

EUCAST – a short introduction

Gunnar Kahlmeter

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2024

Website: www.eucast.org

EUCAST

- **Created** by ESCMID (European Society for Clinical Microbiology and Infectious Diseases) and six national European national breakpoint committees (BSAC, CA-SFM, CRG, DIN, NWGA and SRGA).
- **Organised** and **financed** by ESCMID, and....
- **Financed** by ECDC (European Centre for Disease prevention and Control)
- **Acknowledged** by EMA (European Medicines Agency), MHRA and ECDC
- **Supported** by NACs (national AST committees)
- **In participation with colleagues** all over the world through the public consultation process
- and a **Website** with >80 000 unique page views per month

Organisation

- **General Committee (GC)** with one representative per interested country
- **Steering Committee (SC)** of 12 experts including two representatives of the GC)
- Five 2-day SC meetings per year
- Several public consultations per year
- EUCAST workshop at ECCMID/ESCMID Global each year
- Participation in ESCMID activities
- EUCAST Development Laboratories for bacteria and fungi
- International network of dedicated laboratories with expert interest areas

Acknowledging the chairs and sci secretaries of EUCAST



Ian Philips 1997 - 2000



Gunnar Kahlmeter 2001 - 12



Rafael Canton 2012 - 16



Christian Giske 2016 – 2024



Sören Gatermann 2024 -



Scientific secretaries: Derek Brown (1997 – 2016)



John Turnidge 2016 – 2023.



Mandy Wootton 2023 -

A more recent EUCAST Steering Committee meeting from when the pandemic struck



EDL bacteria



Jenny Åhman

Erika Matuschek



Onur Karatuna

EDL fungi, in Copenhagen, Denmark



Maiken Cavling-Arendrup, SSI, Copenhagen

Milestones in the development of AST

- Fleming developed a broth dilution technique with turbidity as “the reading end point”.
- The WHO commissioned the ICS to achieve standardization...but it failed.
- In the 1970ies, the failure to unite behind one system resulted in the formation of many national systems and breakpoint committees (BSAC, DIN, NCCLS, SRGA, CA-SFM, WRG)
- EUCAST formed by ESCMID in 1997 and restructured in 2001, and I was asked to chair.
- In 2003/04 EMA MoU to invite EUCAST to propose European breakpoints for new antibacterial and antifungal agents.
- In 2004/05 EU and later ECDC decided to assist ESCMID in backing EUCAST financially.



In the beginning everything was simple....

- The MIC was **absolute** - a gift from heaven to the individual organism and microbiologist.
- The MIC has deceptively many decimals (which is what happens when you continue to divide 1 mg/L in two fold dilutions) and "**how can a value with three decimals be inaccurate?**"
- The MIC was directly compared to a concentration in the body (mostly serum).
- Mathematical algorithms taking pharmacokinetics and MIC-values into account were tried, and later discarded. Instead PK/PD, much more sophisticated, was born.
-and in those days, all species shared the same breakpoint.

TABLE 2. Zone Diameter Interpretive Standards and Approximate Minimum Inhibitory Concentration (MIC) Correlates



Antimicrobial Agent	Disc Content	Resistant	Zone Diameter, nearest whole mm		Approximate MIC Correlates ^a	
			Intermediate ^a	Susceptible	Resistant	Susceptible
Amikacin ^b	30 µg	≤ 14	15-16	≥ 17	≥ 20 µg/mL	≤ 10 µg/mL
Ampicillin ^c	10 µg	≤ 10	11-12	≥ 13	≥ 8 µg/mL	≤ 2 µg/mL
Ampicillin ^d	30 µg	≤ 13	14-18	≥ 19	≥ 32 µg/mL	≤ 12 µg/mL
Ampicillin ^e	30 µg	≤ 12	13-16	≥ 17	—	—
Bacitracin ^f	300 µg	≤ 14	15-16	≥ 17	≥ 100 µg/mL	≤ 25 µg/mL
Carbenicillin ^g	10 µg	≤ 10	11-12	≥ 13	≥ 8 µg/mL	≤ 2 µg/mL
Cefazolin ^h	30 µg	≤ 13	14-18	≥ 19	≥ 32 µg/mL	≤ 12 µg/mL
Cefotaxime ⁱ	30 µg	≤ 12	13-16	≥ 17	—	—
Cefoxitin ^j	30 µg	≤ 14	15-16	≥ 17	≥ 100 µg/mL	≤ 25 µg/mL
Cephalexin ^k	30 µg	≤ 13	14-18	≥ 19	≥ 32 µg/mL	≤ 12 µg/mL
Chloramphenicol ^l	30 µg	≤ 12	13-16	≥ 17	—	—
Clindamycin ^m	2 µg	≤ 10	11-12	≥ 13	≥ 8 µg/mL	≤ 2 µg/mL
Colistin ⁿ	10 units	≤ 20	21-28	≥ 29	β-lactamase ^d	≤ 0.1 µg/mL
Erythromycin ^o	15 µg	≤ 11	12-21	≥ 22	≥ 32 µg/mL	≤ 15 µg/mL
Gentamicin ^p	10 µg	≤ 10	11-12	≥ 13	≥ 8 µg/mL	≤ 2 µg/mL
Kanamycin ^q	30 µg	≤ 12	13-16	≥ 17	—	—
Methicillin ^r	1 µg	≤ 10	11-12	≥ 13	≥ 8 µg/mL	≤ 2 µg/mL
Nafcillin^k	1 µg	≤ 10	11-12	≥ 13	≥ 8 µg/mL	≤ 2 µg/mL
Nalidixic Acid ^l	30 µg	≤ 13	14-18	≥ 19	≥ 32 µg/mL	≤ 12 µg/mL
Neomycin	30 µg	≤ 12	13-16	≥ 17	—	—
Nitrofurantoin ^l	300 µg	≤ 14	15-16	≥ 17	≥ 100 µg/mL	≤ 25 µg/mL
Oxacillin^k	1 µg	≤ 10	11-12	≥ 13	≥ 8 µg/mL	≤ 2 µg/mL
Penicillin G when testing <i>staphylococci</i> ^m	10 units	≤ 20	21-28	≥ 29	β-lactamase ^d	≤ 0.1 µg/mL
Penicillin G when testing other microorganisms ⁿ	10 units	≤ 11	12-21	≥ 22	≥ 32 µg/mL	≤ 15 µg/mL

In the beginning there was one table for everything.

The zone diameter breakpoint was considered more exact than the MIC (which were relegated to approximate correlates).

The breakpoint had no caveats!

NCCLS (later CLSI) First Supplement, 1981

It is now many years later.....and much more complicated

Fluoroquinolones ¹	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Ciprofloxacin, <i>S. aureus</i>	0.001	1		5	50 ^A	21 ^A		Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method. 1. For breakpoints for other fluoroquinolones (e.g. pefloxacin and enoxacin), refer to breakpoints set by national breakpoint committees. 2/D. Ofloxacin breakpoints for <i>Staphylococcus</i> spp. have been removed since in systemic infections with staphylococci the agent is inferior to other fluoroquinolones. For topical use of ofloxacin, see tables of topical agents. A. The norfloxacin disk diffusion test can be used to screen for fluoroquinolone resistance. See Note C. B. A disk diffusion test awaits action from the responsible pharmaceutical company. C. Isolates categorised as screen negative can be reported susceptible to moxifloxacin and "susceptible increased exposure" (I) to ciprofloxacin and levofloxacin. Isolates categorised as screen positive should be tested for susceptibility to individual agents or reported resistant.
Ciprofloxacin, Coagulase-negative staphylococci	0.001	1		5	50 ^A	24 ^A		
Delafloxacin (community-acquired pneumonia), <i>S. aureus</i>	0.016	0.016			Note ^B	Note ^B		
Delafloxacin (skin and skin structure infections), <i>S. aureus</i>	0.25	0.25			Note ^B	Note ^B		
Levofloxacin, <i>S. aureus</i>	0.001	1		5	50 ^A	22 ^A		
Levofloxacin, Coagulase-negative staphylococci	0.001	1		5	50 ^A	24 ^A		
Moxifloxacin, <i>S. aureus</i>	0.25	0.25		5	25 ^A	25 ^A		
Moxifloxacin, Coagulase-negative staphylococci	0.25	0.25		5	28 ^A	28 ^A		
Nalidixic acid (screen only)	NA	NA			NA	NA		
Norfloxacin (screen only)	NA	NA		10	17 ^C	17 ^C		
Ofloxacin	Note ²	Note ²			Note ^D	Note ^D		

