ESCMID MANAGING INFECTIONS PROMOTING SCIENCE

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Why follow EUCAST?

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Chair of EUCAST

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Madrid, 24 November 2022

General introduction

EUCAST - Milestones

- 2002 when the 6 national committees in Europe decided to take joint responsibility for a European standard, chaired by Gunnar Kahlmeter
- 2004 when EMA agreed to recognize EUCAST as its breakpoint committee
- 2008 when all existing antimicrobials had EUCAST breakpoints
- 2008 with the decision to develop a EUCAST disk diffusion test
- 2014 when the CA-SFM abandoned the French disk diffusion test
- 2014 when many countries outside Europe decided to leave CLSI and turn to EUCAST
- 2016 when the BSAC abandoned the UK disk diffusion test leaving only EUCAST and CLSI "on the market"
- 2019 rapid AST directly from blood cultures
- 2020 introduction of new SIR-definition

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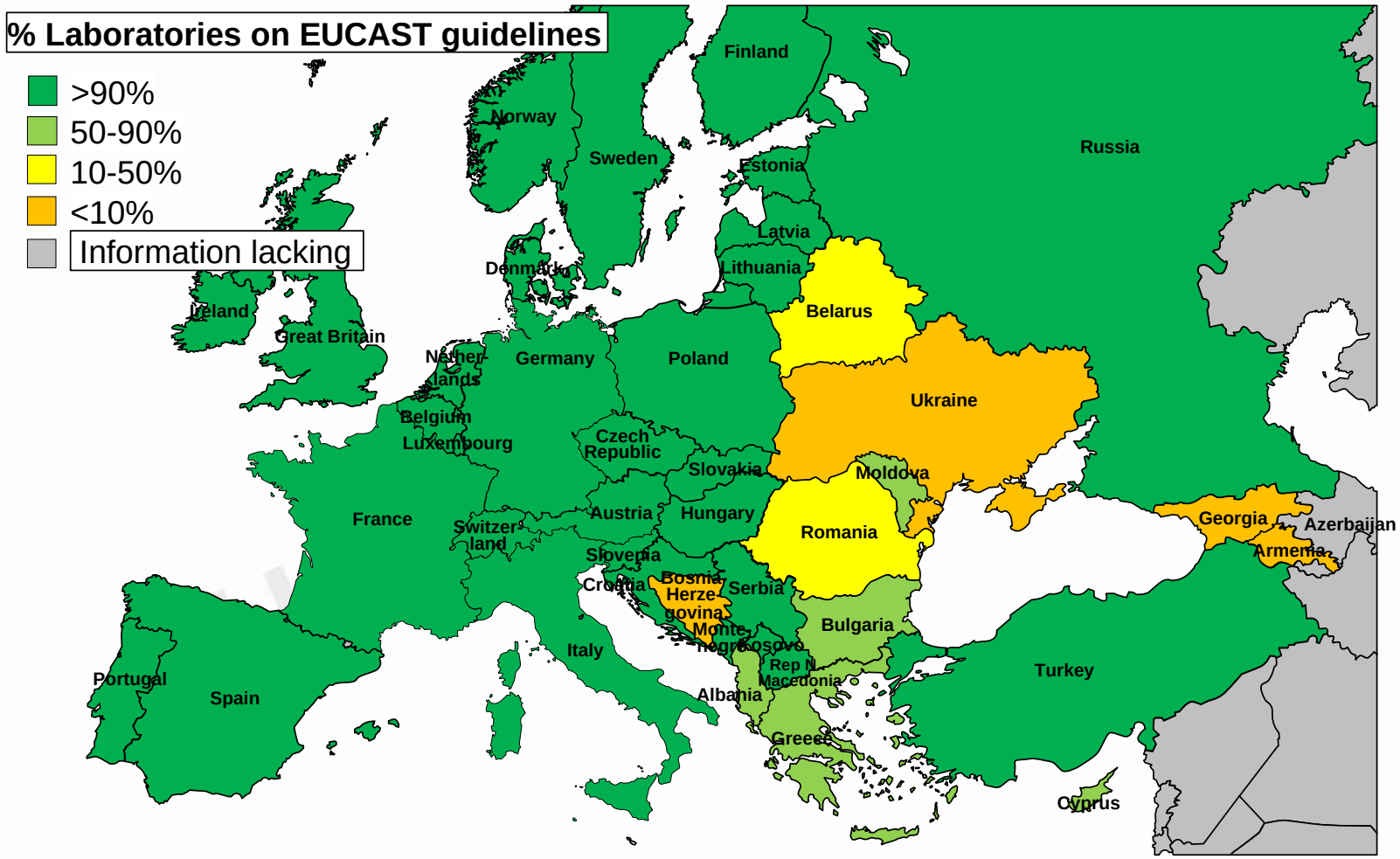
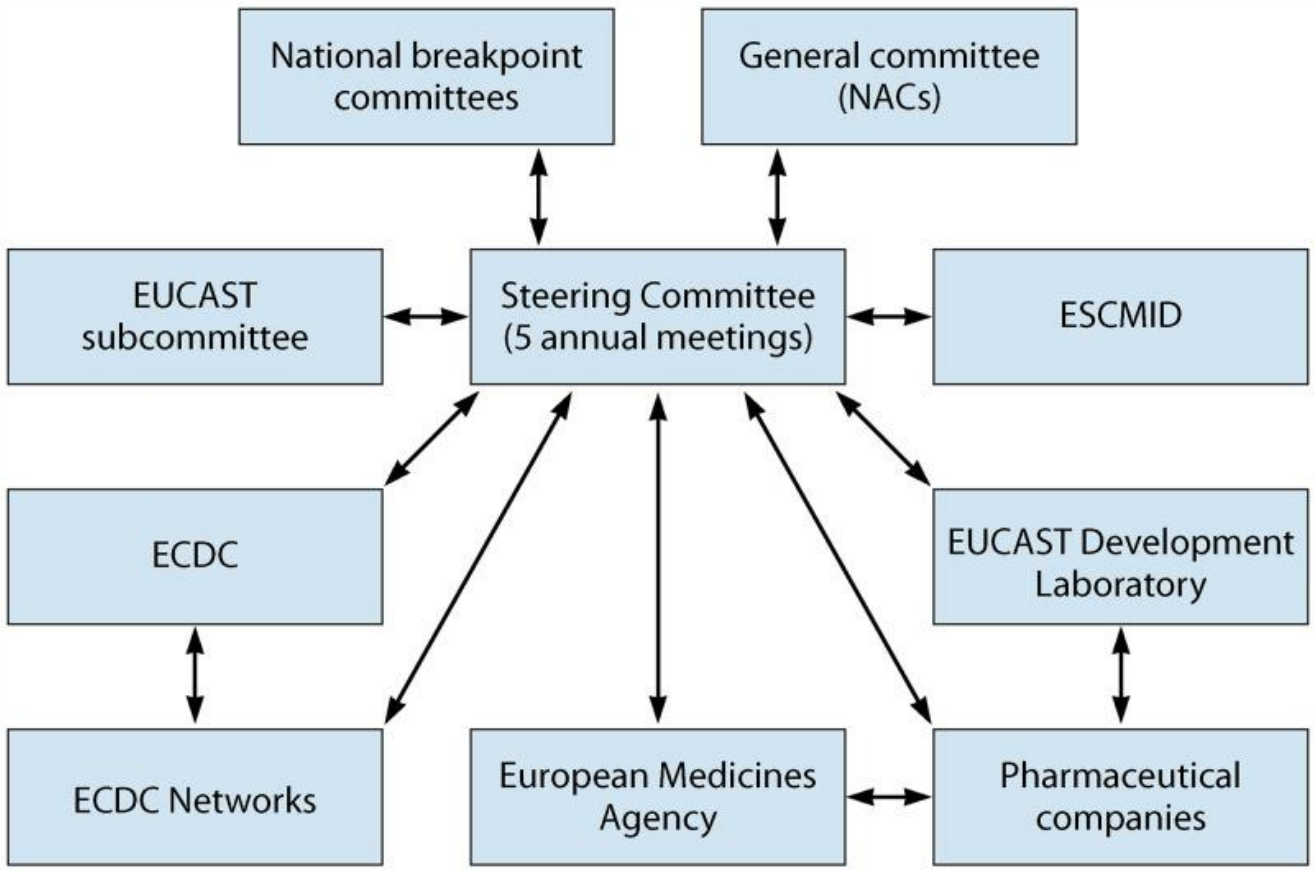
Implementation of EUCAST breakpoints/guidelines, March 2022



