Practical Application of EUCAST

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

ACIBADEM UNIVERSITY SCHOOL OF MEDICINE

22 November 2018 - Riga, Latvia,

How is EUCAST organised?

Organised by the profession (ESCMID) and regulatory authorities (ECDC)

Financed by ESCMID and ECDC

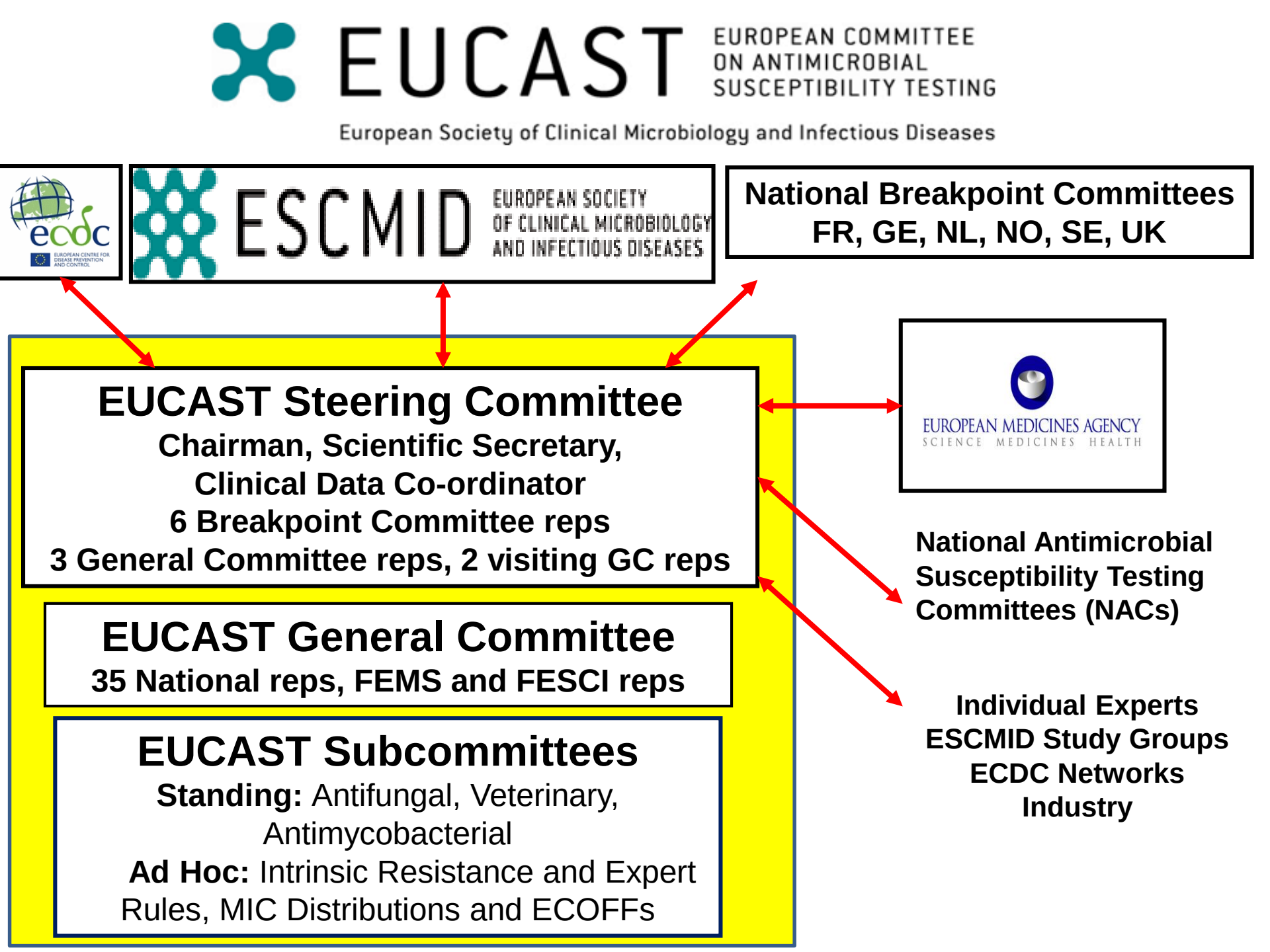
(no commercial activity or dependency)

Utilized by EMA for setting breakpoints on new agents and EFSA for ECOFFs

Steering Committee and General Committee – both with international representation

Network of National AST Committees (NACs) for national implementation of guidelines and/or consultation

ECDC: European Centre for Disease Prevention and Control
EFSA: European Food Safety Authority
EMA: European Medicines Agency
ESCMID: European Society of Clinical Microbiology and Infectious Diseases


EUCAST
EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases
ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL
ESCMID
EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
National Breakpoint Committees
FR, GE, NL, NO, SE, UK
EUCAST Steering Committee
Chairman, Scientific Secretary,
Clinical Data Co-ordinator
6 Breakpoint Committee reps
3 General Committee reps, 2 visiting GC reps
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
National Antimicrobial Susceptibility Testing Committees (NACs)
EUCAST General Committee
35 National reps, FEMS and FESCI reps
Individual Experts
ESCMID Study Groups
ECDC Networks
Industry
EUCAST Subcommittees
Standing: Antifungal, Veterinary, Antimycobacterial
Ad Hoc: Intrinsic Resistance and Expert Rules, MIC Distributions and ECOFFs

EUCAST – milestones

1996: EUCAST was formed

2002: 6 national committees in Europe joined under EUCAST

2004: EMA agreed to recognize EUCAST as its breakpoint committee

2008: All existing antimicrobials received EUCAST breakpoints

2008: Decision taken to develop EUCAST disk diffusion methodology

2014: CA-SFM abandoned French disk diffusion method

2014: Many countries outside Europe decided to implement EUCAST

2016: BSAC abandoned the UK disk diffusion method

EUCAST Steering Committee

Chairman (2016 -): Christian G. Giske, Sweden
Scientific Secretary (2016 -): John Turnidge, Australia
Clinical Data Co-ordinator (2016 -): Rafael Canton, Spain
Technical Data Co-ordinator and Webmaster (2016 -): Gunnar Kahlmeter, Sweden

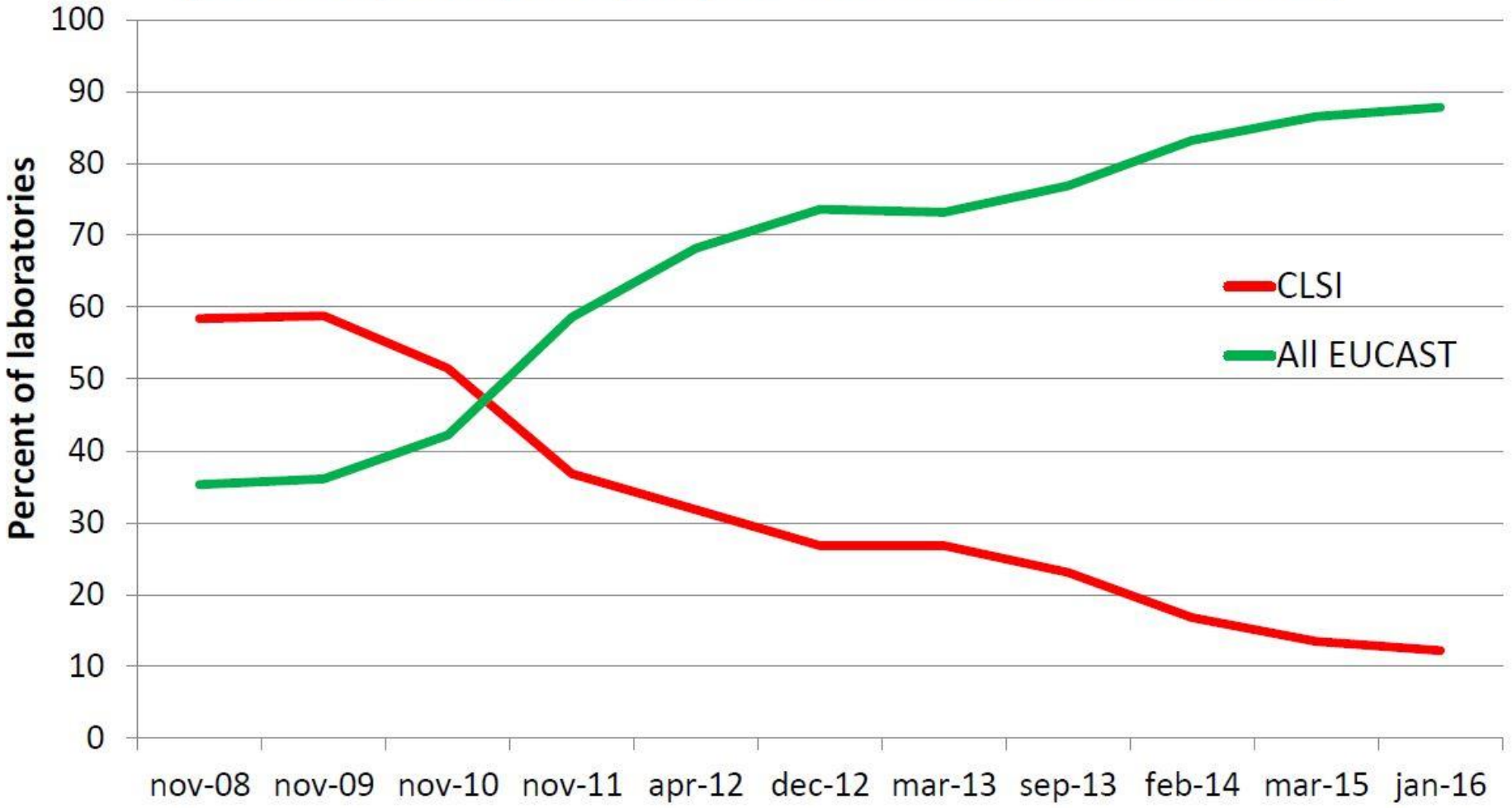
BSAC (The United Kingdom): Alasdair MacGowan, Robin Howe
CA-SFM (France): Gerard Lina, Francois Jehl
CRG (The Netherlands): Johan Mouton
German NAC (Germany): Sören Gatermann
NWGA (Norway): Christoffer Lindemann
SRGA (Sweden): Christian G. Giske
EUCAST Representative 1 (Greece, 2018-2020): Efi Petinaki
EUCAST Representative 2 (Portugal, 2018-2020): Cidalia Pina Vaz