Aminoglycosides ¹	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Amikacin ² , <i>S. aureus</i>	(16) ¹	(16) ¹		30	(15) ^A	(15) ^A		Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method. 1/A. For information on how to use breakpoints in brackets, see https://www.eucast.org/eucastguidancedocuments/ . 2. Resistance to amikacin is most reliably determined by testing with kanamycin (MIC >8 mg/L). The corresponding zone diameter for the kanamycin 30 µg disk is R<18 mm for <i>S. aureus</i> and R<22 mm for coagulase-negative staphylococci.
Amikacin ² , Coagulase-negative staphylococci	(16) ¹	(16) ¹		30	(15) ^A	(15) ^A		
Gentamicin, <i>S. aureus</i>	(2) ¹	(2) ¹		10	(18) ^A	(18) ^A		
Gentamicin, Coagulase-negative staphylococci	(2) ¹	(2) ¹		10	(22) ^A	(22) ^A		
Netilmicin	IE	IE			IE	IE		
Tobramycin, <i>S. aureus</i>	(2) ¹	(2) ¹		10	(18) ^A	(18) ^A		
Tobramycin, Coagulase-negative staphylococci	(2) ¹	(2) ¹		10	(20) ^A	(20) ^A		

Current breakpoint tables (both EUCAST and CLSI) are full of species specific breakpoints, notes, exceptions, brackets, caveats etc

EUCAST 2024

- Solid organisation
- Financial independence
- Commercial independence
- Decision process based on science and agreement
- Public consultation process to allow outside input
- Breakpoints, guidance and methods freely and easily available via website
- FAQ on website
- User helpdesk accessed via website email system

The European Medicines Agency (EMA)

- Since 2003, an agreement between EMA, pharmaceutical companies and EUCAST, has made EUCAST responsible for proposing breakpoints as part of the European process for approval of new agents.
- In 2024, a similar MoU was signed between MHRA (UK) and EUCAST
- All EUCAST proposed breakpoints since daptomycin have been accepted by EMA.



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The European Committee on Antimicrobial Susceptibility Testing - EUCAST

EUCAST is a standing committee jointly organized by ESCMID, ECDC and European national breakpoint committees. EUCAST was formed in 1997. It has been chaired by Ian Phillips (1997 - 2001), Gunnar Kahlmeter (2001 - 2012), Rafael Canton 2012 - 2016) and Christian Giske (2016 - 2024), Sören Gatermann (2024 -). Its scientific secretary is Derek Brown (1997 - 2016), John Turnidge (2016 - 2023) and Mandy Wootton (2023 -).

The EUCAST webmaster is Gunnar Kahlmeter (2001 -), the clinical data coordinator Rafael Canton (2016-), the technical data coordinator Gunnar Kahlmeter (2012 -), the head of the EDL for bacteria Gunnar Kahlmeter (2010 - 2024) and Erika Matuschek (2024 -), the head of the EDL for fungi Maiken Cavling-Arendrup (2010 -).

EUCAST projects for 2024:

- addressing breakpoint criteria and disk diffusion for new agents,
- reviewing criteria for pathogens frequently involved in endocarditis,
- developing disk diffusion methodology for *Neisseria gonorrhoeae*,
- extending the panel of agents with breakpoints and disk diffusion criteria for anaerobic bacteria (*Clostridium ramosum*, *Clostridium innocuum*, *Clostridium tertium*, *Clostridium septicum*, *Cutibacterium avidum*, *Fusobacterium nucleatum*, *Fingoldia magna*, *Parvimonas micra*, *Peptostreptococcus anaerobius*, *Peptoniphilus* spp.)
- evaluating alternative (alternative to MH-F with horse-blood) media for fastidious microorganisms,
- developing RAST criteria for Salmonella enterica,
- developing reference methods and criteria for mycobacteria and for veterinary purposes, participate in the development of reference methodology for Mycobacterium spp and several veterinary agents and pathogens.

The EUCAST **Development Laboratory for antibacterial agents** is located in Sweden and can be addressed through erika.matuschek@eucast.org or gunnar.kahlmeter@eucast.org.

The EUCAST **Development Laboratory for antifungal agents** is located in Denmark and can be addressed through maca@ssi.dk.

QUICK NAVIGATION 

EUCAST News

07.10.2024

Statistics describing the use of EUCAST websites

27.09.2024

Updated information on the China NAC

26.09.2024

Reference MIC testing of Mycobacterium tuberculosis - discussion 9 Oct as followup to public consultation

24.09.2024

EUCAST is interested in collecting Legionella pneumophila MIC distributions

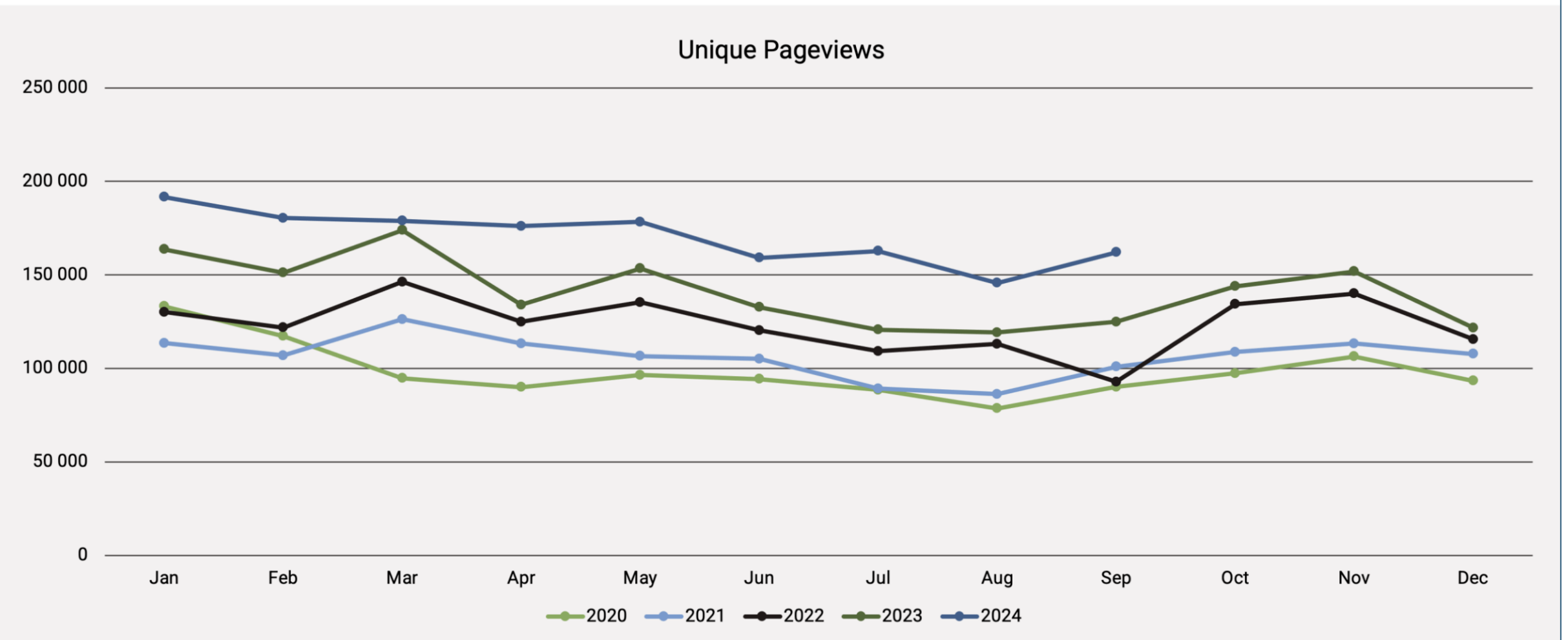
19.09.2024

Aminoglycoside rationale documents updated

[About Newsfeeds](#)

