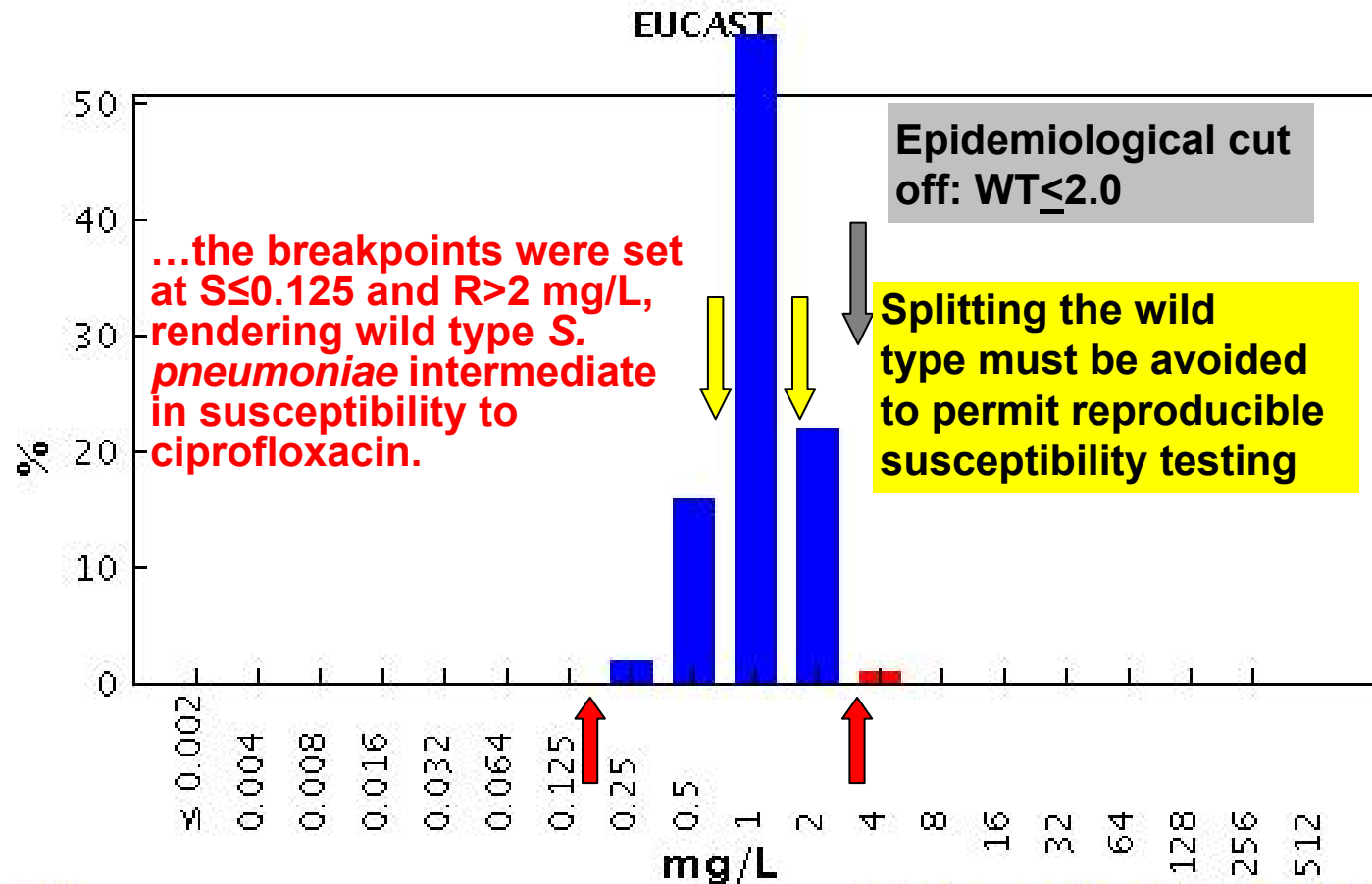
5. Clinical data relating outcome to MIC-values, wild type and resistance mechanisms are assessed in relation to the tentative breakpoint