Implementation of EUCAST breakpoints, January 2018

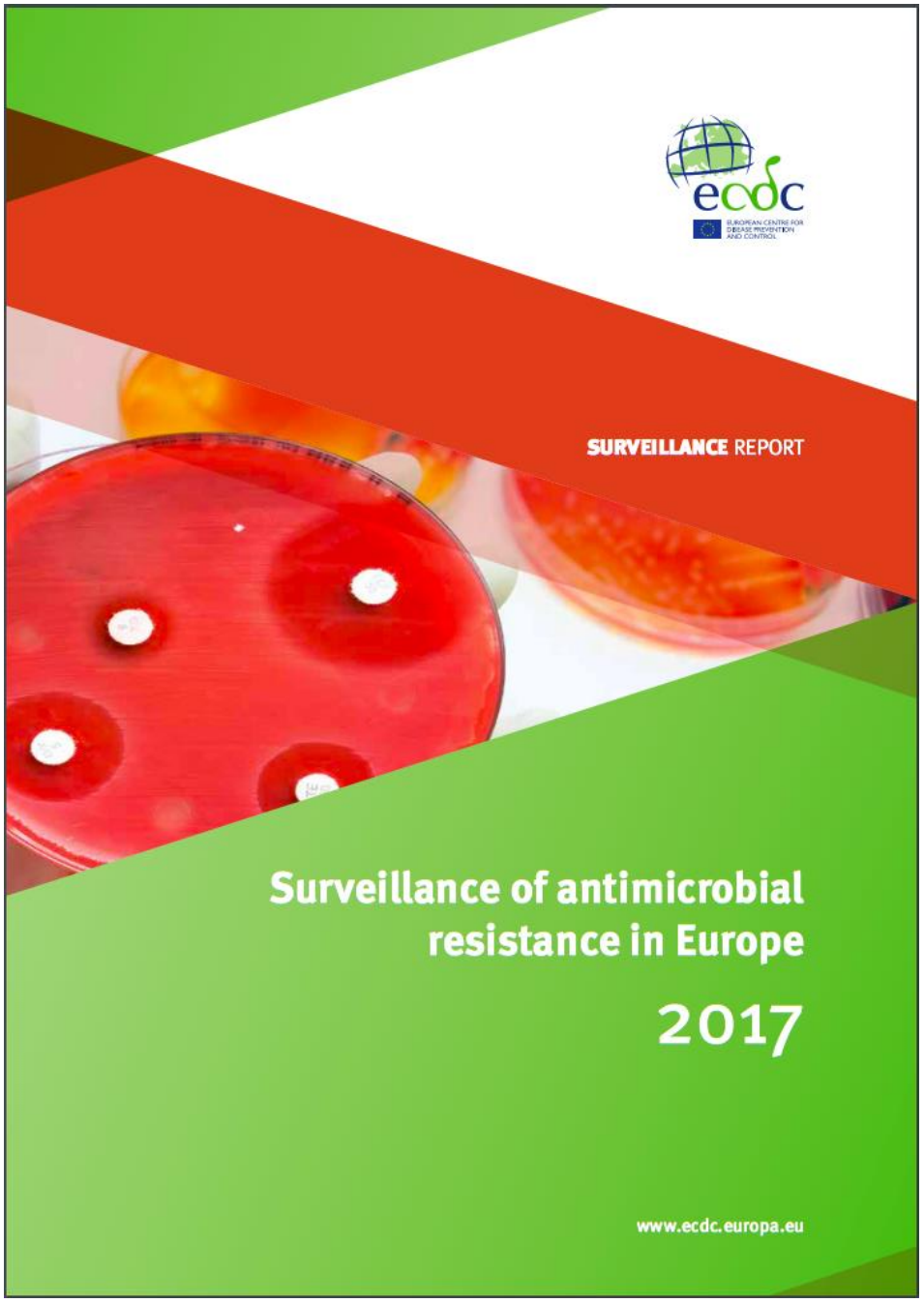
Adoption of the EUCAST disk diffusion method, January 2018

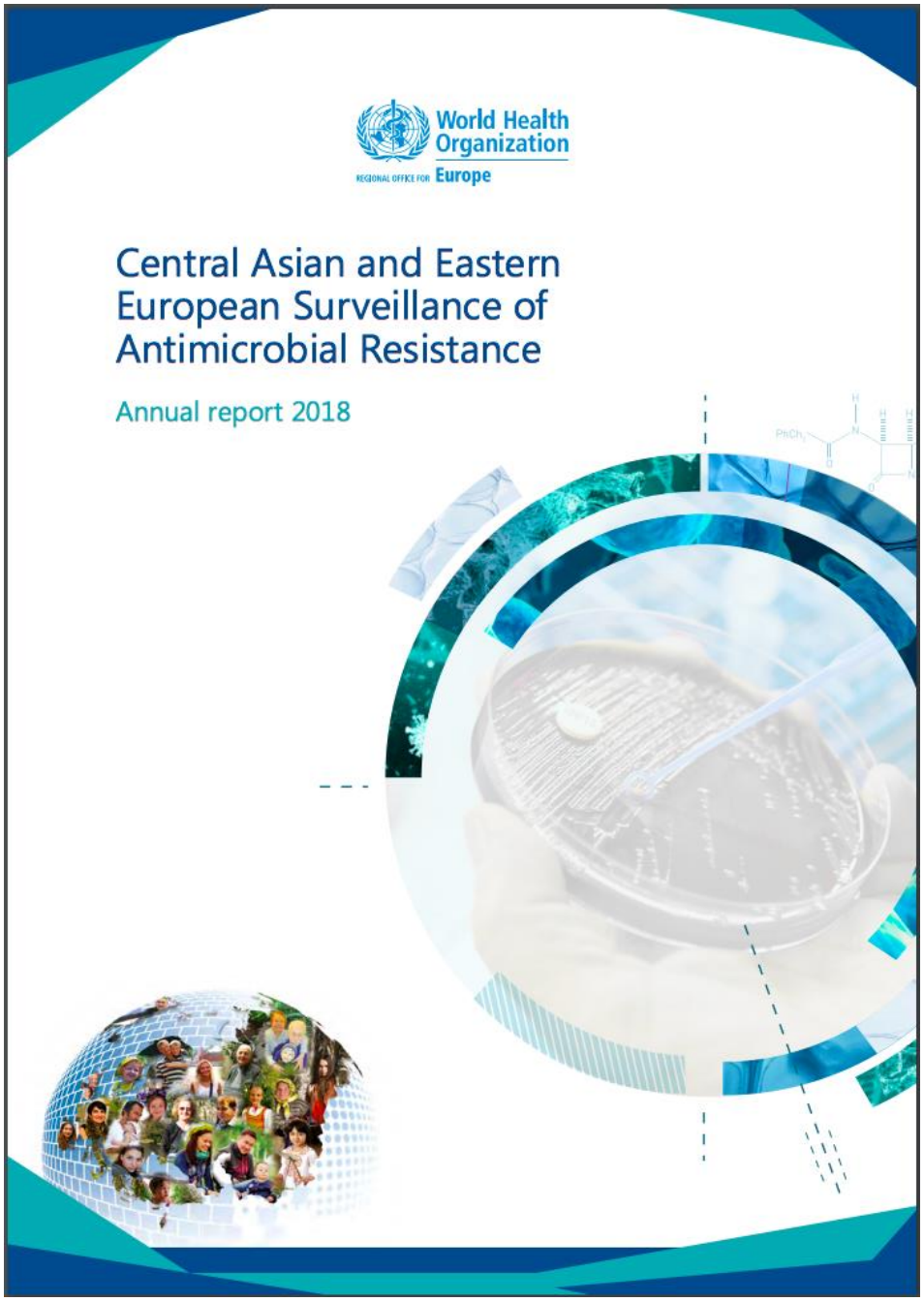
AST guidelines used in UK NEQAS External Quality Assurance

(630-750 participants per year from a total of 40 countries)



UK NEQAS


ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL
SURVEILLANCE REPORT
Surveillance of antimicrobial resistance in Europe
2017
www.ecdc.europa.eu


World Health Organization
REGIONAL OFFICE FOR Europe
Central Asian and Eastern European Surveillance of Antimicrobial Resistance
Annual report 2018

Latvia

Coverage and representativeness of population, hospitals and isolates included in EARS-Net, Latvia, 2014–2017

	2014	2015	2016	2017
Estimated national population coverage (%)	90	90	90	90
Population sample representativeness	Medium	Medium	High	High
Hospital sample representativeness	Medium	Medium	Medium	Medium
Blood culture sets/1000 patient-days	5.7	6.7	6.6	6.1
Isolate sample representativeness	Medium	Medium	Medium	Medium