Unique Pageviews for eucast.org 2020–2024

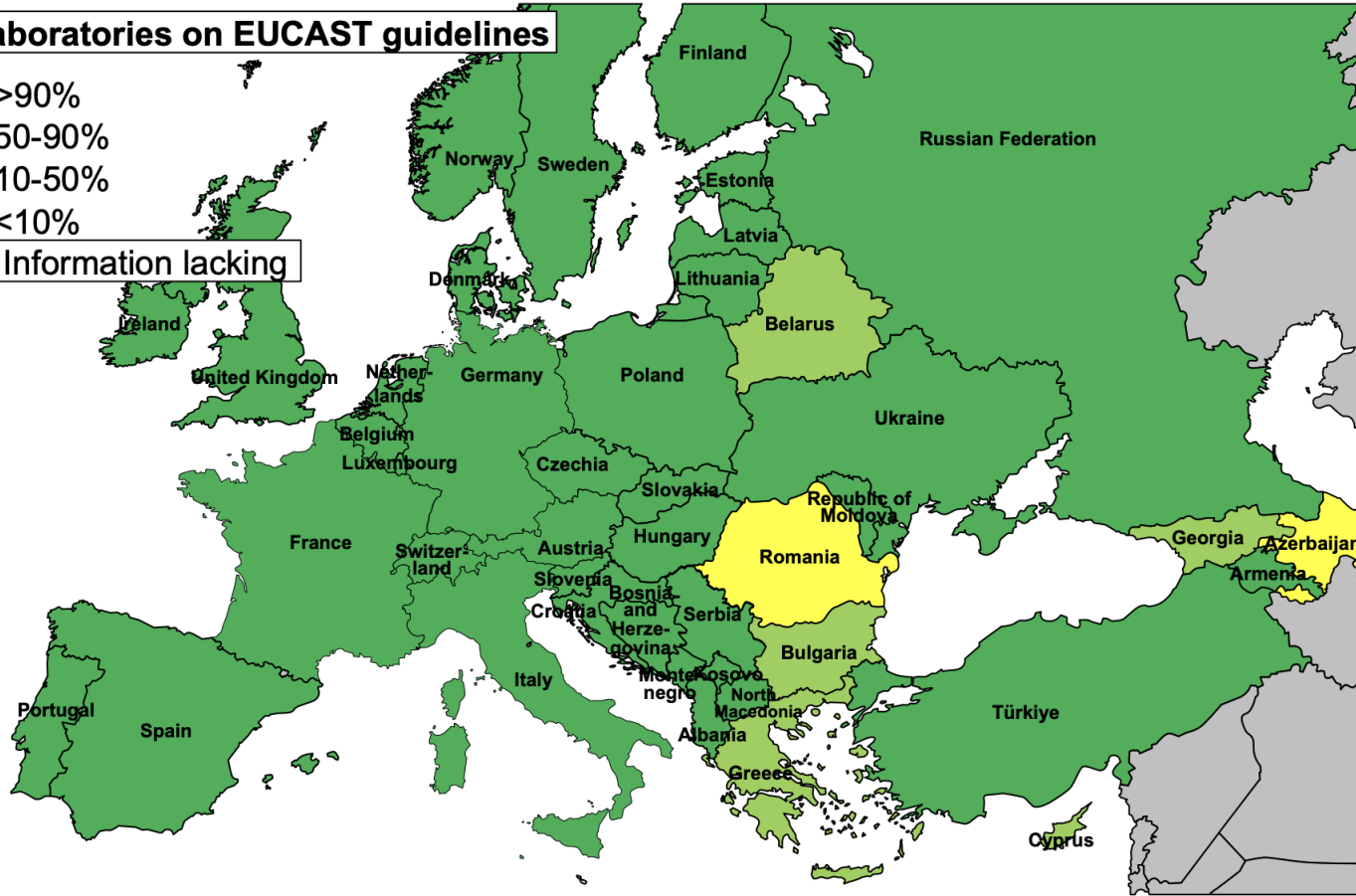
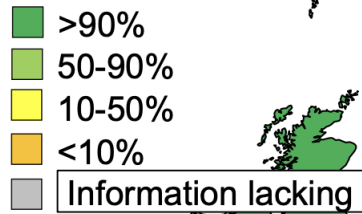
Unique page views per month for <https://www.eucast.org>



Statistics (2020 – 2024) from RedCode, Berlin

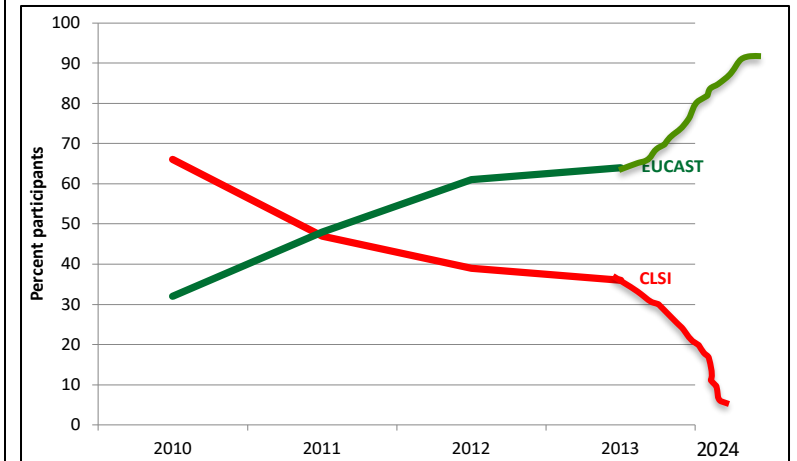
Implementation of EUCAST breakpoints/guidelines, January 2024

% Laboratories on EUCAST guidelines



Countries not on the map: Australia Brazil China Canada Iceland Israel Malta Morocco New Zealand South Africa USA

EUCAST vs. CLSI in Europe



2019: ECDC decision to only accept data generated with EUCAST breakpoints, guidance and methods.

EUCAST methods and guidance

Development of the EUCAST disk diffusion antimicrobial susceptibility testing method and its implementation in routine microbiology laboratories

E. Matuschek¹, D. F. J. Brown² and G. Kahlmeter¹

1) EUCAST Laboratory for Antimicrobial Susceptibility Testing, Växjö, Sweden and 2) EUCAST Scientific Secretary, Peterborough, UK

Article published online: 28 August 2013

Clin Microbiol Infect 2014; **20**: O255–O266

Erika Matuschek will later present EUCAST methods in a separate lecture.

EUCAST recommended media

- MH (Mueller Hinton)
- MH-F (for fastidious organisms; mechanically defibrinated horseblood)
- FAA (Fastidious Anaerobe Agar)

The systematic process has allowed all relevant agents and most species to have breakpoints and methods

- one **agent** after another
- one group of **species** after another

Agents with breakpoints by EUCAST 2002 - 2023

- Benzylpenicillin
- Ampicillin
- Ampicillin-sulbactam
- Amoxicillin w/wo clav acid
- Piperacillin w/wo tazob
- Ticarcillin w/wo clav acid
- Temocillin
- Phenoxymethylpenicillin
- Isoxazolympenicillins
- Mecillinam

- Cefaclor
- Cefadroxil
- Cefalexin
- Cefazolin
- Cefepime
- Cefiderocol
- Cefixime
- Cefotaxime

- Cefoxitin
- Cefpodoxime
- Ceftaroline
- Ceftazidime w/wo avib
- Ceftibuten
- Ceftobiprole
- Ceftolozane-tazobactam
- Ceftriaxone
- Cefuroxime

- Doripenem
- Ertapenem
- Imipenem w/wo releb
- Meropenem w/wo vabor
- Aztreonam

- Ciprofloxacin
- Delafloxacin
- Levofloxacin
- Moxifloxacin
- Ofloxacin
- Norfloxacin
- Amikacin
- Gentamicin
- Netilmicin
- Tobramycin
- Dalbavancin
- Oritavancin
- Teicoplanin
- Telavancin
- Vancomycin
- Azithromycin
- Clarithromycin
- Erythromycin
- Roxithromycin
- Azithromycin
- Clindamycin

- Doxycycline
- Eravacycline
- Minocycline
- Tetracycline
- Tigecycline
- Quinupristin-dalfopristine
- Linezolid
- Tedizolid
- Chloramphenicol
- Daptomycin
- Fosfomicin
- Fusidic acid
- Metronidazole
- Nitrofurantoin
- Nitroxoline
- Rifampicin
- Spectinomycin
- Trimethoprim w/wo sulfa
- Bedaquiline
- Delamanid