EUCAST procedure for setting breakpoints

6a. Tentative breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type to obtain tentative breakpoints

Ciprofloxacin / *Streptococcus pneumoniae*

Antimicrobial wild type distributions of microorganisms - reference database



MIC

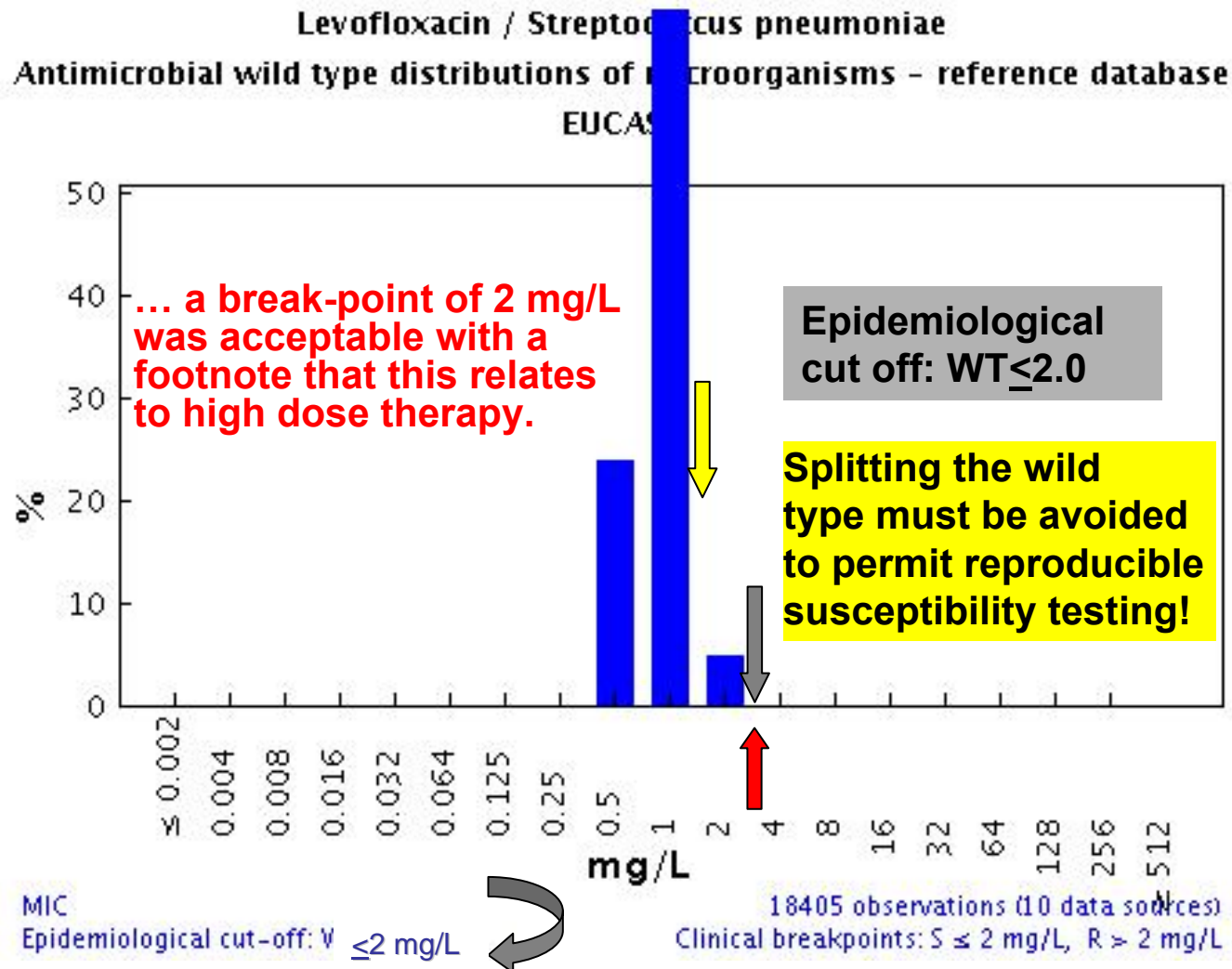
Epidemiological cut-off: $WT \leq 2$ mg/L

41387 observations (33 data sources)

Clinical breakpoints: $S \leq 0.125$ mg/L, $R > 2$ mg/L

EUCAST procedure for setting breakpoints

6b. Tentative breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type to obtain **tentative breakpoints** - example **levofloxacin**



EUCAST procedure for setting breakpoints

7. Tentative breakpoints proposed by the EUCAST Steering Committee are referred to the national breakpoint committees for comments.