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

EUCAST organization



*Abbreviations: NAC = National AST Committee; ESCMID = European Society of Clinical Microbiology and Infectious Diseases; ECDC = European Centre for Disease

The EUCAST Steering Committee

- Christian G. Giske, chair
- John Turnidge, scientific secretary
- Rafael Canton, clinical data coordinator
- Gunnar Kahlmeter, technical data coordinator/webmaster
- Shampa Das, PK-PD expert
- Joseph Meletiadis, PK-PD expert
- Sören Gatermann, Germany
- Christoffer Lindemann, Norway
- Alasdair MacGowan, UK
- Gerard Lina, France
- Gian Maria Rossolini, Italy
- Jorge Sampaio, Brazil
- **Additionally: visiting members from NACs (usually max one per meeting)**

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search term

Organization

The European Committee on Antimicrobial Susceptibility Testing – EUCAST

... National AST Committees (NAC)

National Antimicrobial Susceptibilty Testing Committees (NACs)

EUCAST recommends that countries institute a "National Antimicrobial Susceptibility Testing Committee" (or a committee corresponding to this description). Countries in the process of adopting EUCAST antimicrobial susceptibility testing guidelines will find this particularly useful during the implementation process. The chairperson, or another committee officer, should represent the country on the EUCAST General Committee.

This document presents EUCAST suggestions on
How to organise and form a NAC.

NACs are invited to provide a link to their website for EUCAST to post here.

List of and brief information on National breakpoint committees and NACs:

Australia

NAC objectives

- To formulate strategy at a national level
  - Action through government, professional organizations or societies
  - Inclusive decision to follow EUCAST breakpoints
- To implement breakpoints and methods
  - Identify stakeholders and provide information
  - Communicate with device manufacturers to ensure no practical limitations
  - Communicate with laboratory staff to ensure that all are informed
  - Communicate with clinicians on consequences of breakpoint changes
  - Communicate with government to ensure that they are on board
  - Communicate with professional organizations/societies
  - Communicate with quality assurance agencies to ensure that they use
- EUCAST breakpoints
  - Provide guidance and support to clinical laboratories
  - Provide practical guidelines for introducing methods
  - Provide breakpoint tables, method descriptions

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National AST Committees (NACs), March 2022

Other countries: Australia | Brazil | China | Canada | Iceland | Israel | Malta | Morocco | New Zealand | South Africa | USA

~~Why should you follow EUCAST?~~

Why should you continue following EUCAST, despite EUCAST making silly changes all of the time, even in the middle of an ongoing pandemic?

(Why was Sergio Busquets used as a centre back vs Costa Rica)?

What are the good things about EUCAST?

- Data-driven decisions
- A system with internal logic
- A dynamic system
- Public consultations/transparency
- Documents free of charge
- One European standard (also beyond Europe)

Data-driven decisions

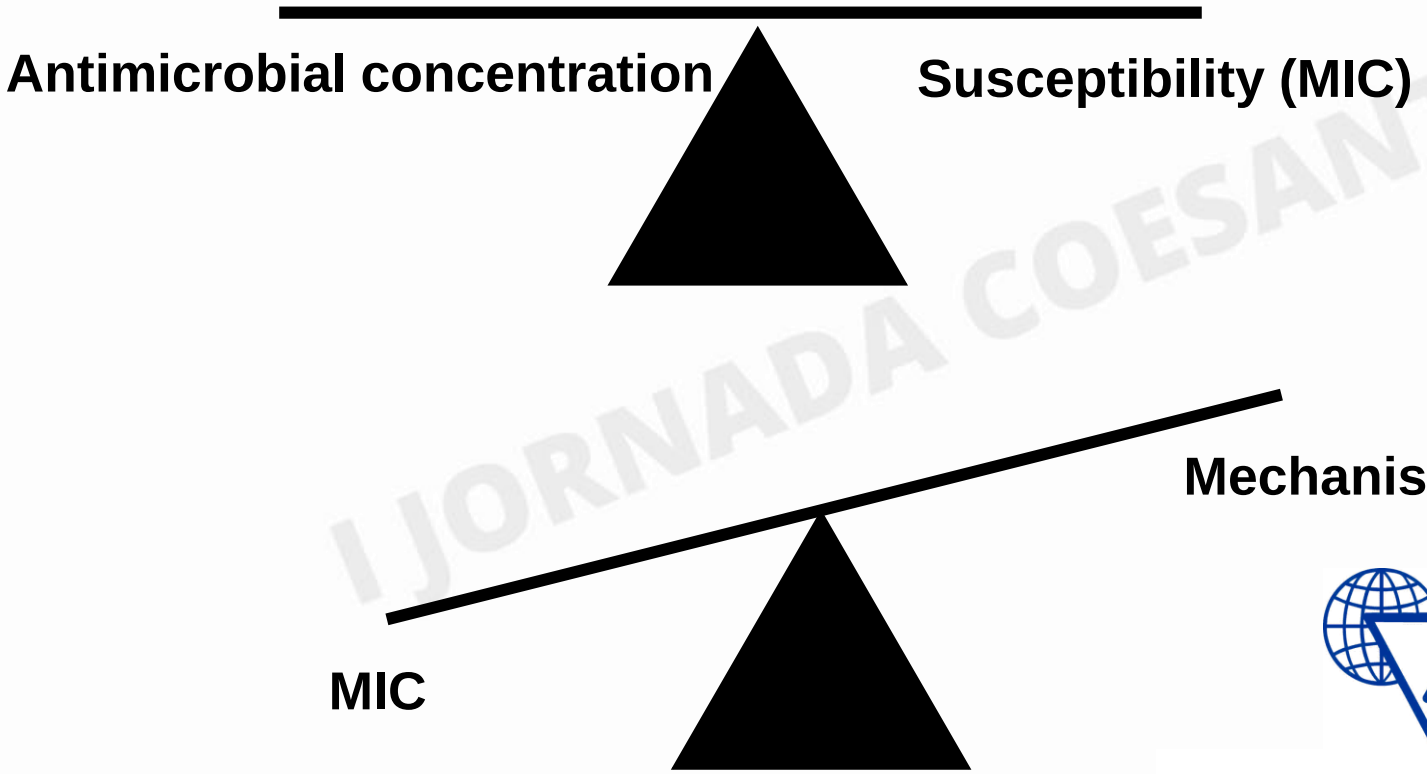
Breakpoint setting

- Systematic review (and revision) process for all breakpoints
- Open consultation on all major decisions except on breakpoints for new agents where confidentiality is respected
- Rapid turnaround time on all decisions
  - 5 meetings per year; not restricted by industry or national agencies; turnaround time on questions normally 1 h – 24 h
- All output free of charge on website (www.eucast.org)
- Laboratory facilities for AST guarantee unbiased data to base the decisions on

The steps needed to set breakpoints

- Defining formulations, dosing regimens, indications, target microorganisms
- Establishing MIC-distributions for relevant species
- Defining pharmacokinetic (PK) data
- Defining pharmacodynamic (PD) data (exposure vs response)
- Modelling variation in pharmacokinetics
- Considering clinical data related to MICs
- Considering important resistance mechanisms
- Integrating data