Laboratories contributing data to EARS-Net: participation in EARS-Net EQA and use of clinical guidelines, Latvia, 2014–2017

	2014	2015	2016	2017
Percentage laboratories participating in EARS-Net EQA	100	100	94	88
Percentage laboratories using EUCAST or EUCAST harmonised guidelines	13	13	27	21

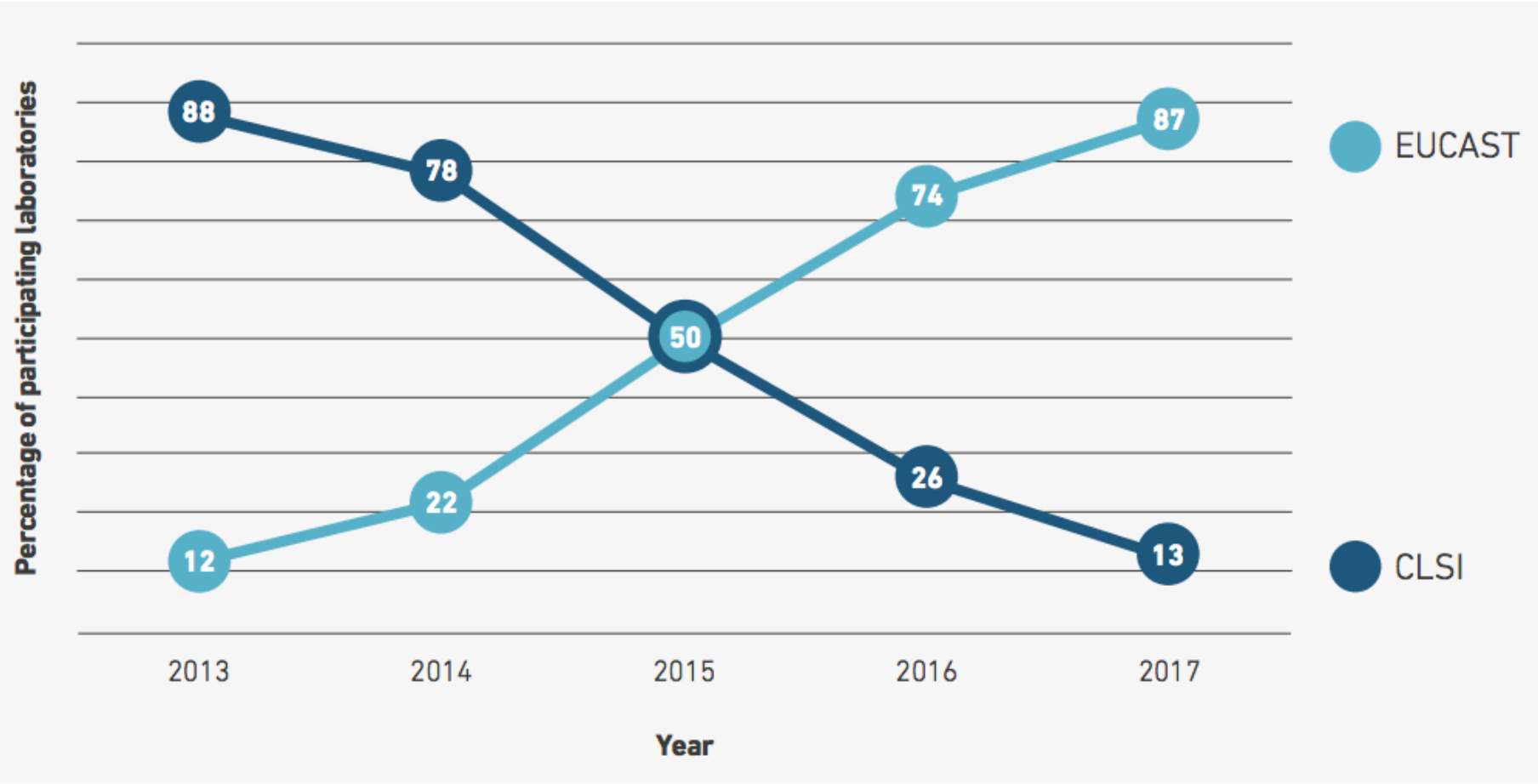
”In 2017, approximately 89% of the participating laboratories used EUCAST, or EUCAST-harmonised, clinical breakpoints,…”

Annual number of reporting laboratories*, number of reported isolates and proportion of isolates reported from patients in intensive care units (ICU), Latvia 2014–2017

Pathogen	2014			2015			2016			2017		
	Laboratories (N)	Isolates (N)	Isolates from ICUs (%)	Laboratories (N)	Isolates (N)	Isolates from ICUs (%)	Laboratories (N)	Isolates (N)	Isolates from ICUs (%)	Laboratories (N)	Isolates (N)	Isolates from ICUs (%)
E. coli	10	182	33	11	201	29	11	253	18	12	205	20
K. pneumoniae	12	118	47	11	115	51	8	95	33	7	116	41
P. aeruginosa	6	18	44	6	13	15	5	16	31	4	14	64
Acinetobacter spp.	6	52	60	6	61	56	7	82	56	7	34	62
S. pneumoniae	7	51	71	9	64	53	8	63	60	9	53	38
S. aureus	13	222	25	15	253	18	14	286	19	11	229	22
E. faecalis	8	44	30	10	60	37	12	89	33	8	74	36
E. faecium	6	35	37	10	34	47	6	56	46	5	39	54

* Number of laboratories reporting at least one isolate during the specific year. Total number of laboratories participating in EARS-Net might be higher.

Fig. 9.3 Trends in AST guidelines used by CAESAR EQA participating laboratories, 2013–2017



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European Society of Clinical Microbiology and Infectious Diseases

search term

Organization

... National AST Committees (NAC)

National Antimicrobial Susceptibilty Testing Committees (NACs)

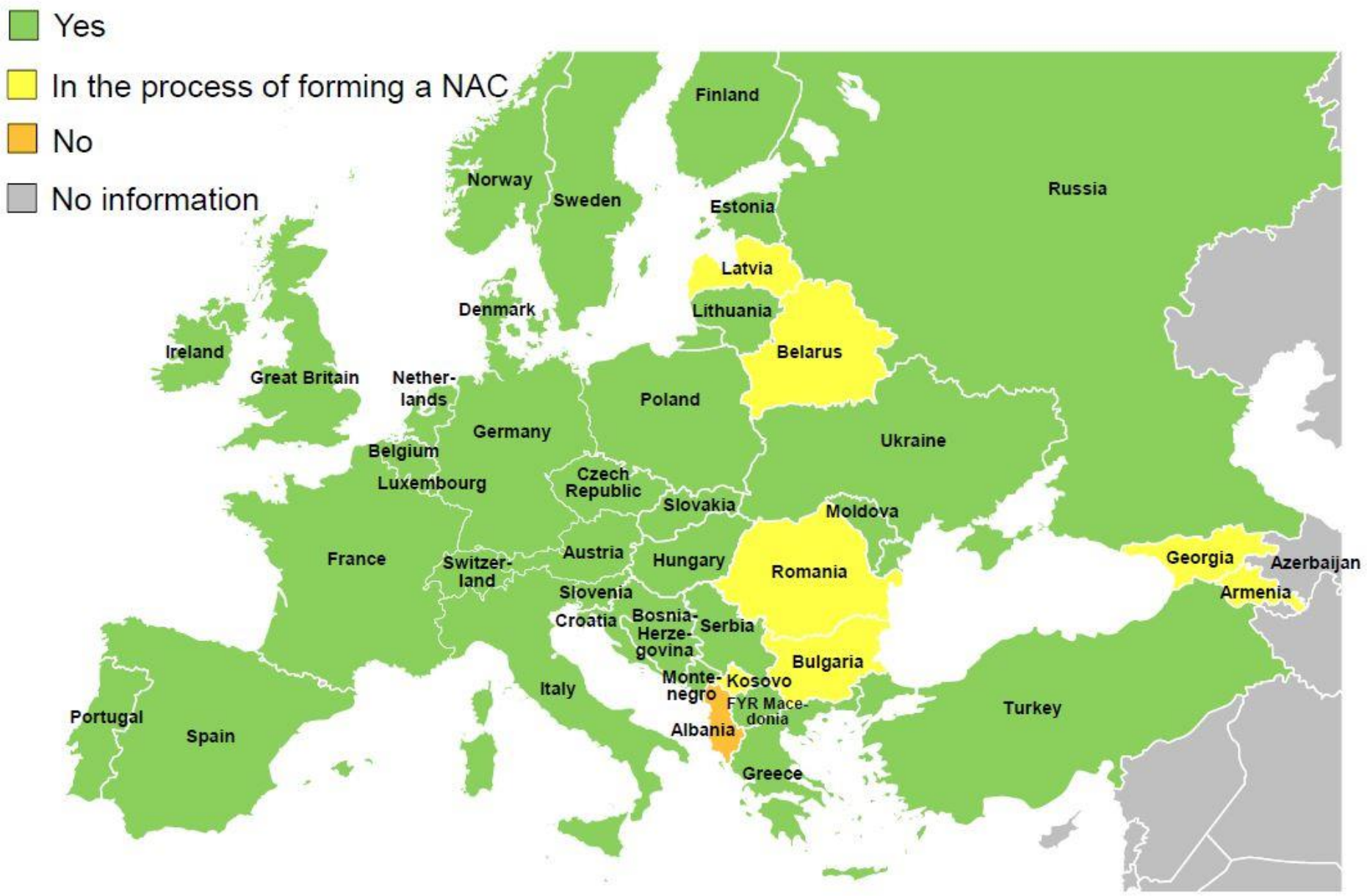
EUCAST recommends that countries institute a "National Antimicrobial Susceptibility Testing Committee" (or a committee corresponding to this description). Countries in the process of adopting EUCAST antimicrobial susceptibility testing guidelines will find this particularly useful during the implementation 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:

National AST Committees (NACs), January 2018



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

EUCAST NAC SOP

- **Structure:**
  - independent committee or a subcommittee of a group with a wider antimicrobial remit

- **Membership:**
  - experts and stakeholders in antimicrobial susceptibility testing:
    - Individual experts
    - Representatives of professional organisations/societies
    - Representatives of government
    - Representatives of antibiotic use, resistance surveillance committees
    - Representatives of quality assurance agencies

Organisms with EUCAST clinical breakpoints

Enterobacteriaceae
Pseudomonas spp.
Acinetobacter spp.
Staphylococcus spp.
Enterococcus spp.
Streptococcus groups A, B, C and G
Streptococcus pneumoniae
Viridans group streptococci
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
Neisseria meningitidis
Gram-positive anaerobes
Gram-negative anaerobes

Version 1.0 December 2009

Clostridium difficile **2010**
Stenotrophomonas maltophilia **2012**
Helicobacter pylori **2012**
Listeria monocytogenes **2012**
Pasteurella multocida **2013**
Campylobacter jejuni and *coli* **2013**
Corynebacterium spp. **2014**
Mycobacterium spp. **2015**
Aerococcus sanguinicola and *urinae* **2017**
Kingella kingae **2017**
Aeromonas spp. **2018**
Bordetella pertussis
***Nocardia* spp.**
Plesiomonas
Bacillus
Streptomyces
Lactobacillus
Leuconostoc
Erysipelothrix rhusopathiae

Consultations 2018

Current consultations

1. Piperacillin-tazobactam breakpoints for *H. influenzae* (7–30 Nov. 2018)
2. Oral amoxicillin breakpoints for *S. pneumoniae* (24 Oct.–30 Nov. 2018)
3. Tigecycline breakpoints (24 Oct.–30 Nov. 2018)

Recently closed

1. General consultation on dosages and modes of administration (15 Sep. 2018)
2. General consultation of carbapenem breakpoints (15 Sep. 2018)
3. Breakpoint changes necessary with new definitions of S, I and R categories (4 Nov. 2018)
4. Modifying the definitions of S, I and R and introducing the Area of Technical Uncertainty (10 Apr. 2018)

Upcoming

1. Aminoglycoside breakpoints
2. Temocillin

Breakpoint table v8.1

European Committee on Antimicrobial Susceptibility Testing

Breakpoint tables for interpretation of MICs and zone diameters

Version 8.1, valid from 2018-05-15

This document should be cited as "The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 8.1, 2018. http://www.eucast.org."

EUCAST Approach

Antimicrobial susceptibility testing

Performance of AST

Categorization of results according to breakpoints (S/I/R)

The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 8.1, 2018. http://www.eucast.org.

Detection of specific resistance mechanisms

Giske CG, Martinez-Martinez L, Cantón R *et al.* EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance. Version 2.0, 2017. http://www.eucast.org.

Implementation of expert rules

Intrinsic resistances

Unexpected phenotypes (usually resistance)

Interpretive rules

Leclerq R, Cantón R, Brown DFJ *et al.* EUCAST expert rules in antimicrobial susceptibility testing. *Clin Microbiol Infect* 2013; 19:141–160.
EUCAST intrinsic resistance and exceptional phenotypes, Expert rules version 3.1, 26 September 2016.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing is performed with phenotypic or genotypic methods. The basis of phenotypic methods is the minimum inhibitory concentration (MIC). Clinical MIC breakpoints determine whether the organism is categorised as susceptible, intermediate or resistant to the agent in question. Other methods should be calibrated to reference MIC methods.

Users of EUCAST breakpoints should use the **EUCAST disk diffusion method** or other susceptibility testing systems calibrated to EUCAST breakpoints and terminology in accordance with EUCAST breakpoint tables.

For videos on how to perform disk diffusion testing according to EUCAST - **CLICK here**!
For more information - **CLICK here**.

- **Media preparation**
  On how to prepare media for MIC and disk testing
- **MIC determination** of nonfastidious and fastidious organisms
  Broth microdilution methodology according to ISO and EUCAST
- **Disk diffusion methodology**
  Detailed description of the EUCAST disk diffusion test
- **Disk diffusion implementation**
  Guidance documents on how to implement the disk diffusion test
- **Compliance of manufacturers**
  Compliance of manufacturers of susceptibility testing products with EUCAST guidelines
- **Breakpoint tables**
  Current MIC and zone diameter breakpoint tables
- **QC tables**
  Current tables of MIC and zone diameter ranges for quality control strains
- **Calibration and validation**
  Data used in the development and calibration of EUCAST disk diffusion breakpoints
- **Guidance documents**
  Guidance notes on specific susceptibility testing issues
- **Projects and data submission**
  Invitations to laboratories to participate in projects to develop EUCAST methods
- **Previous breakpoints and QC tables**
  Earlier versions of breakpoint and QC tables

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European Committee on Antimicrobial Susceptibility Testing

Routine and extended internal quality control for MIC determination and disk diffusion as recommended by EUCAST

Version 8.0, valid from 2018-01-01

This document should be cited as
"The European Committee on Antimicrobial Susceptibility Testing. Routine and extended internal quality control for MIC determination and disk diffusion as recommended by EUCAST. Version 8.0, 2018. http://www.eucast.org."

Routine QC

Extended QC

REVIEW 10.1111/j.1469-0691.2011.03703.x

EUCAST expert rules in antimicrobial susceptibility testing

R. Leclercq[1,2], R. Cantón[2,3,4], D. F. J. Brown[4], C. G. Giske[2,4,5], P. Heisig[2,6], A. P. MacGowan[4,7], J. W. Mouton[4,8], P. Nordmann[2,9], A. C. Rodloff[4,10], G. M. Rossolini[2,11], C.-J. Soussy[4,12], M. Steinbakk[4,13], T. G. Winstanley[2,14] and G. Kahlmeter[4,15]

1) Laboratoire de Microbiologie, CHU Côte de Nacre, Caen, France, 2) EUCAST Subcommittee on Expert Rules, 3) Servicio de Microbiología and CIBER en Epidemiología y Salud Pública (CIBERESP), Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain, 4) EUCAST Steering Committee, 5) Clinical Microbiology, MTC-Karolinska Institutet, Karolinska University Hospital, Solna, Sweden, 6) Department of Pharmacy, Biology & Microbiology, University of Hamburg, Hamburg, Germany, 7) Department of Medical Microbiology, Southmead Hospital, Bristol, UK, 8) Department of Medical Microbiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherland, 9) Service de Bactériologie-Virologie, Hôpital de Bicêtre, Le Kremlin-Bicêtre, France, 10) Institut fur Medizinische Mikrobiologie der Universitat Leipzig, Leipzig, Germany, 11) Dipartimento di Biotecnologie, Sezione di Microbiologia, Siena, Italy, 12) Hôpital Henri Mondor, Service de Bactériologie, Creteil, France, 13) Department of Bacteriology and Immunology, Division of Infectious Disease Control, Norwegian Institute of Public Health, Oslo, Norway, 14) Department of Microbiology, Royal Hallamshire Hospital, Sheffield, UK and 15) Clinical Microbiology, Central Hospital, Växjö, Sweden

Clin Microbiol Infect, 2013; 19:141-60.

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EUCAST Expert Rules Version 3.1

Intrinsic Resistance and Exceptional Phenotypes Tables

EUCAST Expert Rules version 2.0 was published on 29 October 2011(http://www.eucast.org/expert_rules). The expert rules have been under review over the past year and changes to the intrinsic resistance and exceptional phenotypes tables have been agreed following wide consultation (October-December 2015) and further discussion in the EUCAST Steering Committee. The revised intrinsic resistance and exceptional phenotypes tables 1-7 (version 3.0), together with a summary of changes from version 2.0, were published on 9 September 2016. Version 3.1includes corrections to typographical errors in version 3.0.

Intrinsic Resistance in Non-fermentative Gram-negative Bacteria

Table 2. Intrinsic resistance in non-fermentative Gram-negative bacteria. Non-fermentative Gram-negative bacteria are also generally intrinsically resistant to benzylpenicillin, first and second generation cephalosporins, glycopeptides, fusidic acid, macrolides, lincosamides, streptogramins, rifampicin, daptomycin and linezolid.