When Steering Committee and national committees agree the tentative breakpoints are subjected to the EUCAST consultation process:

8. Consultation process on tentative breakpoints:

- EUCAST General Committee**
- Expert groups (eg *Neisseria*, anaerobes)**
- Pharmaceutical industry, AST device manufacturers**
- Others via EUCAST website**

9. Rationale document prepared and published on website

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

A		B	C	D	E	F	G
1	Enterobacteriaceae						
2							
3	Penicillins¹	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes
4		S ≤	R >		S ≥	R <	Number Letter
5							1. For aminopenicillins, a susceptible breakpoint of ≥8 mg/L ensures that all isolates with resistance mechanisms are reported as resistant. The wide range of dosages and intravenous versus oral administration significantly affects clinical efficacy. The unspecified susceptible breakpoint enables the user to categorize wild type <i>Enterobacteriaceae</i> as either susceptible or intermediate to the aminopenicillins depending on dosing, route of administration and whether the infection is systemic or affects the urinary tract only.
6	Benzylpenicillin	-	-	-	-	-	
7	Ampicillin	Note ¹	8	10	Note ^A	-	2. Different dosing and reporting practices in different countries mean that wild type (without resistance mechanisms) <i>Enterobacteriaceae</i> may be categorized as either susceptible or intermediate to aminopenicillins. If it is common practice to categorize wild type <i>Enterobacteriaceae</i> as susceptible, use breakpoints of S ≥14mm, R <14 mm; to categorize the wild type as intermediate use S ≥50 mm, R <14 mm.
8	Ampicillin-sulbactam²	Note ¹	8	10-15	IP	IP	2. For susceptibility testing purposes, the concentration of sulbactam is fixed at 4 mg/L.
9	Amoxicillin	Note ¹	8	10	Note ^B	Note ^B	B. Susceptibility inferred from ampicillin.
10	Amoxicillin-clavulanate³	Note ¹	8	20-10	Note ^A	12	3. For susceptibility testing purposes, the concentration of clavulanate is fixed at 2 mg/L.
11	Piperacillin	8	16	30	18	15	
12	Piperacillin-tazobactam⁴	8	16	30-6	18	15	4. For susceptibility testing purposes, the concentration of clavulanate is fixed at 4 mg/L.
13	Ticarcillin	8	16	75	23	22	
14	Ticarcillin-clavulanate³	8	16	75-10	23	22	
15							
16	Phenoxymethylpenicillin	-	-	-	-	-	
17							
18	Oxacillin	-	-	-	-	-	
19	Clxacillin	-	-	-	-	-	
20	Dicxacillin	-	-	-	-	-	
21	Flucxacillin	-	-	-	-	-	
22							
23	Mecillinam (uncomplicated UTI only)⁵	8	8	10	15	15	5. Mecillinam (pivmecillinam) breakpoints relate to <i>E. coli</i> , <i>Klebsiella</i> spp. and <i>P. mirabilis</i> only.
24							
25							
26	Cephalosporins¹	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes
27		S ≤	R >		S ≥	R <	Numbers for comments on MIC breakpoints Letters for comments on disk diffusion
28							1. The cephalosporin breakpoints for <i>Enterobacteriaceae</i> will detect all clinically important resistance mechanisms (including ESBL, plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for infection control purposes.
29	Cefaclor	-	-	-	-	-	
30	Cefadroxil (uncomplicated UTI only)	16	16	30	12	12	
31	Cefalexin (uncomplicated UTI only)	16	16	30	-	-	
32	Cefazolin	-	-	-	-	-	
33	Cefepime	1	4	30	24	21	
34	Cefixime (uncomplicated UTI only)	1	1	5	17	17	
35	Cefotaxime	1	2	5	21	18	
36	Cefoxitin	NA	NA	NA	NA	NA	
37	Cefpodoxime (uncomplicated UTI only)	1	1	10	21	21	
38	Ceftazidime	1	4	10	21	18	