- Antifungal agents

Species with breakpoints and methodology by EUCAST

- Enterobacterales
- Pseudomonas spp
- Acinetobacter spp
- Stenotrophomonas maltophilia
- Staphylococcus spp
- Enterococcus faecalis and E. faecium
- Streptococcus A, B, C and G
- Streptococcus, viridans group
- Haemophilus influenzae
- Moraxella catarrhalis
- Pasteurella multocida
- Campylobacter jejuni and C. coli
- Kingella kingae
- Aerococcus spp
- Aeromonas spp
- Achromobacter xylosoxidans
- Neisseria gonorrhoeae*
- Neisseria meningitidis*

- Bacteroides spp
 - Prevotella spp
 - Fusobacterium necrophorum
 - Clostridium perfringens
 - Clostridioles difficile
 - Cutibacterium acnes
- Anaerobic bacteria
- Vibrio cholerae, V. alginolyticus, V. fluvialis, V. parahemolyticus, V. vulnificus
 - Corynebacterium spp, including C. diphtheriae and C. ulcerans
 - Burkholderia pseudomallei
 - Bacillus anthracis
 - Brucella melitensis

 - Mycobacterium tuberculosis (ongoing)*
 - Extended list of anaerobic bacteria*
 - Atypical mycobacteria*
 - Nocardia spp (ongoing)*

*Methodological development ongoing

EUCAST Guidance documents

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The European Committee on Antimicrobial Susceptibility Testing – EUCAST

Guidance Documents

EUCAST Guidance Documents

- [Cefiderocol MIC broth microdilution guide](#) (1 January, 2024). See also the [Warning on cefiderocol susceptibility testing](#).
- [When there are no breakpoints](#) (3 September, 2024), [Previous version](#) (29 February, 2024). [Previous version](#) (30 June, 2023), [Previous version](#) (1 December 2021 - 30 June, 2023), [Previous version](#) (5 July, 2016 - 1 December 2021).
- [Guidance on the use of fosfomycin intravenously](#) (28 May, 2024); [Previous version](#) (5 December, 2023).
- [ATU - the Area of Technical Uncertainty - Guidance to laboratories on how to deal with the antimicrobial susceptibility testing](#) (originally published 2018; updated 2019, 2020, 2022, and 8 February 2024).
[Graphs to illustrate ATUs](#) (Updated 5 February, 2024).
- [Guidance on the use of ceftriaxone and cefotaxime in Staphylococcus aureus](#) (8 February, 2023)
- [Aminopenicillin breakpoints Enterobacterales following revision 2023 - guidance on implementation](#) (14 January, 2023; an error in the flowchart was corrected on Sept 15, 2023).
- [Setting breakpoints for agent-inhibitor combinations](#) (14 December, 2021). [Previous version of Setting breakpoints for agent-inhibitor combinations](#) (2 October, 2017).
- [Breakpoints in brackets in breakpoint tables](#) (2 December 2021)
- [Phenotypic screening tests to detect and exclude resistance of clinical relevance](#) (update 22 August, 2022). [Previous version](#) (13 June, 2022). [Previous version](#) (2 Febr, 2022). [Previous version](#) (1 Dec 2021)
- [Implementation and use of the 2022 revised colistin breakpoints](#) (January, 2022; minor edits on previous version from Nov, 2021)
- [Legionella pneumophila susceptibility testing](#) (30 May, 2021); previous version [Legionella pneumophila susceptibility testing](#) (11 Dec, 2017)
- [Implementation and use of the 2020 revised aminoglycoside breakpoints](#) (first published 21 Jan, 2020; updated April 2020)
- [Daptomycin in endocarditis and bloodstream infections caused by enterococci](#) (also available in CMI as a [EUCAST position paper](#); 2020)
- [Breakpoints for topical use of antimicrobial agents](#) (revised 12 April 2022, 21 Nov, 2019; 22 Dec, 2016)
- [Guidance for industry on the working order between pharmaceutical industry, EMA and EL](#) (5 May, 2019)
- [Cefotaxime and ceftazidime disks with and without clavulanic acid for ESBL confirmation](#) (12 February, 2019)
- [Guidance on tigecycline dosing](#), 21 July, 2022. [Previous version](#) (23 December, 2018)
- [The 2019 modifications of susceptibility categories S, I and R categories](#) (22 October, 2018).
This presentation also informs laboratories on how to implement the Area of Technical Uncertainty.
- [EUCAST system for antimicrobial name abbreviations](#) (January 2022). [Previous version](#) (13 July, 2018)
- [Recommendations for colistin \(polymyxin E\) MIC testing - joint EUCAST and CLSI recommendation](#) (22 March, 2016)
- [Burkholderia cepacia complex](#) (20 July, 2013)
- [Stenotrophomonas maltophilia](#) (1 Feb 2012)
- [Oral cephalosporins and Enterobacterales breakpoints](#) (14 July, 2020). [Previous version](#) (16 Feb 2012)
- [Direct susceptibility testing](#) (16 Feb 2012). See also

EUCAST, CLSI, and FDA all use the same ingredients to determine a clinical breakpoint but with different emphasis and priority.

- Microbiological data organised by
 - Target species – MIC, wild type vs. non-wild type; resistance mechanisms
 - Methods (primarily reference BMD), disk diffusion
- Defined target infections (BSI, uUTI, cUTI, SSSTI, etc)
- PK/PD
 - Dosing (dose and frequency) and exposure.
 - Mode of administration (oral, IV, IV infusion).
 - TA, Population simulations
 - Sites of infection
 - Species
- Clinical outcome
 - By target species
 - By target infection
 - By MIC (mg/L)
 - By resistance mechanisms (MRSA vs. MSSA, ESBL producers vs. Others etc)
 - Wild type vs. Non-wild type
- Tolerance

A EUCAST format for determining breakpoints

- Breakpoints for an agent – i
- Collect/Develop MIC distrib
- Pharmacokinetics (PK)
- Pharmacodynamics (PD) – v
and Johan Mouton, later Sh
- Dosing and modes of administration – and how PK/PD is influenced
- Target infections
- Clinical outcome data on wild type isolates – which species and infections are suitable targets for the agent
- Clinical outcome on isolates with resistance mechanisms (if available)

Review > Clin Microbiol Infect. 2012 Mar;18(3):E37-45. doi: 10.1111/j.1469-0691.2011.03752.x.

Epub 2012 Jan 20.

The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach

J W Mouton ¹, D F J Brown, P Apfalter, R Cantón, C G Giske, M Ivanova, A P MacGowan, A Rodloff, C-J Soussy, M Steinbakk, G Kahlmeter

Antimicrobial Susceptibility Testing (AST)

- To predict clinical outcome
 - to inform of what is needed to achieve a successful outcome
- For AMR surveillance
 - Clinical resistance
 - Biological resistance (ECOFFs, genes, mechanisms)