Rule no.	Organisms	Ampicillin	Amoxicillin-Clavulanic acid	Ampicillin-sulbactam	Ticarcillin	Ticarcillin-clavulanic acid	Piperacillin	Piperacillin-tazobactam	Cefazolin, Cefalothin Cefalexin, Cefadroxil	Cefotaxime	Ceftriaxone	Ceftazidime	Cefepime	Aztreonam	Ertapenem	Imipenem	Meropenem	Ciprofloxacin	Chloramphenicol	Aminoglycosides	Trimethoprim	Fosfomycin	Tetracyclines	Tigecycline	Polymyxin B/Colistin
2.1	*A. baumannii*, *A. pittii* , and *A. nosocomialis*, *Acinetobacter calcoaceticus* complex	R	R	Note[1]					R	R	R			R	R						R	R	R[2]	Note[2]	
2.2	*Achromobacter xylosoxydans*	R							R	R	R				R										
2.3	*Burkholderia cepacia* complex[3]	R	R	R	R	R	R	R	R	R	R			R	R			R	R	R[4]	R	R			R
2.4	*Elizabethkingia meningoseptica*	R	R	R	R	R	R		R	R	R	R	R	R	R	R	R								R
2.5	*Ochrobactrum anthropi*	R	R	R	R	R	R	R	R	R	R	R	R	R	R										
2.6	*Pseudomonas aeruginosa*	R	R	R					R	R	R				R				R	Note[5]	R		R	R	
2.7	*Stenotrophomonas maltophilia*	R	R	R	R		R	R	R	R	R			R	R	R	R			R[4]	R[6]	R	R[7]		

R = resistant

Intrinsic Resistance in Non-fermentative Gram-negative Bacteria

Antimicrobial	*Acinetobacter* spp.*	*Pseudomonas aeruginosa*
Ampicillin	*R*	*R*
Amoxicillin-clav. acid	*R*	*R*
Ampicillin-sulbactam	*Note[1]*	*R*
Cefazolin, cephalothin, cefalexin, cefadroxil	*R*	*R*
Cefotaxime	*R*	*R*
Ceftriaxone	*R*	*R*
Aztreonam	*R*	-
Ertapenem	*R*	*R*
Chloramphenicol	-	*R*
Aminoglycosides	-	*Note[3]*
Trimethoprim	*R*	*R*
Fosfomycin	*R*	-
Tetracyclines	*R[2]*	*R*
Tigecycline	*Note[2]*	*R*

** A. baumannii, A. pittii, A. nosocomialis, A. calcaaceticus complex*

Note[1] A. baumannii may appear to be susceptible to ampicillin-sulbactam due to activity of sulbactam with this species.

Note[2] Acinetobacter is intrinsically resistant to tetracycline and doxycycline but not to minocycline and tigecycline.

Note[3] P. aeruginosa is intrinsically resistant to kanamycin and neomycin due to low level APH(3')-IIb activity.

AST results that require special consideration – Exceptional resistance phenotypes

Table 5. Exceptional resistance phenotypes of Gram-negative bacteria

Rule no.	Organisms	Exceptional phenotypes
5.1	Any Enterobacteriaceae (except Proteeae and *Serratia marcescens*)	Resistant to colistin[1]
5.2	*Salmonella* Typhi	Resistant to fluoroquinolones and/or carbapenems
5.3	*Pseudomonas aeruginosa* and *Acinetobacter* spp.	Resistant to colistin[1]
5.4	*Haemophilus influenzae*	Resistant to any third-generation cephalosporin, carbapenems, fluoroquinolones
5.5	*Moraxella catarrhalis*	Resistant to ciprofloxacin and any third-generation cephalosporin
5.6	*Neisseria meningitidis*	Resistant to any third generation cephalosporins, fluoroquinolones
5.7	*Neisseria gonorrhoeae*	Resistant to any third generation cephalosporins, spectinomycin and azithromycin

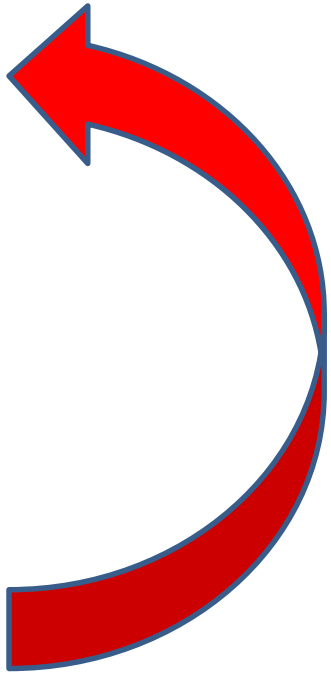
[1] Except in countries where colistin resistance is not rare. Certain *Salmonella* serotypes have colistin MICs slightly higher than current breakpoint (2 mg/L).

EUCAST Expert Rules – Interpretive Rules

1. To establish the susceptibility phenotype

2. To infer the potential resistance mechanism

3. To predict a previously defined phenotype from the resistance mechanisms



Leclercq R et al. Clin Microbiol Infect, 2013; 19:141-60.
http://www.eucast.org

EUCAST Expert Rules – Interpretive Rules

actions to be taken on the basis of specific AST results

Rule no.	Organisms	Agents tested	Agents affected	Rule	Exceptions, scientific basis and comments	Evidence grade	References
8.1	*Staphylococcus* spp.	Oxacillin, cefoxitin (disk diffusion) or detection of *mecA* gene or PBP2a	All beta-lactams	IF resistant to isoxazolyl-penicillins (as determined with oxacillin, cefoxitin, or by detection of *mecA*-gene or of PBP2a) THEN report as resistant to all β-lactams.	Production of PBP2a (encoded by *mecA*) leads to cross resistance to β-lactams except ceftobiprole and ceftaroline.	A	Chambers HF *et al*, 1990 Page MG *et al*, 2006

Agents tested

Agents affected

IF … THEN…

Exceptions, scientific basis and comments

Leclercq R et al. Clin Microbiol Infect, 2013; 19:141-60.; http://www.eucast.org

Resistance mechanism associated with clinical failure that is not reliably detected by routine conventional testing

Example of MRSA

The presence of *mec*A has been associated with clinical failure

Methicillin resistance is heterogeneously expressed by many strains

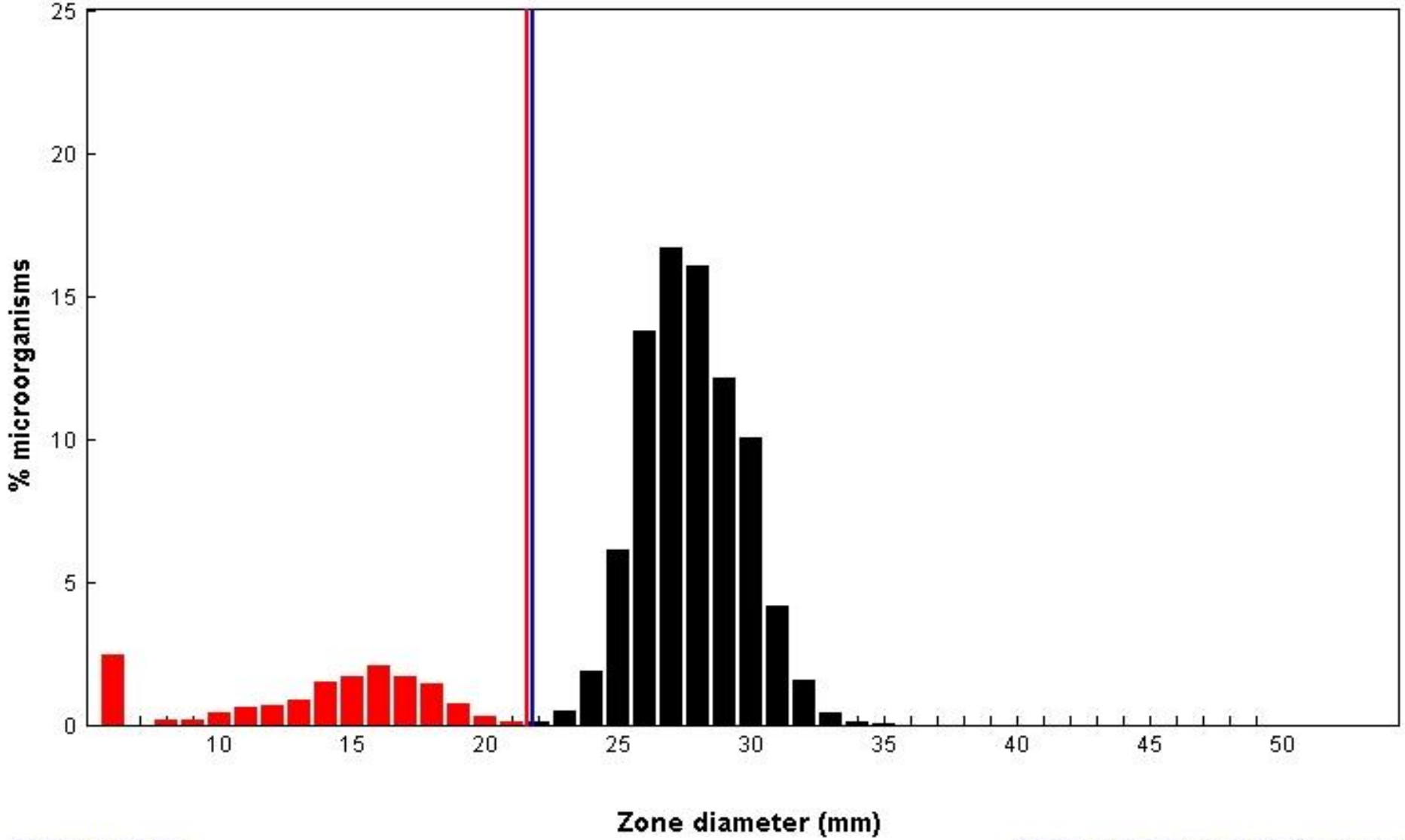
Even with optimisation, results with different beta-lactams are unreliable