Click on MIC breakpoint to access MIC distribution

Click on zone breakpoint to access zone diameter distribution

Click on name to access rationale document

"Dashed" – do not test against this species. May be reported resistant.
IE = Insufficient evidence. An MIC may be reported without SIR-categorization.

EUCAST rationale documents

- The rationale for decisions on breakpoints (for new drugs or as a result of harmonising breakpoints for existing drugs) are given in EUCAST rationale documents.
- An abbreviated version of each rationale document is published as a EUCAST technical note in *Clinical Microbiology and Infection*, either on the drug in question (new drugs) or the class of drugs. The first, which describes daptomycin, was published in 2006.
- Rationale documents are available via the EUCAST website via the EUCAST clinical breakpoint tables.

EUCAST agreed breakpoints

- **Penicillins** benzylpenicillin , ampicillin, ampicillin-sulbactam, amoxicillin, amoxicillin-clavulanate, piperacillin, piperacillin-tazobactam, ticarcillin, ticarcillin-clavulanate, phenoxymethylpenicillin, mecillinam, oxacillin, cloxacillin, dicloxacillin, flucloxacillin
- **Monobactams** aztreonam
- **Cephalosporins** cefazolin, cefepime, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, cefaclor, cefadroxil, cefalexin, cefixime, cefpodoxime, ceftibuten
- **Carbapenems** doripenem, ertapenem, imipenem, meropenem
- **Fluoroquinolones** ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin
- **Aminoglycosides** amikacin, gentamicin, netilmicin, tobramycin
- **Glycopeptides** vancomycin, teicoplanin
- **Macrolides** azithromycin, clarithromycin, erythromycin, roxithromycin, telithromycin, clindamycin, quinupristin-dalfopristin
- **Tetracyclines** doxycycline, minocycline, tetracycline, tigecycline
- **Miscellaneous** chloramphenicol, colistin, daptomycin, fosfomicin, fusidic acid, linezolid, metronidazole, nitrofurantoin, rifampicin, spectinomycin, trimethoprim, trimethoprim-sulfamethoxazole

How to implement EUCAST breakpoints

- The national breakpoint committees have committed themselves to implementing EUCAST breakpoints – which means that anyone using any of the European national systems will gradually adhere to the EUCAST breakpoint system.
- 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 (currently being implemented – most of them available during 2010).
- A disk diffusion method based on the Kirby-Bauer procedure but with zone diameter breakpoints calibrated to EUCAST MIC breakpoints has been developed with the support of ESCMID. Manuals, QC-tables, Educational slide-shows, Frequently Asked Questions and more are available on the website.

European Medicines Agency (EMA) SOP for setting breakpoints through EUCAST



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.

Available from the EUCAST (www.eucast.org) and EMA websites

EMEA SOP for setting breakpoints through EUCAST

- Co-ordinated process between the company, EMEA (rapporteurs and co-rapporteurs) and EUCAST
- Where the company applies for registration of a new agent
 - EMEA decides on indications
 - EUCAST decides on breakpoints.
- EUCAST breakpoints for new drugs are included as the only breakpoints in the SPC (Summary of Product Characteristics).

EMEA SOP for setting breakpoints through EUCAST



European Medicines Agency
Standard Operating Procedure

Title: Harmonisation of European Breakpoints set by
EMEA/CHMP and EUCAST

Document no.: SOP/H/3043

The cooperation between EUCAST and EMEA
will be continued and extended

		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.



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

The EUCAST presentation can be freely downloaded from the EUCAST website at www.eucast.org and slides may be used to give EUCAST details in further presentations

Comments and suggestions are invited:
gunnar.kahlmeter@ltkronoberg.se