Breakpoints and testing are based on the MIC

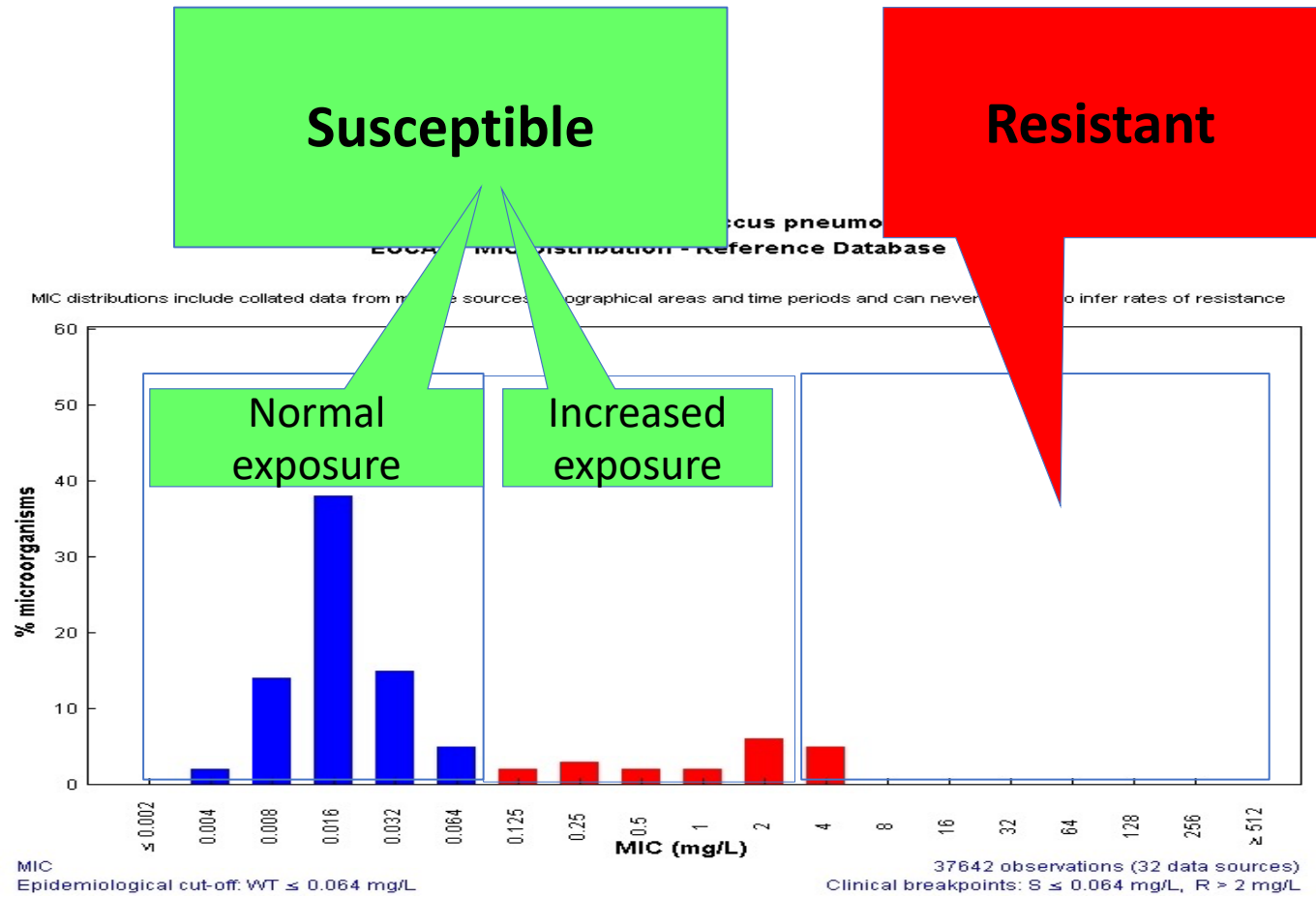
In a standardised system, the MIC is a reproducible, but **relative** measurement.

In a standardised system, the inhibition zone diameter is a reproducible but **relative** measurement.

Susceptibility categories

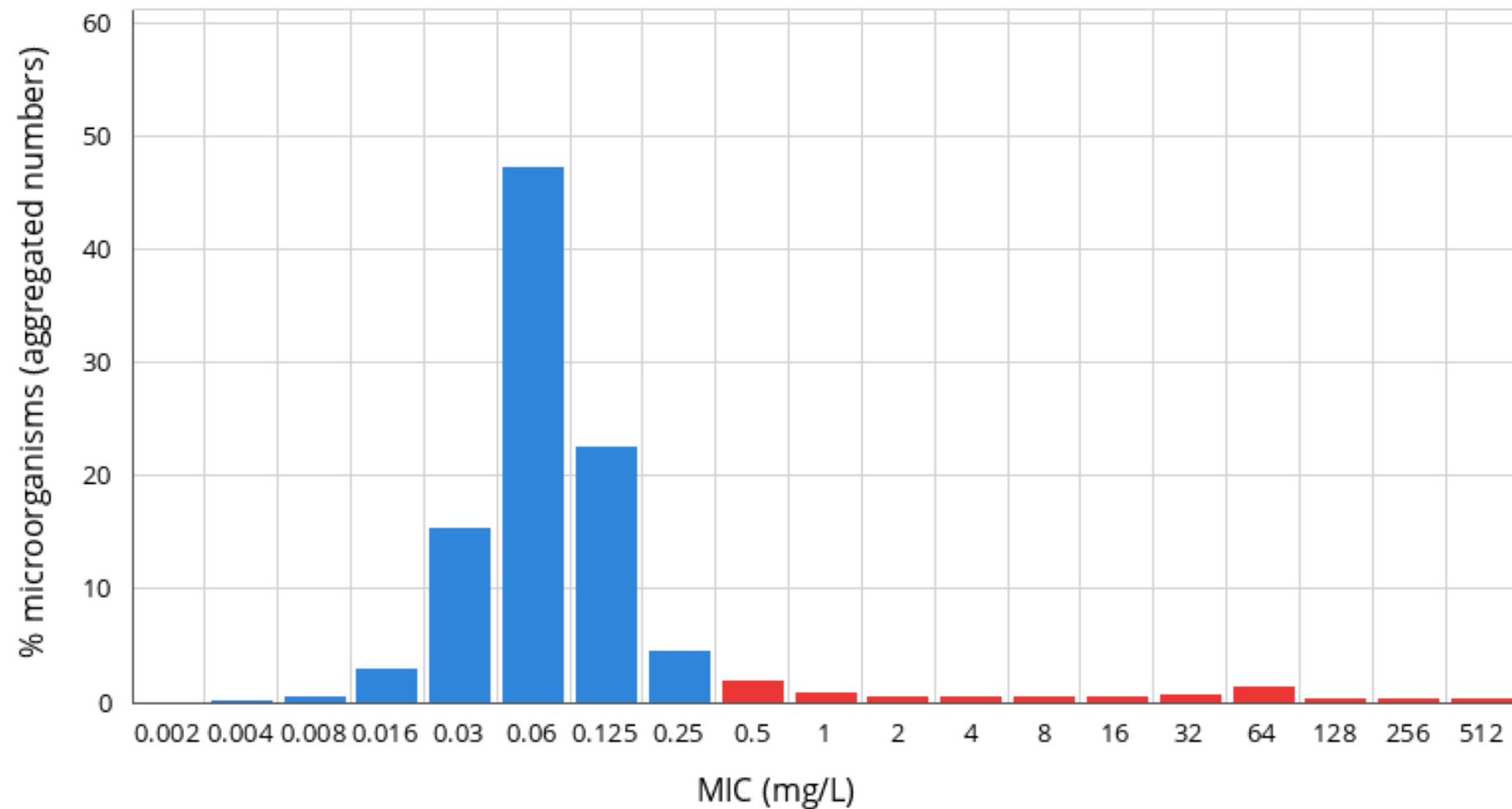
- S – susceptible, at normal exposure
- I – susceptible, at increased exposure
- R – resistant irrespective of exposure
- (S) or (I) – susceptible under certain conditions
- Dash – resistant irrespective of testing
- IE – insufficient evidence to determine a breakpoint

SIR – new definitions 2019



Cefotaxime / Escherichia coli
International MIC distribution - Reference database 2023-03-20
Based on aggregated distributions

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



MIC
Epidemiological cut-off (ECOFF): 0.25 mg/L
Wildtype (WT) organisms: ≤ 0.25 mg/L

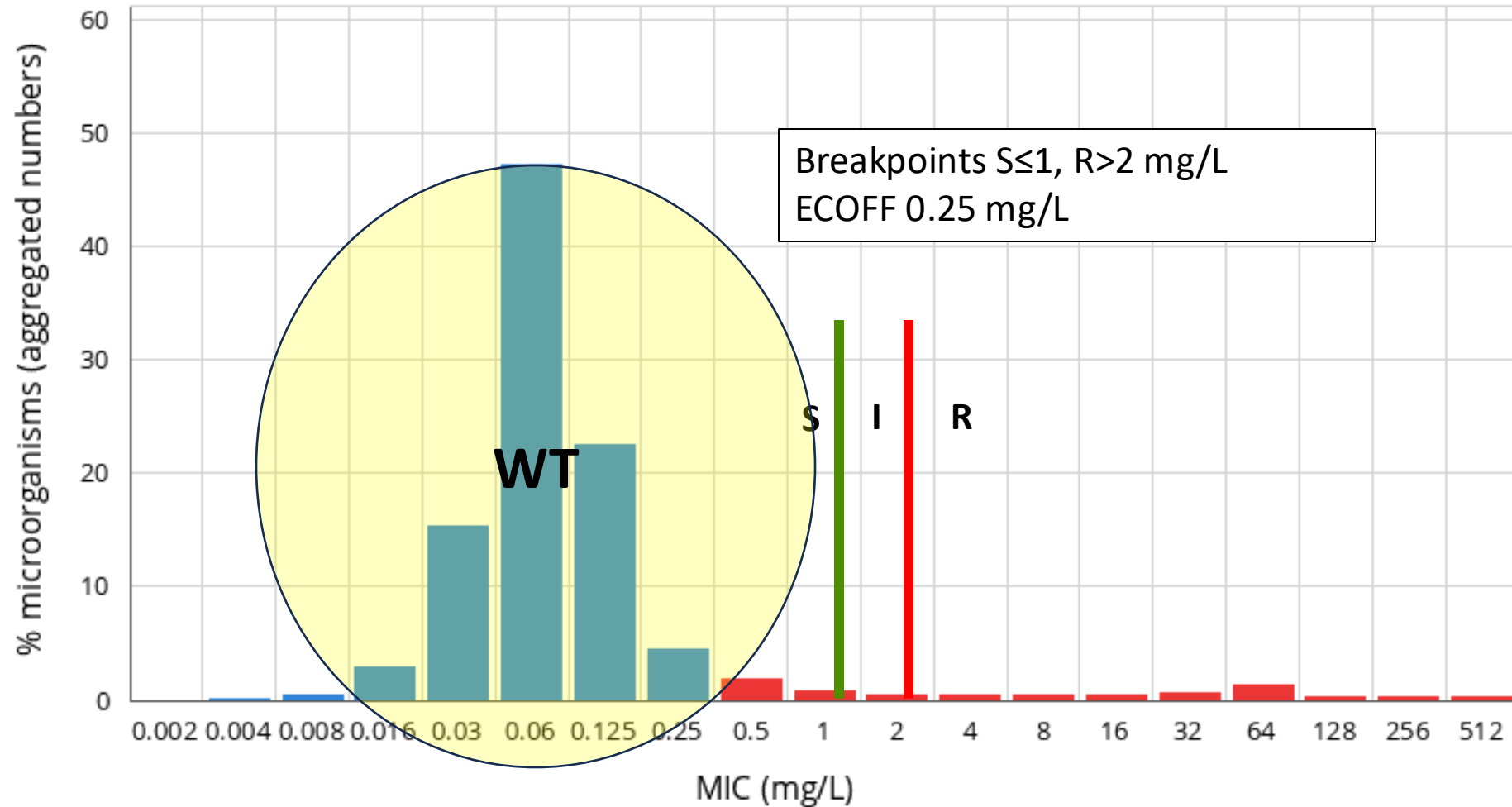
Confidence interval: 0.125 - 0.25
10487 observations (44 data sources)

Cefotaxime / Escherichia coli

International MIC distribution - Reference database 2023-03-20

Based on aggregated distributions

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

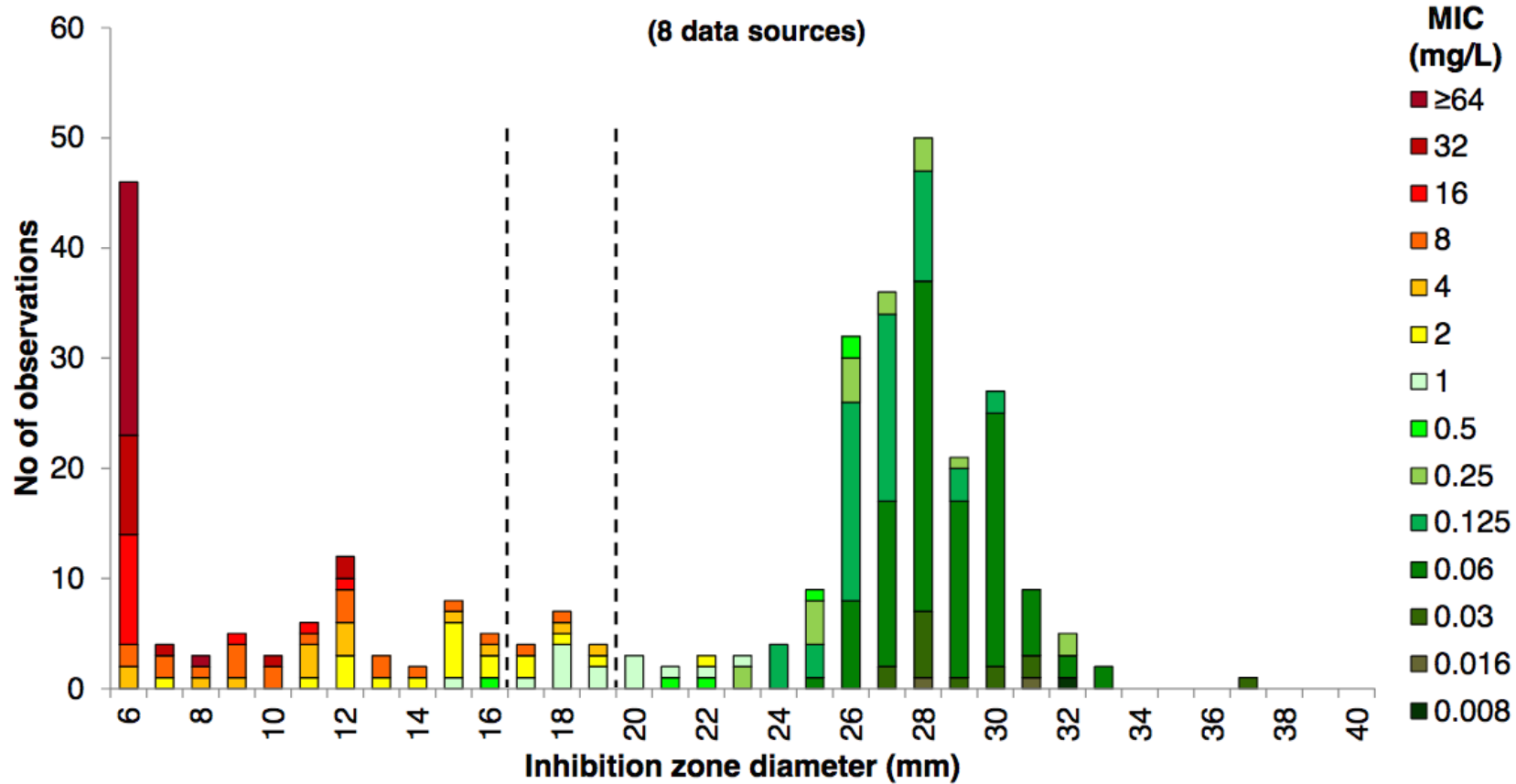


MIC
Epidemiological cut-off (ECOFF): 0.25 mg/L
Wildtype (WT) organisms: ≤ 0.25 mg/L

Confidence interval: 0.125 - 0.25
10487 observations (44 data sources)

Establishing the correlates between MciC and inhibition zone diameter for a defined species and disk content

Cefotaxime 5 µg vs. MIC *E. coli*, 288 isolates (319 correlates)



Breakpoints

MIC S≤1, R>2 mg/L
Zone diameter S≥20, R<17 mm

ECOFF

0.25 mg/L

EUCAST website assets and how to use them

1

The screenshot shows the EUCAST website homepage. At the top, there is a navigation bar with links for Home, Contact, Sitemap, and Newsletter, along with social media icons. The main header includes the EUCAST logo and the text 'EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING' and 'European Society of Clinical Microbiology and Infectious Diseases'. A search bar is located in the top right. Below the header, there is a 'QUICK NAVIGATION' dropdown menu. The main content area features a large group photo of the committee members with the title 'The European Committee on Antimicrobial Susceptibility Testing - EUCAST'. To the right of the photo, there is a 'EUCAST News' section with several news items, including 'Statistics describing the use of EUCAST websites' (dated 07.10.2024), 'Updated information on the China NAC' (dated 27.09.2024), 'Reference MIC testing of Mycobacterium tuberculosis - discussion 9 Oct as followup to public consultation' (dated 26.09.2024), and 'EUCAST is interested in collecting Legionella pneumophila MIC distributions' (dated 24.09.2024). Below the news items, there is a section for 'EUCAST projects for 2024' which lists several ongoing projects, such as addressing breakpoint criteria for new agents, reviewing criteria for pathogens frequently involved in endocarditis, and developing reference methods for Mycobacterium spp. and several veterinary agents and pathogens. At the bottom of the page, there is a 'Website changes' section.