Cefoxitin / Staphylococcus aureus

EUCAST zone diameter distribution - Reference database 2013-03-27

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

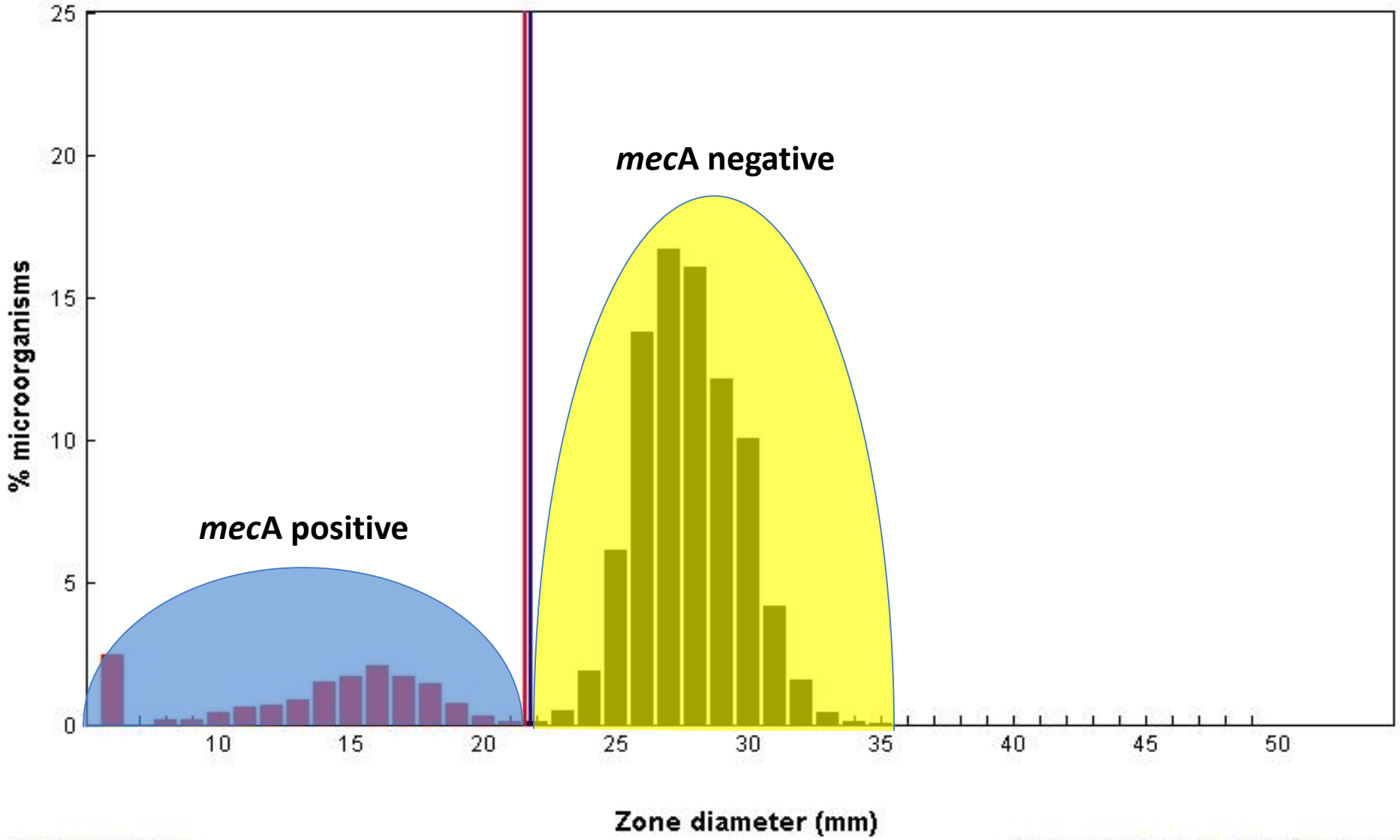


Disk content: 30

Epidemiological cut-off: WT ≥ 22 mm (MIC ≤ 4 mg/L)

11096 observations (8 data sources)

Clinical breakpoints: S ≥ 22 mm, R < 22 mm (inappropriate)


Cefoxitin / Staphylococcus aureus
EUCAST zone diameter distribution - Reference database 2013-03-27
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
mecA negative
mecA positive
% microorganisms
0
5
10
15
20
25
10
15
20
25
30
35
40
45
50
Zone diameter (mm)
Disk content: 30
Epidemiological cut-off: WT ≥ 22 mm (MIC ≤ 4 mg/L)
11096 observations (8 data sources)
Clinical breakpoints: S ≥ 22 mm, R < 22 mm (inappropriate)

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance

Version 2.0[1]

July 2017

[1] **Based on version 1.0 from December 2013 by the EUCAST subcommittee for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance.** Authors of the original version are acknowledged: Christian G. Giske (Sweden, EUCAST and EARS-Net Coordination Group; chairman), Luis Martinez-Martinez (Spain), Rafael Cantón (Spain, EUCAST), Stefania Stefani (Italy), Robert Skov (Germany), Youri Glupczynski (Belgium), Patrice Nordmann (France), Mandy Wootton (UK), Vivi Miriagou (Greece), Gunnar Skov Simonsen (Norway, EARS-Net Coordination Group), Helena Zemlickova (Czech Republic, EARS-Net Coordination Group), James Cohen-Stuart (The Netherlands), and Marek Gniadkowski (Poland).

Importance of detection of resistance mechanism
Required for antimicrobial susceptibility categorization
Infection control
Public health

Contents

Organization
EUCAST News
New definitions of S, I and R
Clinical breakpoints
Rapid AST in blood cultures
Expert rules and intrinsic resistance
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Guidance documents
Consultations - New!
MIC and zone distributions and ECOFFs
AST of bacteria
AST of mycobacteria
AST of fungi
AST of veterinary pathogens
Frequently Asked Questions (FAQ)
Meetings
Presentations and statistics
Warnings!
Documents

Instruction videos from EUCAST

In collaboration with the World Health Organisation (WHO), EUCAST publishes instruction videos on how to perform antimicrobial susceptibility testing (AST) using EUCAST recommended methods and interpretation.

The videos are published on Youtube™ and have an English speaker voice and English subtitles. Since not all countries may access Youtube™ videos in some languages are made available directly on the EUCAST web page.

The following topics are covered:

1. Preparation of inoculum (English).
2. Inoculation of agar plates for disk diffusion (English).
3. Application of antibiotic disks and incubation of plates (English).
4. Reading of inhibition zone diameters (English).
5. Guidance on the use of the breakpoint table (English).

Instruction videos on EUCAST susceptibility testing with subtitles in other languages than English:

Instruction videos - English subtitles.
- Alternative access to **instruction videos in English with english subtitles**.

Instruction videos - German subtitles.

Instruction videos - Russian subtitles.

Instruction videos - Turkish subtitles.

Instruction videos - French subtitles.

Instruction videos - Spanish subtitles.

Instruction videos - Portuguese subtitles.

Instruction videos - Arabic subtitles.

Instruction videos - Czech subtitles.

Instruction videos - Chinese subtitles.
- Alternative access to instruction videos in english with **chinese subtitles**.

Translations

EUCAST documents translated to other languages

Documents in Czech
Documents in German
Documents in Italian
Documents in Scandinavian languages
Documents in Spanish
Documents in Turkish
Documents in French
Documents in Serbian (Breakpoint Table v 8.0 for screen and for printing)
Documents in Chinese

The translation to Chinese of the EUCAST guidelines was initiated by Dr Yuqing Liu at Shandong Academy of Agricultural Sciences within the framework of the Sino-Swedish IMPACT project, funded by the Swedish Research Council (grant D0879801) and National Natural Science Foundation of China (grant 81361138021).

EUCAST takes full responsibility for the english version of all EUCAST documents available on the website. These are dated and assigned a version number.

National AST Committees (NACs) take responsibility for translating and updating the EUCAST national documents.

Current EUCAST Projects

ARTICLE IN PRESS

Clinical Microbiology and Infection xxx (2018) 1–7

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

The quality of antimicrobial discs from nine manufacturers—EUCAST evaluations in 2014 and 2017

J. Åhman*, E. Matuschek, G. Kahlmeter

EUCAST Development Laboratory, Växjö, Sweden

Table 2. Results for disks from nine manufacturers vs. EUCAST QC targets and ranges.

Manufacturer	Abtek	BD	Bio-analyse	BioRad	HiMedia	Liofil-chem	Mast	Oxoid	SirScan
Antimicrobial disk	**STUDY 2014**								
Benzylpenicillin 1 unit		L	H		NA				H
Amoxicillin-clav. 30 µg	L			H	H				
Piperacillin-tazo. 36 µg	L				NA				H
Oxacillin 1 µg		L	L		H	L			L
Mecillinam 10 µg	L		H		H				H
Cefotaxime 5 µg[1]	NA				NA				
Cefoxitin 30 µg	NA			H*	L*	H			
Ceftazidime 10 µg	L				L				
Meropenem 10 µg[1]	L			H	H	H*		H	
Ciprofloxacin 5 µg[1]		L			H		L		
Pefloxacin 5 µg	NA	L			H	L			NA
Norfloxacin 10 µg[1]	L				H*				L
Gentamicin 10 µg[1]		H			H				NA
Tobramycin 10 µg				NA	H*	H			
Erythromycin 15 µg	L	L	L*		H	L			L
Tetracycline 30 µg	L	L*	L			L	L		L*
Antimicrobial disk	**STUDY 2017**								
Benzylpenicillin 1 unit		L							NA
Amoxicillin-clav. 30 µg	L			H	L	L			
Piperacillin-tazo. 36 µg	L		H		L		H		
Oxacillin 1 µg				H	H				
Mecillinam 10 µg									
Cefotaxime 5 µg									
Cefoxitin 30 µg		L	H		L				
Ceftazidime 10 µg	L				L*				
Meropenem 10 µg					L*				
Ciprofloxacin 5 µg									
Pefloxacin 5 µg					H	L			
Norfloxacin 10 µg									
Gentamicin 10 µg					H		H		
Tobramycin 10 µg					H				
Erythromycin 15 µg									
Tetracycline 30 µg					L				

[1]Data reanalyzed due to changes in QC criteria since 2014.