The MIC paradigm: MIC>mechanism



CLINICAL AND LABORATORY STANDARDS INSTITUTE ™

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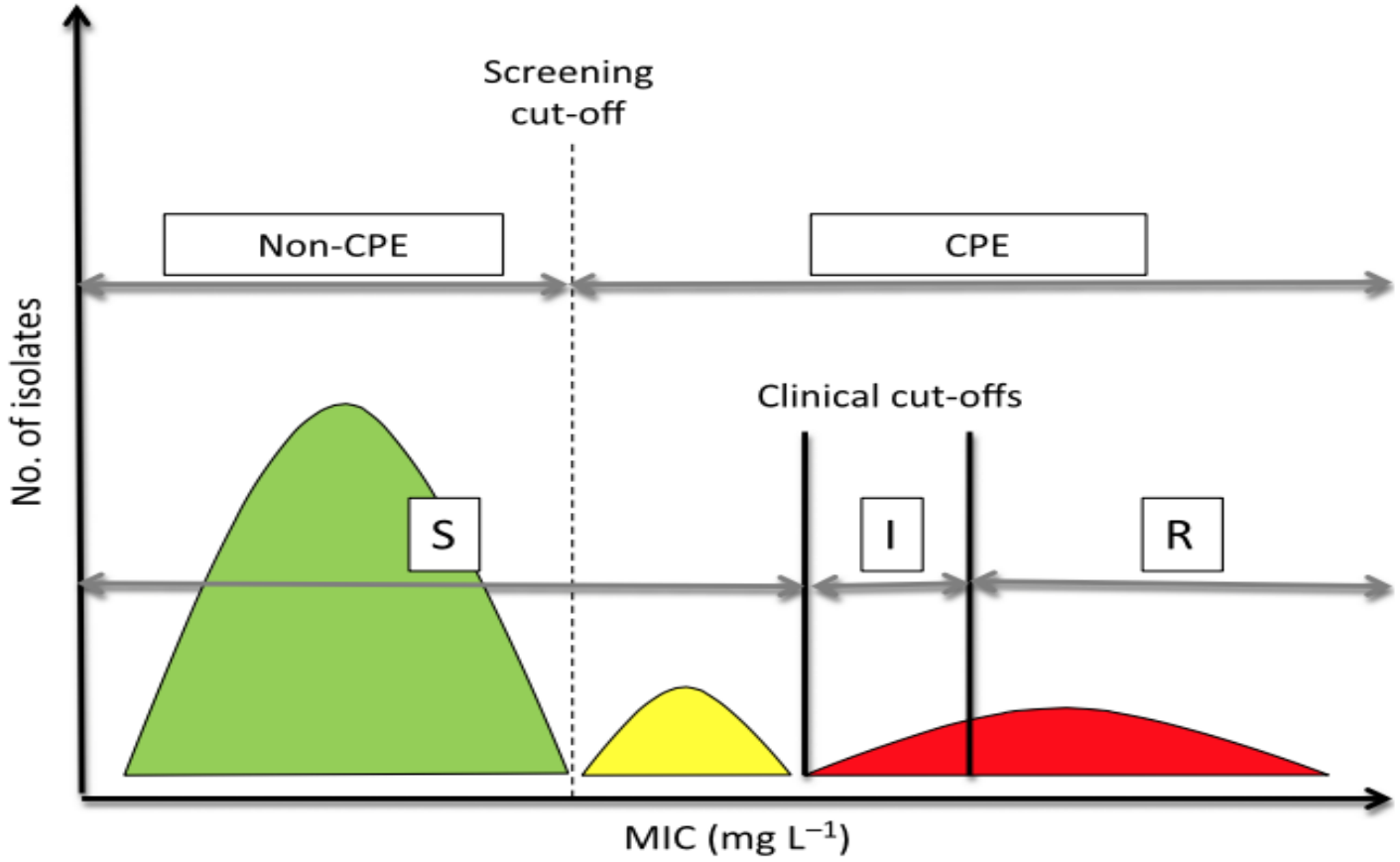
Where can the breakpoint be set?



Tängdén T and Giske CG. J Intern Med. 2015;277(5):501-12.

Always consensus-based decisions

A system with internal logic

The process of revising breakpoints

- With time, new evidence will be generated to suggest that some breakpoints should be revised
- While other breakpoint committees may look isolated at one antimicrobial-microbe combination, EUCAST will look at all antimicrobials in the same drug class vs all microbes with a breakpoint
- The dosing tab and the SIR-definition ensures that there is only one meaning of the SIR-categories, and how this relates to dosing regimens
- When there is no data to support a breakpoint for a rare species, EUCAST will refrain from using historical breakpoints used elsewhere and instead generate data to align with other species in the tables
- The breakpoint tables are constantly scrutinized for internal logic and every year adjustments are done

Dosing and SIR-categorization

Dosages

EUCAST Clinical Breakpoint Tables v. 12.0, valid from 2022-01-01

EUCAST breakpoints are based on the following dosages (see section 8 in Rationale Documents). Alternative dosing regimens may result in equivalent exposure. The table should not be considered a guidance for dosing in clinical practice, and does not replace specific local, national, or regional dosing guidelines. However, if national practices significantly differ from those listed below, EUCAST breakpoints may not be valid. Situations where less antibiotic is given as standard or high dose should be discussed locally or regionally.

Uncomplicated UTI: acute, sporadic or recurrent lower urinary tract infections (uncomplicated cystitis) in patients with no known relevant anatomical or functional abnormalities within the urinary tract or comorbidities.

Penicillins	Standard dosage	High dosage	Uncomplicated UTI	Special situations
Benzylpenicillin	0.6 g (1 MU) x 4 iv	1.2 g (2 MU) x 4-6 iv		**Meningitis caused by *S. pneumoniae:*** For a dose of 2.4 g (4 MU) x 6 iv, isolates with MIC≤0.06 mg/L are susceptible. **Pneumonia caused by *S. pneumoniae:* breakpoints are related to dosage:** For a dose of 1.2 g (2 MU) x 4 iv, isolates with MIC ≤0.5 mg/L are susceptible. For a dose of 2.4 (4 MU) g x 4 iv or 1.2 g (2 MU) x 6 iv, isolates with MIC ≤1 mg/L are susceptible. For a dose of 2.4 g (4 MU) x 6 iv, isolates with MIC ≤2 mg/L are susceptible.
Ampicillin	2 g x 3 iv	2 g x 4 iv		**Meningitis:** 2 g x 6 iv
Ampicillin-sulbactam	(2 g ampicillin + 1 g sulbactam) x 3 iv	(2 g ampicillin + 1 g sulbactam) x 4 iv		
Amoxicillin iv	1 g x 3-4 iv	2 g x 6 iv		**Meningitis:** 2 g x 6 iv
Amoxicillin oral	0.5 g x 3 oral	0.75-1 g x 3 oral	0.5 g x 3 oral	
Amoxicillin-clavulanic acid iv	(1 g amoxicillin + 0.2 g clavulanic acid) x 3-4 iv	(2 g amoxicillin + 0.2 g clavulanic acid) x 3 iv		
Amoxicillin-clavulanic acid oral	(0.5 g amoxicillin + 0.125 g clavulanic acid) x 3 oral	(0.875 g amoxicillin + 0.125 g clavulanic acid) x 3 oral	(0.5 g amoxicillin + 0.125 g clavulanic acid) x 3 oral	Amoxicillin-clavulanic acid has separate breakpoints for systemic infections and uncomplicated UTI. When amoxicillin-clavulanic acid is reported for uncomplicated UTI, the report must make clear that the susceptibility category is only valid for uncomplicated UTI.

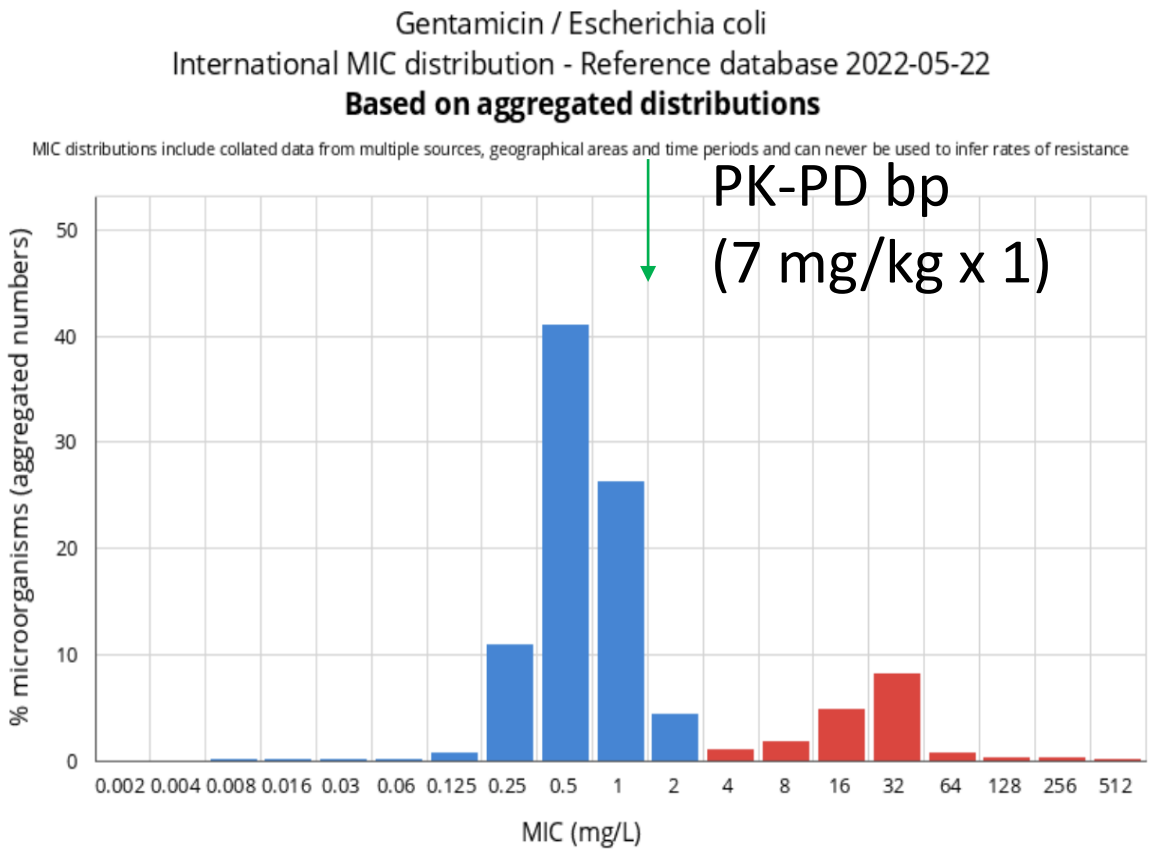
A dynamic system

Some of the highlights of recent years

- Revision of the SIR-system (including introduction of ATU)
- Revision of aminoglycoside breakpoints
- Revision of polymyxin breakpoints
- Revision of fosfomycin breakpoints (ongoing)
- Revision of oral aminopenicillin breakpoints
- Introduction of breakpoints in brackets to address agents with insufficient activity
- Rapid AST (disk diffusion) for blood isolates
- Disk diffusion for anaerobes