2

Antimicrobial wild type distributions of microorganisms

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

[Search database](#)

MIC and Inhibition zone diameter distributions of microorganisms without and with phenotypically evident resistance mechanisms

MIC and inhibition zone diameter distributions

The database of MIC and zone diameter distributions was created by Gunnar Kahlmeter for EUCAST from 2002 and onwards. More data is regularly added and all data is curated by Gunnar Kahlmeter and John Turnidge, EUCAST. Distributions are shown as "aggregated distributions" and as "aggregated weighted distributions". For aggregated distributions all accepted distributions (as defined in SOP 10) were added to form one common distribution. For aggregated weighted distributions each individual distribution was converted to contribute equally to the common aggregated distribution. In this way large distributions are prevented from drowning out smaller distributions.

For additional information on "Wild type distributions and ECOFFs", see Gunnar Kahlmeter & John Turnidge. How to: ECOFFs-the why, the how, and the don'ts of EUCAST epidemiological cutoff values. Clinical Microbiology and Infection 2022 Jul;28(7):952-954. DOI: 10.1016/j.cmi.2022.02.024

Gunnar Kahlmeter & John Turnidge. Wild-type distributions of minimum inhibitory concentrations and epidemiological cut-off values-laboratory and clinical utility. Clinical Microbiology Reviews 2023. DOI: 10.1128/cmr.00100-22

1. MIC distributions

The website gives MIC distributions for individual micro-organisms (bacteria and fungi) and antimicrobial agents in tables and histograms. The distributions are based on collated data from an increasing total of more than 30 000 MIC distributions from worldwide sources. Unless otherwise specifically stated, the data are representative of results obtained with MIC methods performed by or calibrated to reference broth microdilution using ISO-20776-2. Different 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 MIC distributions encompass the variation between different investigators, laboratories, geographic locations and time periods.

2. Inhibition zone diameter distributions

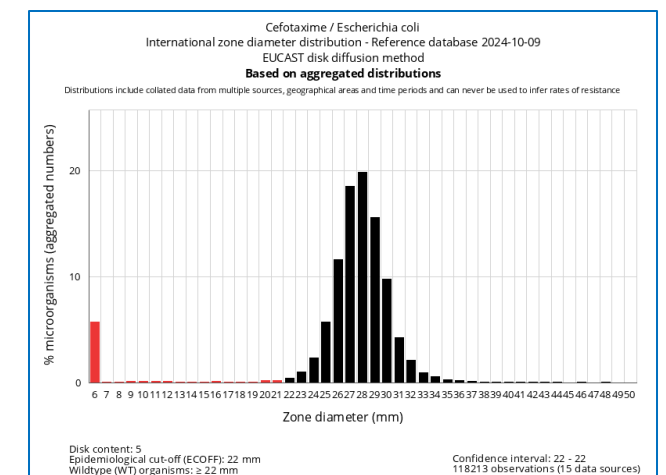
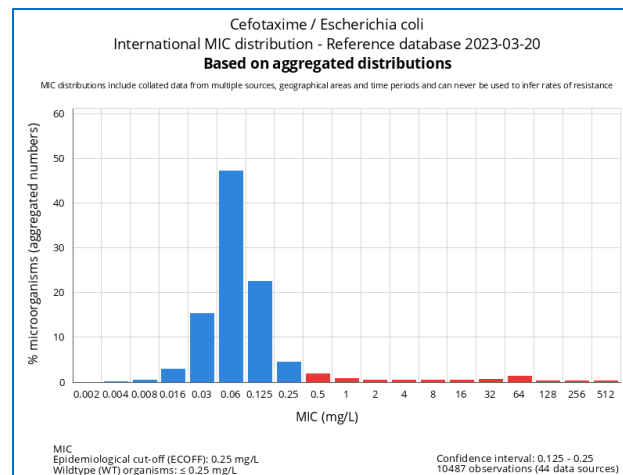
The website gives inhibition zone diameter distributions for individual organisms and antimicrobial agents in tables and histograms. The distributions are based on collated data from an increasing number of sources worldwide. The data are representative of results obtained with the EUCAST disk diffusion method (launched in 2009 - see www.eucast.org).

Clinical MIC and Zone diameter breakpoints

These are not shown on this website - please consult the EUCAST breakpoint tables for bacteria and fungi on www.eucast.org.

Epidemiological cut-off values (ECOFF) and tentative epidemiological cut-off values (TECOFF)

ECOFFs (and TECOFFs) distinguish microorganisms without (wild type) and with phenotypically detectable acquired resistance mechanisms (non-wild type) to the agent in question. The epidemiological cut-off value is shown in the tables and the bottom left-hand corner of each MIC and zone diameter graph. TECOFFs (ECOFFs in parentheses) are based on 3 or 4 distributions and ECOFFs on at least 5 and up to 100 or more distributions.



Breakpoint tables for interpretation of MICs and zone diameters

Version 14.0, valid from 2024-01-01

1

This document should be cited as "The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 14.0, 2024. <http://www.eucast.org>."

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Expert Rules	-	Link to EUCAST Expert Rules and Expected Phenotypes
Detection of Resistance Mechanisms	-	Link to EUCAST Guidelines on Detection of Resistance Mechanisms
Antimicrobial susceptibility tests on groups of organisms or agents for which there are no EUCAST breakpoints	-	Link to Guidance Document on how to test and interpret results when there are no breakpoints
Guidance on breakpoints in brackets	-	Link to Guidance Document on breakpoints in brackets
Guidance on screening tests	-	Link to Guidance Document on screening tests
EUCAST Reading Guide for broth microdilution	-	Link to EUCAST Reading Guide for broth microdilution
EUCAST Reading Guide for disk diffusion	-	Link to EUCAST Reading Guide for disk diffusion

A light yellow background (and underlined text) is used throughout to announce one or more changes since the previous table.

MIC determination (broth microdilution according to ISO standard 20776-1)
 Medium:
 Inoculum:
 Incubation:
 Reading:
 Quality control:

EUCAST methodology and quality control for MIC determination

Disk diffusion (EUCAST standardised disk diffusion method)
 Medium:
 Inoculum:
 Incubation:
 Reading:
 Quality control:

EUCAST methodology and quality control for disk diffusion

An arbitrary "off scale" breakpoint which categorises wild-type organisms as "Susceptible, increased exposure (I)".

Breakpoints with a species name apply only to that particular species (in this example *S. aureus*)

The I category is not listed but is interpreted as the values between the S and the R breakpoints. If the S and R breakpoints are the same value there is no I category.

Agent A: No I category
 Agent B: I category: 4 mg/L, 23-25 mm
 Agent H: I category: 1-2 mg/L, 24-29 mm

Area of Technical Uncertainty
 See specific information on how to handle technical uncertainty in antimicrobial susceptibility testing.

Antimicrobial agent	MIC breakpoint (mg/L)			Disk content (µg)	Zone diameter breakpoint (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Antimicrobial agent A	1 ¹	1 ¹		X	20 ^A	20 ^A		Numbered notes relate to general comments and/or MIC breakpoints. Lettered notes relate to the disk diffusion method. 1. Notes that are general comments and/or relating to MIC breakpoints. 2. New comment Removed comment A. Comment on disk diffusion
Antimicrobial agent B	2 ²	4		Y	26	23		
Antimicrobial agent C	0.001	8		X	50	18		
Antimicrobial agent D, <i>S. aureus</i>	IE	IE			IE	IE		
Antimicrobial agent E	-	-			-	-		
Antimicrobial agent F	IP	IP			IP	IP		
Antimicrobial agent G (screen only)	NA	NA		Y	25	25		
Antimicrobial agent H	0.5	2		Z	30	24		
Antimicrobial agent I	(8) ¹	(8) ¹		30	(18) ^A	(18) ^A		

A screening test that uses one agent to predict resistance or susceptibility to one or more antimicrobial agents in the same class

Not Applicable

MIC breakpoints in blue are linked to MIC distributions

In Preparation

Changes from previous version highlighted in yellow

The agent is unsuitable for treatment. Susceptibility testing is not recommended

Antimicrobial agents in blue are linked to EUCAST rationale documents

Breakpoints in brackets are used to distinguish between organisms with and without acquired resistance mechanisms (see Notes)

Insufficient evidence that the organism or group is a good target for therapy with the agent

Zone diameter breakpoints in blue are linked to zone diameter distributions

Pseudomonas aeruginosa

Fluoroquinolones	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Ciprofloxacin	0.001	0.5		5	50	26	
Delafloxacin	IE	IE			IE	IE	
Levofloxacin	0.001	2		5	50	18	
Moxifloxacin	-	-			-	-	
Nalidixic acid (screen only)	NA	NA			NA	NA	

"IE" in breakpoint tables indicate a lack of evidence for clinical efficacy on which to determine breakpoints - however, EUCAST has not disqualified the agent. Laboratories are recommended to consult guidance document on "What to do when there are no breakpoints".

Aminoglycosides ¹	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Amikacin (systemic infections)	(16) ¹	(16) ¹		30	(15) ^A	(15) ^A	
Amikacin (infections originating from the urinary tract)	16	16		30	15	15	
Gentamicin (systemic infections)	IE	IE			IE	IE	
Gentamicin (infections originating from the urinary tract)	IE	IE			IE	IE	
Netilmicin	IE	IE			IE	IE	
Tobramycin (systemic infections)	(2) ¹	(2) ¹		10	(18) ^A	(18) ^A	
Tobramycin (infections originating from the urinary tract)	2	2		10	18	18	

Pseudomonas aeruginosa

Fluoroquinolones	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Ciprofloxacin	0.001	0.5		5	50	26	
Delafloxacin	IE	IE			IE	IE	
Levofloxacin	0.001	2		5	50	18	
Moxifloxacin	-	-			-	-	
Nalidixic acid (screen only)	NA	NA			NA	NA	

Dash (“-“) indicates that the agent is unsuitable for systemic infections caused by the species.

EUCAST refrained from determining breakpoints and recommend that the agent is not included in susceptibility test reports. If included, report **resistant** without prior testing.

Aminoglycosides ¹	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Amikacin (systemic infections)	(16) ¹	(16) ¹		30	(15) ^A	(15) ^A	
Amikacin (infections originating from the urinary tract)	16	16		30	15	15	
Gentamicin (systemic infections)	IE	IE			IE	IE	
Gentamicin (infections originating from the urinary tract)	IE	IE			IE	IE	
Netilmicin	IE	IE			IE	IE	
Tobramycin (systemic infections)	(2) ¹	(2) ¹		10	(18) ^A	(18) ^A	
Tobramycin (infections originating from the urinary tract)	2	2		10	18	18	

Pseudomonas aeruginosa

Fluoroquinolones	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Ciprofloxacin	0.001	0.5		5	50	26	
Delafloxacin	IE	IE			IE	IE	
Levofloxacin	0.001	2		5	50	18	
Moxifloxacin	-	-			-	-	
Nalidixic acid (screen only)	NA	NA			NA	NA	
Norfloxacin (uncomplicated UTI only)	-	-			-	-	
Ofloxacin	-	-			-	-	

Arbitrary breakpoints (S ≤0.001 mg/L; S≥50 mm) prevent the reporting of "S" (Susceptible at normal dosing).

Aminoglycosides ¹	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Amikacin (systemic infections)	(16) ¹	(16) ¹		30	(15) ^A	(15) ^A	
Amikacin (infections originating from the urinary tract)	16	16		30	15	15	
Gentamicin (systemic infections)	IE	IE			IE	IE	
Gentamicin (infections originating from the urinary tract)	IE	IE			IE	IE	
Netilmicin	IE	IE			IE	IE	
Tobramycin (systemic infections)	(2) ¹	(2) ¹		10	(18) ^A	(18) ^A	
Tobramycin (infections originating from the urinary tract)	2	2		10	18	18	

Pseudomonas aeruginosa

Fluoroquinolones	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Ciprofloxacin	0.001	0.5		5	50	26	
Delafloxacin	IE	IE			IE	IE	
Levofloxacin	0.001	2		5	50	18	
Moxifloxacin	-	-			-	-	
Nalidixic acid (screen only)	NA	NA			NA	NA	

Breakpoints in brackets – the agent should not be used without supplementary active therapy (another active agent or measure). The breakpoint in bracket will distinguish between organisms with and without resistance mechanisms. The caveat for use should be made clear in reports.

Aminoglycosides ¹	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Amikacin (systemic infections)	(16) ¹	(16) ¹		30	(15) ^A	(15) ^A	
Amikacin (infections originating from the urinary tract)	16	16		30	15	15	
Gentamicin (systemic infections)	IE	IE			IE	IE	
Gentamicin (infections originating from the urinary tract)	IE	IE			IE	IE	
Netilmicin	IE	IE			IE	IE	
Tobramycin (systemic infections)	(2) ¹	(2) ¹		10	(18) ^A	(18) ^A	
Tobramycin (infections originating from the urinary tract)	2	2		10	18	18	

EUCAST Guidance Documents

- **Cefiderocol MIC broth microdilution guide** (1 January, 2024). See also the **Warning on cefiderocol susceptibility testing**.
- **When there are no breakpoints!** (29 February, 2024). **Previous version** (30 June, 2023), **Previous version** (1 December 2021 - 30 June, 2023), **Previous version** (5 July, 2016 - 1 December 2021).
- **Guidance on the use of fosfomycin intravenously** (28 May, 2024); **Previous version** (5 December, 2023).
- **ATU - the Area of Technical Uncertainty - Guidance to laboratories on how to deal with the antimicrobial susceptibility testing** (originally published 2018; updated 2019, 2020, 2022, and 8 February 2024).
Graphs to illustrate ATUs (Updated 5 February, 2024).
- **Guidance on the use of ceftriaxone and cefotaxime in Staphylococcus aureus** (8 February, 2023)
- **Aminopenicillin breakpoints Enterobacterales following revision 2023 - guidance on implementation** (14 January, 2023; an error in the flowchart was corrected on Sept 15, 2023).
- **Setting breakpoints for agent-inhibitor combinations** (14 December, 2021). Previous version of **Setting breakpoints for agent-inhibitor combinations** (2 October, 2017).
- **Breakpoints in brackets in breakpoint tables** (2 December 2021)
- **Phenotypic screening tests to detect and exclude resistance of clinical relevance** (update 22 August, 2022). **Previous version** (13 June, 2022). **Previous version** (2 Febr, 2022). **Previous version** (1 Dec 2021)
- **Implementation and use of the 2022 revised colistin breakpoints** (January, 2022; minor edits on previous version from Nov, 2021)
- **Legionella pneumophila susceptibility testing** (30 May, 2021); previous version **Legionella pneumophila susceptibility testing** (11 Dec, 2017)
- **Implementation and use of the 2020 revised aminoglycoside breakpoints** (first published 21 Jan, 2020; updated April 2020)
- **Daptomycin in endocarditis and bloodstream infections caused by enterococci** (also available in CMI as a **EUCAST position paper**; 2020)
- **Breakpoints for topical use of antimicrobial agents** (revised 12 April 2022, 21 Nov, 2019; 22 Dec, 2016)
- **Guidance for industry on the working order between pharmaceutical industry, EMA and EI** (5 May, 2019)
- **Cefotaxime and ceftazidime disks with and without clavulanic acid for ESBL confirmation** (12 February, 2019)
- **Guidance on tigecycline dosing**, 21 July, 2022. **Previous version** (23 December, 2018)
- **The 2019 modifications of susceptibility categories S, I and R categories** (22 October, 2018). This presentation also informs laboratories on how to implement the Area of Technical Uncertainty.
- **EUCAST system for antimicrobial name abbreviations** (January 2022). **Previous version** (13 July, 2018)
- **Recommendations for colistin (polymyxin E) MIC testing** - joint EUCAST and CLSI recommendation (22 March, 2016)
- **Burkholderia cepacia complex** (20 July, 2013)
- **Stenotrophomonas maltophilia** (1 Feb 2012)
- **Oral cephalosporins and Enterobacterales breakpoints** (14 July, 2020). **Previous version** (16 Feb 2012)
- **Direct susceptibility testing** (16 Feb 2012). See also **"EUCAST Rapid AST directly from positive blood culture bottles"**

What to do when there are no breakpoints?

- **CLSI**

- some breakpoints are still based on values for other/"similar" species (*Acinetobacter* breakpoints to predict susceptibility in *Burkholderia cepacia* complex etc).
- there is no CLSI recommendation for what to do when a species without a breakpoint is identified in the laboratory.

- **FDA** (Dimitri Larikov) could not identify a proposed FDA action.

- **EUCAST**

Guidance document "What to do when there are no breakpoints"

- Determine the MIC
- Assess wild type vs. non-wild type if possible
 - Consider NWT resistant
 - For WT, consult the EUCAST table of "best case"/"most used" breakpoints in the guidance document.

Thank you!

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