2014

2017

Mean value within ± 1 mm of the target value
Mean value >1 mm but within ± 2 mm of the target value
Mean value >2 mm from target value but still within the QC range
Mean value out of the QC range

NA = Not Available
H = High, mean value > 1 mm above target
L = Low , mean value > 1 mm below target
* One or more readings out of QC range

Challenges in AST

- Colistin
- Fosfomycin
- Beta-lactam + inhibitors (including amoxicillin-clavulanic acid and piperacillin-tazobactam)
- Beta-lactam resistance in *H. influenzae*

Colistin

Recommendations for MIC determination of colistin (polymyxin E) As recommended by the joint CLSI-EUCAST Polymyxin Breakpoints Working Group

Colistin (polymyxin E) MIC determination is associated by several methodological issues. The issues have been extensively investigated by the CLSI-EUCAST joint Polymyxin Breakpoints Working Group and the following method for determination of colistin MIC was agreed:

1. Reference testing of Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter* spp. is by the ISO-standard broth microdilution method (20776-1). Note:
    a. Cation-adjusted Mueller-Hinton Broth is used
    b. No additives may be included in any part of the testing process (in particular, no polysorbate-80 or other surfactants)
    c. Trays must be made of plain polystyrene and not treated in any way before use
    d. Sulphate salts of polymyxins must be used (the methanesulfonate derivative of colistin must not be used - it is an inactive pro-drug that breaks down slowly in solution)

2. Susceptibility testing by other methods, including agar dilution, disk diffusion and gradient diffusion, cannot be recommended until historical data have been reviewed or new study data have been generated. Work on these methods is ongoing.

Warning published on www.eucast.org 22 March 2016

Colistin

- **Broth micro dilution = reference method and currently only recommended method.**
  - Quality control of colistin must be performed with both a susceptible QC strain (*E. coli* ATCC 25922 or *P. aeruginosa* ATCC 27853) and the colistin resistant *E. coli* NCTC 13846 (*mcr*-1 positive; colistin target MIC value is 4 mg/L and should only occasionally be 2 or 8 mg/L).

- **The following techniques are not acceptable for colistin AST**
  - Disk diffusion not possible
  - Gradient testing not possible
  - Agar dilution?? Screening plates??
  - Semi-automated (Vitek 2, Phoenix, Micro-Scan)??

Link from the EUCAST ”Warnings” page to publication…

Matuschek E, *et al.*, Antimicrobial susceptibility testing of colistin - evaluation of seven commercial MIC products against standard broth microdilution for *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp., Clinical Microbiology and Infection (2017), https://doi.org/10.1016/j.cmi.2017.11.020

Colistin AST with gradient strips

VME = False susceptible

Essential and categorical agreements for colistin MIC tests for 75 Gram-negative bacteria with MICs on frozen broth microdilution panels as reference

	Organism	*E. coli* and *K. pneumoniae* (*n*=32)	*P. aeruginosa* (*n*=21)	*Acinetobacter* spp. (*n*=22)	All isolates (*n*=75)
	Colistin reference MIC range (mg/L)	0.25–32	0.25–128	0.5–32	0.25–128
Number of very major errors (VME)[g]	Sensititre custom plate	0	0	0	0
	MICRONAUT-S	0	2	0	2
	MICRONAUT MIC-Strip	0	2	0	2
	SensiTest	0	1	0	1
	UMIC	0	1	2	3
	Etest, Oxoid MH	0	6	6	12
	Etest, BBL MH	1	7	7	15
	Etest, MHE	0	5	4	9
	MTS, Oxoid MH	6	6	4	16
	MTS, BBL MH	5	6	7	18

Matuschek E, *et al.*, Antimicrobial susceptibility testing of colistin - evaluation of seven commercial MIC products against standard broth microdilution for *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp., Clinical Microbiology and Infection (2017), https://doi.org/10.1016/j.cmi.2017.11.020

Colistin AST with commercial BMD methods

Essential agreement (target ± 1 dilution of reference MIC):

Sensititre (Thermo Fisher Scientific):	96%
MICRONAUT-S (Merlin Diagnostika):	96%
MICRONAUT MIC-Strip (Merlin Diagnostika):	99%
SensiTest (Liofilchem):	88%
UMIC (Biocentric):	82%

Major Errors (false resistance) - No MEs of a total of 75

Sensititre (Thermo Fisher Scientific):	4
MICRONAUT-S (Merlin Diagnostika):	6
MICRONAT MIC-Strip (Merlin Diagnostika):	5
SensiTest (Liofilchem):	7
UMIC (Biocentric):	3

Very Major Errors (false susceptibility) - No VMEs of a total of 75

Sensititre (Thermo Fisher Scientific):	0
MICRONAUT-S (Merlin Diagnostika):	2
MICRONAT MIC-Strip (Merlin Diagnostika):	2
SensiTest (Liofilchem):	1
UMIC (Biocentric):	3

Matuschek E, *et al.*, Antimicrobial susceptibility testing of colistin - evaluation of seven commercial MIC products against standard broth microdilution for *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp., Clinical Microbiology and Infection (2017), https://doi.org/10.1016/j.cmi.2017.11.020

Rapid AST directly from positive blood culture bottles

A EUCAST standard method
Implementation 2018

The pressing need for rapid AST

Rapid diagnostic tests

- rapid Strep A
- meningitis panel
- multiplex PCR (sepsis, respiratory, enteritis etc.)

- MALDI-TOF MS

Main problem with clinical microbiology laboratory

Speed

Main problem with clinical microbiology laboratory

Louis Pasteur (1822-1895)

THE AMERICAN JOURNAL OF CLINICAL PATHOLOGY
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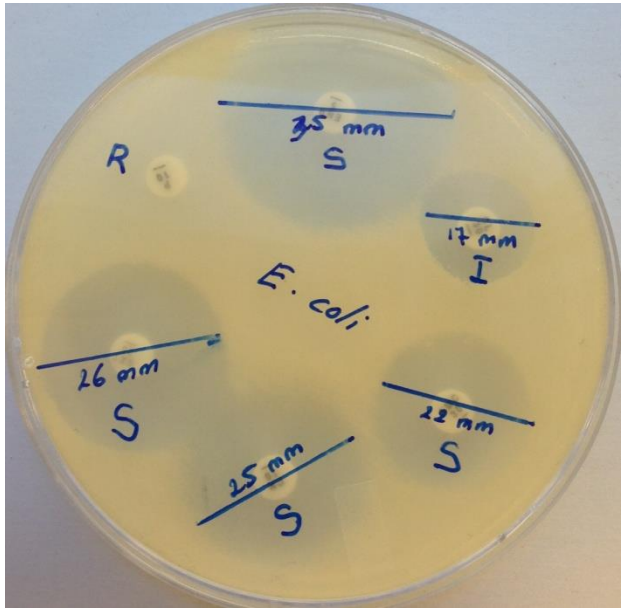
Vol. 45, No. 4 *Printed in U.S.A.*

Reprinted from TECHNICAL BULLETIN OF THE REGISTRY OF MEDICAL TECHNOLOGISTS
Vol. 36, No. 3, 1966

ANTIBIOTIC SUSCEPTIBILITY TESTING BY A STANDARDIZED SINGLE DISK METHOD

A. W. BAUER, M.D., W. M. M. KIRBY, M.D., J. C. SHERRIS, M.D., AND M. TURCK, M.D.



1966

Progress has been achieved on other fields of medicine for rapid diagnostics using biomarkers

- Troponine
- D-dimer
- BNP
- Procalcitonin

Bacterial culture (growth) based diagnostics

- Delay in the correct diagnosis

  which organism?

  which antimicrobial?