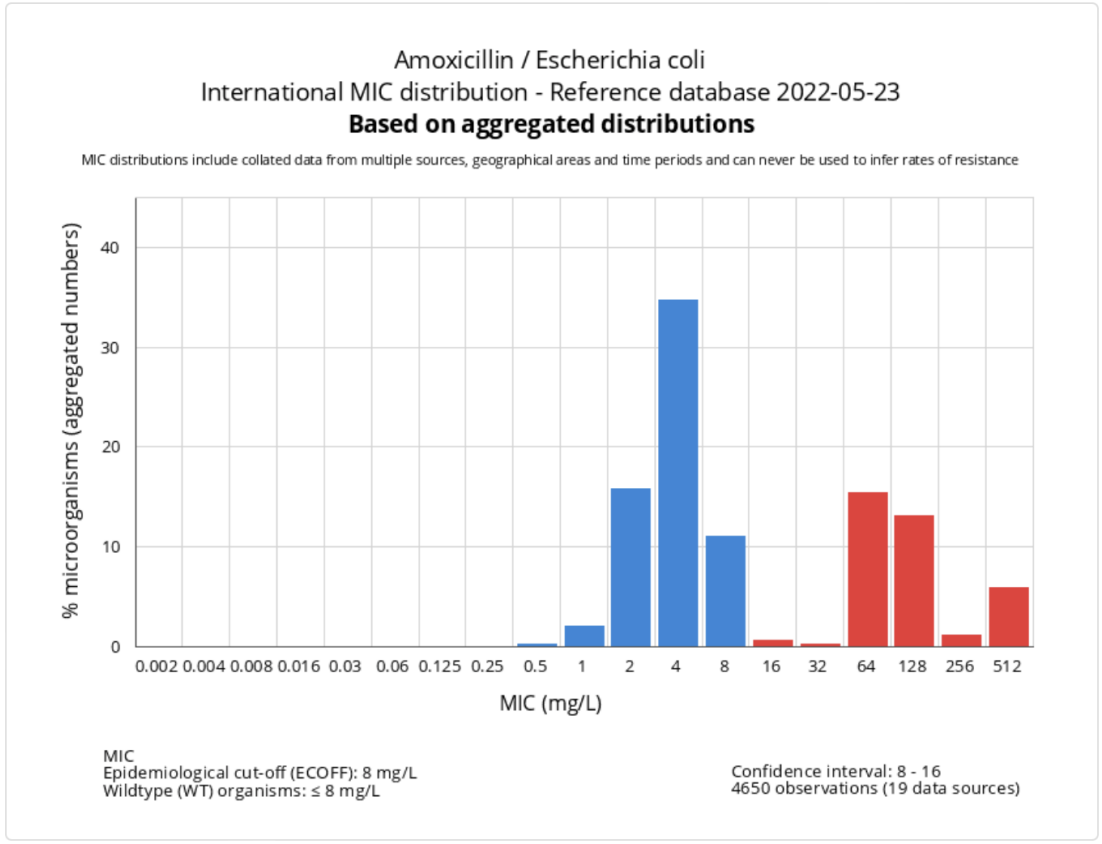
- Never evading difficult issues
- Always open for innovative solutions

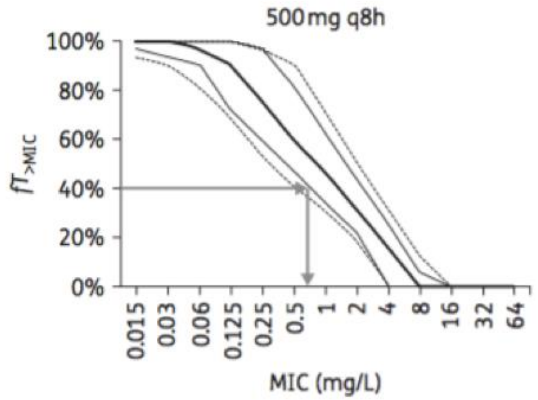
Why breakpoints in brackets?

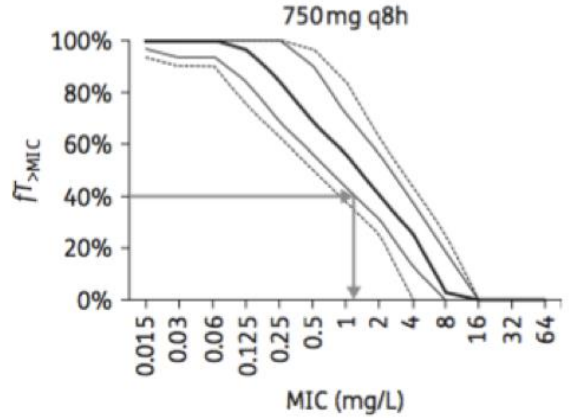


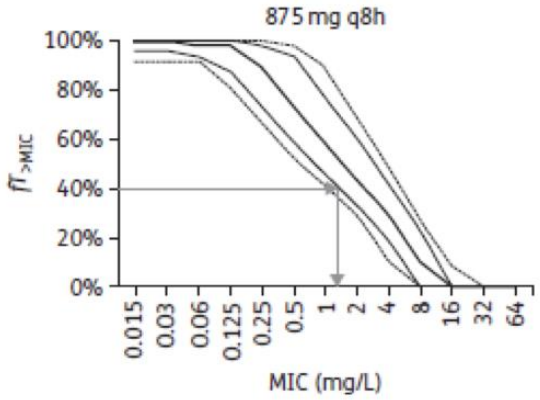
- Possible solutions
  - Split WT: NO (reproducibility)
  - Increase dosage: NO (toxicity)
  - Remove bp: NO (good data remain for urinary focus)
  - Place the WT in the I-group: NO (contradicts new def.)
- A new tool for expressing breakpoint caveats

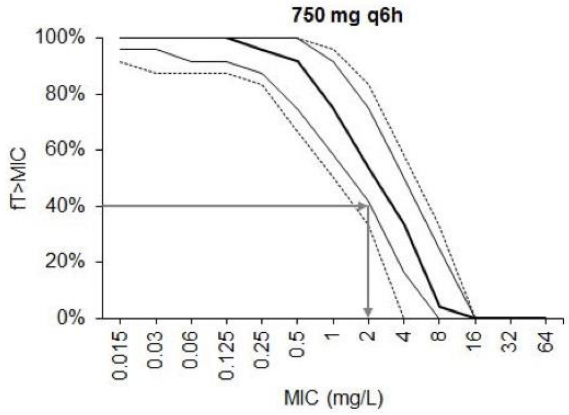
Bracketing for oral aminopenicillins











Public consultations

The EUCAST decision process

- EUCAST, EMA, ECDC, EFSA, Colleagues, Laboratories, Industry may all suggest topics and decisions
- Steering Committee (or subcommittee) will prepare decisions
- Once Steering Committee members agree, national breakpoint committees are consulted
- Suggestions from national breakpoint committees are discussed in the Steering Committee and a revised decision prepared
- All major decisions go to a 6 week open General Consultation published on the website with a document for comments
- Comments (from colleagues, institutions, companies, etc) are discussed and a response to each (and a modified decision) prepared.
  Anonymous comments are not accepted
- The final decision with comments and responses are published on the website
- Decisions on new agents are between EMA, EUCAST and the pharmceutical company. Confidentiality issues prevent open consultation

A constant flow of consultations

- EUCAST General Consultation (closed 11 September, 2022) on **Proposed revision of chloramphenicol breakpoints**. Comments will be collated and discussed by the steering committee September 26-27, 2022.
- EUCAST General Consultation closed 11 September, 2022) on **Breakpoints for Corynebacterium diphtheriae and Corynebacterium ulcerans**. Comments will be collated and discussed by the steering committee September 26-27, 2022.
- **EUCAST General Consultation on Fosfomycin IV breakpoints** (14 May - 15 July 2022). Comments will be collated and discussed by the steering committee September 26-27, 2022.
- **Aminopenicillin breakpoints for Enterobacterales** (30 November, 2021 - 14 January, 2022).
  Comments and responses will be published eventually (January, 2022)
- **Breakpoints for anaerobic bacteria** and supplementary **MIC distributions** (4 October - 15 November, 2021).
  Comments and EUCAST response (2 January, 2022)
- **Colistin breakpoints** (6 October - 15 November, 2021). All responders agreed to the proposed change.
- **Breakpoint table v 12.0**. Consultation closed and finalized table published.
- **Vibrio species - general consultation on EUCAST clinical breakpoints for five species pa** (1 October - 15 November). **Comments and EUCAST responses** (2 January, 2022).
- **Breakpoint table v. 11.0** (the 2021 table, valid from the 1 January, 2021). Consultation closed 18 December, 2020. **Comments and EUCAST responses** (19 December, 2020)
- **Fosfomycin breakpoints revision**. Consultation closed 30 November, 2020.
  Comments and EUCAST response (15 December, 2020).
- **Fluoroquinolone breakpoint adjustments (Campylobacter, Corynebacteria, Bacillus)**. Consultation closed 31 October, 2020. There were no comments.
- **Achromobacter xylosoxidans - proposed method and breakpoints**. Consultation closed 31 October, 2020. **Comments and EUCAST response** (15 December, 2020).
- **Meningitis breakpoints - proposed EUCAST revisions**. Consultation closed 16 October, 2020. **Comments and EUCAST response** (15 December, 2020).
- **Bacillus spp (except B. anthracis) - proposed breakpoints and AST method**. Consultation closed 25 September, 2020. **Comments and EUCAST response** (15 December, 2020).
- **Piperacillin-tazobactam breakpoints for Enterobacterales** - proposed change. Consultation closed 15 September, 2020. **Comments and EUCAST response** (15 December, 2020).
- Consultation on "**Procedure for optimizing disk contents (potencies) for disk diffusion testing**".
  Comments and responses published 10 January, 2020.
- **Revised aminoglycoside breakpoints**. Consultation closed 30 June, 2019. **Comments and responses** published 2 March, 2020.
- **Cefazolin breakpoints** for Enterobacterales in UTI. Consultation closed 8 November 2019. No comments received.
- Revision of **ceftolozane-tazobactam breakpoints** following updated indications for the agent.
  Comments and EUCAST response (13 December, 2019)
- **Temocillin clinical breakpoints** - EUCAST consultation.
  Comments and EUCAST response (a file released on 9 Dec has been replaced - a section was lacking by mistake), 12 December, 2019.
- EUCAST **proposed breakpoints for *Burkholderia pseudomallei*.**
  Consultation 23 May - 30 June, 2019.
  Comments and EUCAST response 23 July, 2019.
- **EUCAST proposes that agents and species currently categorised as Susceptible^{HE} (S^{HE} are re-categorised as "Susceptible, increased exposure" (I)**.
  Comments and EUCAST response 22 Juli, 2019

Most recent and upcoming consultations

Current consultations.

- **Changes proposed in breakpoints for bacterial meningitis**. General consultation 26 September - 7 November, 2022. Send comments to the EUCAST Scientific Secretary.
- **Staphylococcus spp. vs. cephalosporins.** General consultation 26 September - 7 November, 2022. Send comments to the EUCAST Scientific Secretary.

Upcoming consultations:

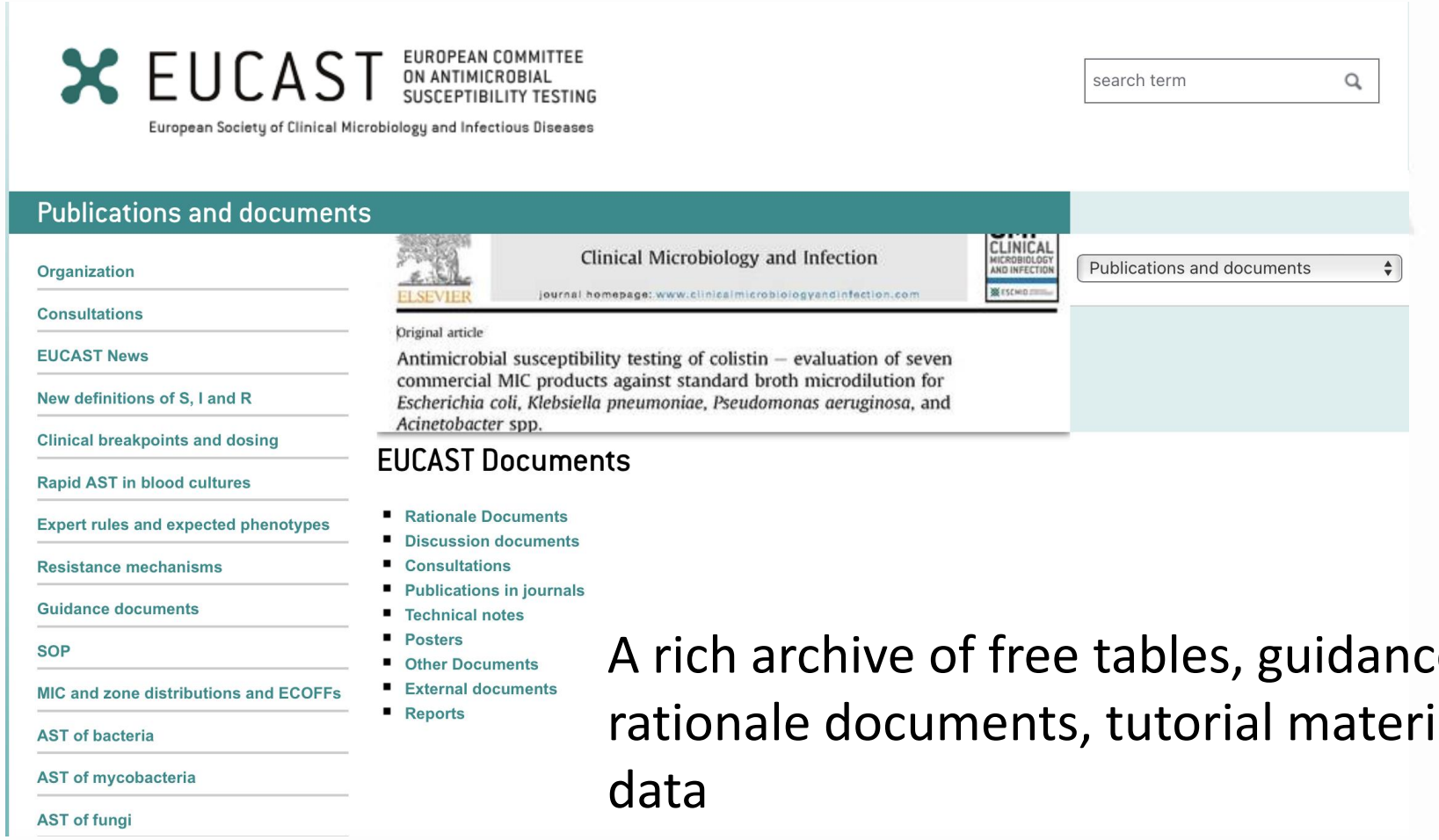
- Viridans group streptococci - breakpoint review and MIC/zone diameter distributions and criteria for streptococci identified to species level
- Nocardiae spp - breakpoints and MIC/Zone diameter distributions and criteria.
- EUCAST dosing table "converted" to dosing in children

What is the purpose of the consultations?

- A forced peer review process for EUCAST decisions
- All comments are responded to
- Sometimes comments lead to substantial changes or that no change is implemented
- Sometimes comments lead to a second or third round of consultation
- Old consultation remain on the website and the key information is moved into rationale documents

Documents free of charge

A rich source of open access documents



A rich archive of free tables, guidance documents, rationale documents, tutorial material, SOPs, background data

One European standard

1975-2001: national breakpoint committees

Committee	Country
BSAC	United Kingdom
CA-SFM	France
CRG	The Netherlands
DIN	Germany
NWGA	Norway
SRGA	Sweden
NCCLS (CLSI)	USA

1975-2001: *Enterobacterales* breakpoints

Committee	Amoxicillin	Cefotaxime	Piperacillin-tazob.
BSAC (UK)	8 / 16	2 / 2	16 / 16
CA-SFM (F)	4 / 16	4 / 32	8 / 64
CRG (NL)	2 / 16	4 / 8	0.25 / 4
DIN (D)	2 / 8	2 / 8	0.12 / 1
NCCLS (USA)	8 / 16	8 / 32	16 / 64
NWGA (N)	0.5 / 8	1 / 2	8 / 16
SRGA (S)	1 / 8	0.5 / 1	16 / 16

EUCAST is endorsed by all EU agencies

- EMA
- ECDC (one standard for surveillance)
- EFSA

- Extensive efforts to ensure there is one European standard

Final remarks

- With time, the EUCAST system has increased in comprehension and internal logic
- At the same time the system has remained quickly adaptive to necessary changes and further developing the consultation system
- The work done at the EUCAST Development Lab strengthens the quality of data to base decisions on
- The system has been acknowledged by all EU agencies as the standard for Europe, with possibility of increasing standardization
- EUCAST still has a low turnaround-time for decisions and remains open for discussions and inputs from colleagues everywhere
- A data-driven approach leads to frequent changes – sometimes leading to frustration, but often as a result of a backlog of unresolved issues

Acknowledgements

- Colleagues in EUCAST – past and present

Karolinska Institute, South Campus

Karolinska University Hospital