25-40% of septic patients receive inappropriate antimicrobial therapy

Ibrahim EH, Chest 2000:118;146-55

Conventional vs. Rapid Methodology

Day 0 | Day 1 | Day 2 | Day 3 | Day 4

Blood culture

Growth in blood culture bottle

Identification and antimicrobial susceptibility testing

Gram stain

Empiric treatment → Broad spectrum Abx → Targeted treatment

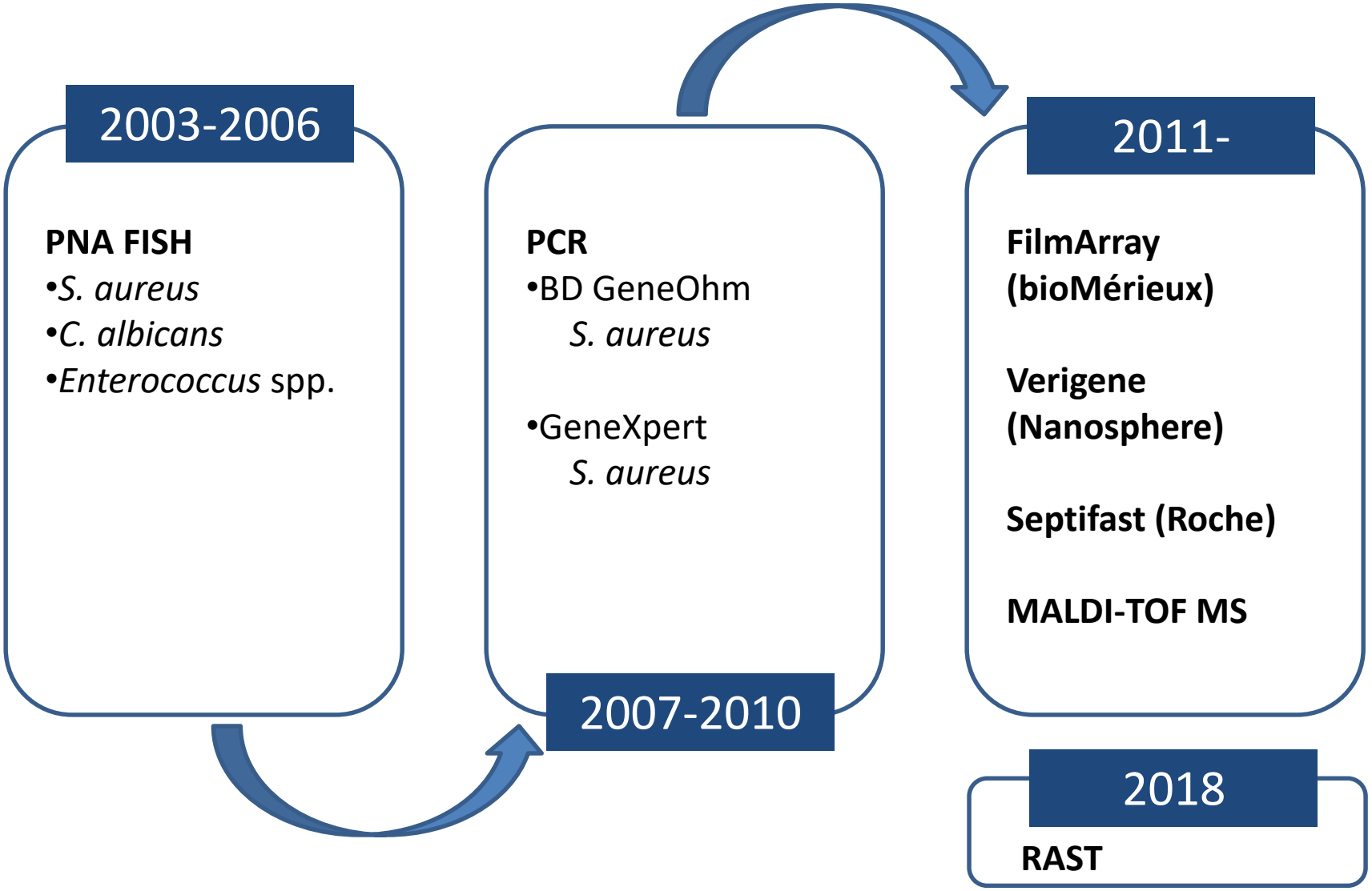
Blood culture

Growth in blood culture bottle

Gram stain

Identification

Empiric Abx → Targeted treatment


2003-2006
PNA FISH
•S. aureus
•C. albicans
•Enterococcus spp.
2007-2010
PCR
•BD GeneOhm
S. aureus
•GeneXpert
S. aureus
2011-
FilmArray (bioMérieux)
Verigene (Nanosphere)
Septifast (Roche)
MALDI-TOF MS
2018
RAST

Growth in blood culture

MALDI-TOF MS

20-30 min

Rapid Antimicrobial Susceptibility Testing

4-8 hours

⇒ **Same day results** for identification

+

antimicrobial susceptibility profile

Conventional	Rapid
Growth in blood culture, Gram-positive, chain-forming cocci in Gram stain	Growth in blood culture, Gram-positive, chain-forming cocci in Gram stain
Vancomycin and gentamicin initiated	Direct identification (MALDI-TOF MS) from positive blood culture bottle: *E. faecalis* (***E. faecalis*** **> 99% S to ampicillin**)
24 h incubation – start of identification tests	High dose ampicillin initiated as monotherapy
48 h – identified as *E. faecalis*	Susceptibility confirmed in 8 hours
72 h – growth detected in repeat blood cultures	Creatinine stabile (1.5 mg/dL)
Ampicillin S, vancomycin and high-level gentamicin R	Planned mitral valve open heart surgery performed
Creatinine 2.7 mg/dL	Treatment completed in 4 weeks
Switched to ampicillin	
Hemodialysis is required Planned operation postponed	
Healed after 8 weeks - Need for hemodialysis continues at 12 months	

Rapid AST directly from positive blood culture bottles

- A new EUCAST standard procedure with zone diameter breakpoints for reading at 4, 6 and 8 hours.
- Three blood culture systems validated.
- Keep “system” warm!
- ID directly from blood culture bottles.
- Inoculate directly from blood culture bottles (no spinning, no dilution)
- *E. coli, K. pneumoniae, S. aureus, P. aeruginosa, S. pneumoniae, E. faecalis* and *E. faecium,* (*H. influenzae*).
- Only for agents important in septicemia.
- Breakpoints will be available on EUCAST website in species-specific tables

Slide Courtesy of Prof Gunnar Kahlmeter

Rapid AST directly from positive blood culture bottles

- Take the sample
- Inoculate blood culture bottles
- Place in machine within 2 hours (BD, bioMerieux, Thermofisher).
- Bottles positive in 8 – 16 h.
- Inoculate from bottle as soon as possible (0.5h - 14h).
- Direct ID on mass spec or molecular.
- Direct swab of “warm plate” for immediate disk diffusion.
- Incubate and read after 4, 6 and 8 hours.
- Report S and R
  - No intermediate results, only **S** and **R**
  - Do not report ATU (leave blank or with comment)

Rapid AST directly from positive blood culture bottles

EUCAST RAST Field Trial Study

- 40 laboratories participated and delivered results and all strains
  - Denmark (3), Finland (3), Iceland (1), Ireland (1), Norway (11) and Sweden (21)
- Blood culture systems:
  - BD BACTEC n=17
  - bioMerieux BacT/ALERT n=23
- Disk manufacturers: 4
- MH manufacturers: 6
- Reference: BMD + standard EUCAST disk diffusion (16-20 h)

Rapid AST directly from positive blood culture bottles

EUCAST RAST Field Trial Study – Isolates tested

Species	Number
E. coli	436
K. pneumoniae	64
P. aeruginosa	37
Other gram negatives	52
S. aureus	270
Coagulase negative staph.	357
S. pneumoniae	35
Total number	**1251**

Slide Courtesy of Prof Gunnar Kahlmeter

Rapid AST directly from positive blood culture bottles

RAST vs. Standard Disk Diffusion

	S. aureus **(n=242)** Cefoxitin, norfloxacin, erythromycin, gentamicin		
Incubation time	**4h**	**6h**	**8h**
Number of possible tests[a]	968	968	968
Number of performed tests[b]	952	956	892
Number of zones registered[c]	623	880	844
	Categorical agreement (%)		
Correct	66	92	95
mE	0.0	0.0	0.0
ME	8.5	0.3	0.4
VME	0.2	0.3	0.5
ATU	25	7.2	4.0

a) Number of possible tests = Total number of possible isolate-agent combinations
b) Number of performed tests = Number of possible tests after excluding missing data (e.g. disk forgotten or laboratory opening hours too short)
c) Number of zones registered = Number of performed tests with readable inhibition zones

Slide Courtesy of Prof Gunnar Kahlmeter

Rapid AST directly from positive blood culture bottles

RAST vs. Standard Disk Diffusion

	E. coli **(n=386)** Cefotaxime, ceftazidime, piperacillin-tazobactam, meropenem, ciprofloxacin,			***E. coli*** **(n=386)** Piperacillin-tazobactam excluded		
Incubation time	**4h**	**6h**	**8h**	**4h**	**6h**	**8h**
Number of possible tests[a]	3 088	3 088	3 088	2 702	2 702	2 702
Number of performed tests[b]	3 034	3 027	2 768	2 651	2 645	2 419
Number of zones registered[c]	2 756	2 993	2 752	2 415	2 613	2 404
	Categorical agreement (%)					
Correct	77	81	84	88	93	95
mE	0.3	0.1	0.1	0.2	0.2	0.1
ME	1.6	0.4	0.2	1.8	0.5	0.3
VME	0.1	0.1	0.1	0.1	0.1	0.1
ATU	20	18	16	10	6.2	4.0

a) Number of possible tests = Total number of possible isolate-agent combinations
b) Number of performed tests = Number of possible tests after excluding missing data (e.g. disk forgotten or laboratory opening hours too short)
c) Number of zones registered = Number of performed tests with readable inhibition zones

Slide Courtesy of Prof Gunnar Kahlmeter

Rapid AST directly from blood culture bottles

EUCAST will shortly publish recommendations for short incubation (4, 6 and 8 hours) AST directly from positive blood culture bottles using EUCAST standard disk diffusion. These are the characteristics of the rapid method:

- direct inoculation of disk diffusion plates (MH, MH-F) using 100 - 150 µL directly from a positive blood culture bottle (BD, bioMerieux and Thermo Fisher).
- no centrifugation or dilution of the inoculum - inoculate plates as for standard EUCAST disk diffusion.
- shortened incubation - 4, 6 and 8 hours with breakpoints adapted to each incubation time.
- breakpoints for each species and each reading time.
- identity of species must be known prior to interpretation of AST results.
- the method is currently validated for the following species.
  - *Escherichia coli*
  - *Klebsiella pneumoniae*
  - *Pseudomonas aeruginosa*
  - *Staphylococcus aureus*
  - *Streptococcus pneumoniae*
  - *Enterococcus faecalis* and *Enterococcus faecium*
- a positive blood culture bottle should be processed 0 - 18 hours after the positive signal.
- zone diameters are read from the front of the plate after removal of the lid.
- not all zone diameters can be read after 4 or 6 hours.
- read zone diameters ONLY when an obvious zone edge can be identified - otherwise reincubate and read after 6 or 8 hours.
- the breakpoint table is specific for EUCAST Rapid AST - do not use the regular breakpoint table. Each species has its own TAB in the table and each reading time (4, 6 and 8 hours) its own section.

Breakpoint table and method to be published before the end of November, 2018.

Thank you!

www.eucast.org

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EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases