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

EUCAST

2012 and on

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ESCMID
EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

Clinical breakpoints are likely determined by…..

- breakpoint committees.
- by medicines agencies as part of the regulatory process (FDA, EMA, national medicines agencies).
- by companies (…..after all they own the drug).
- by AST manufacturers - because flexibility of machines is low and older breakpoints remain for years!
- by colleagues who know better … than anyone else.

Breakpoint comittees

- **BSAC - UK**
- **CA-SFM - France**
- **CLSI - USA**
- **CRG - Netherlands**
- **DIN - Germany (folded 2011)**
- **NWGA - Norway**
- **SRGA - Sweden**

EUCAST was formed in 1996 and reformed in 2001.

Committee	Country	Regulatory agreement
EUCAST [1] 	Europe	Yes[1]
CLSI 	USA	No
FDA[2] 	USA	As part of the regulatory process

[1]EUCAST is the umbrella for national breakpoint committees in Europe: BSAC, CA-SFM, CRG, (DIN), NWGA & SRGA and is the breakpoint committee of EMA.

[2]FDA has no committee; breakpoints are suggested by company and evaluated by individual rapporteurs as part of approval process.

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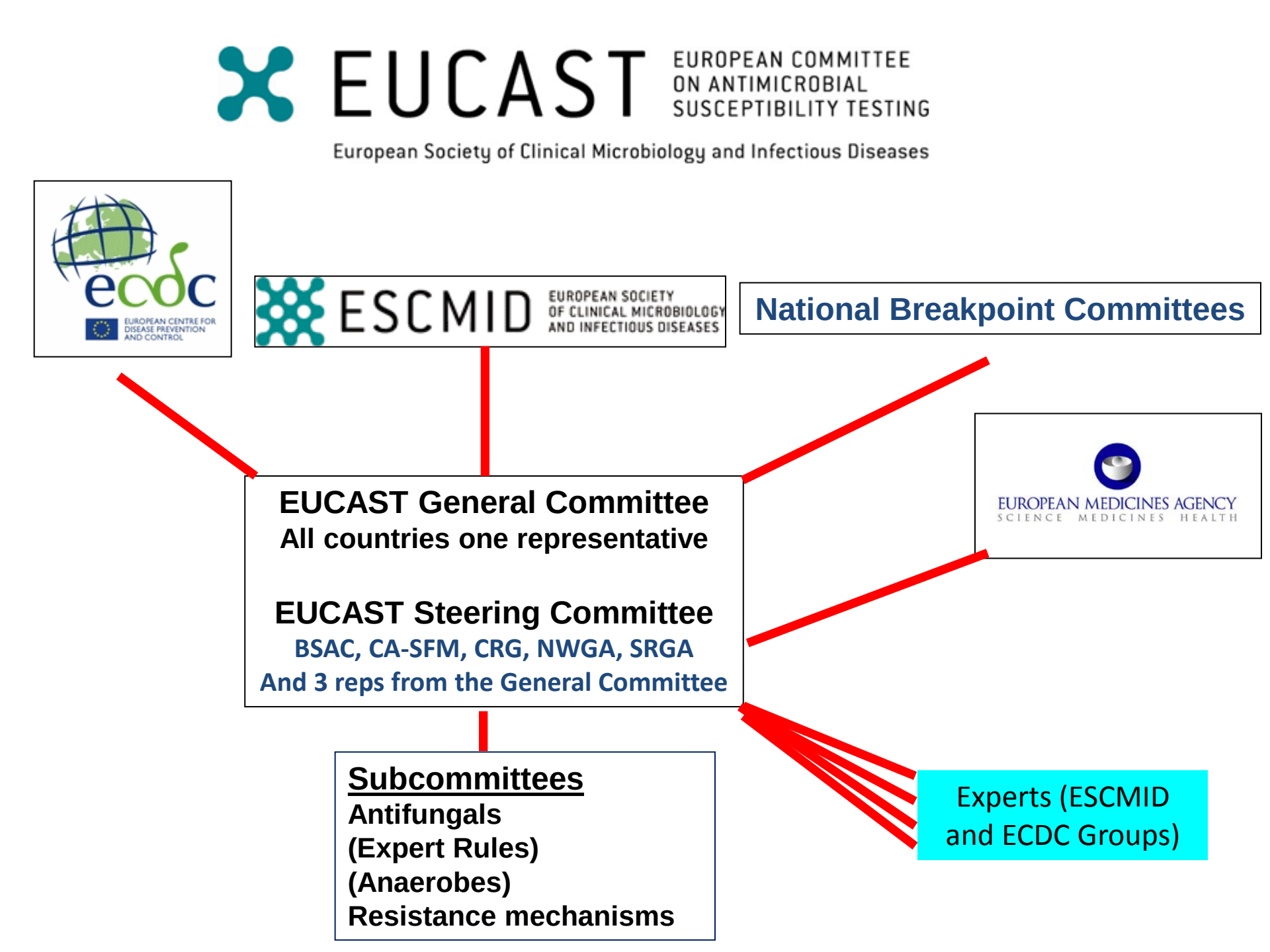
- Breakpoints for existing antimicrobials (harmonisaton; finalized)
- Breakpoints for new antimicrobials (with EMA; regulatory)
- Methods for susceptibility testing and QC
- MIC- and zone diameter distributions and ECOFFs on website
- Liaison with authorities (medicines and disease control agencies)
- Education

- Recognized by the **profession**, the **authorities** and **industry**
  - The profession – more an more laboratories are adopting EUCAST recommendations
  - Authorities - ECDC, EMA, EFSA (European legislation)
  - Industry - Pharmaceutical, Manufacturers of AST material and devices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EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
National Breakpoint Committees
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
EUCAST General Committee
All countries one representative
EUCAST Steering Committee
BSAC, CA-SFM, CRG, NWGA, SRGA
And 3 reps from the General Committee
Subcommittees
Antifungals
(Expert Rules)
(Anaerobes)
Resistance mechanisms
Experts (ESCMID and ECDC Groups)

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The European Committee on Antimicrobial Susceptibility Testing

- **ESCMID**
  - Administration of EUCAST
  - Scientific and educational backbone
  - Financiation of the development and upkeep of the EUCAST disk diffusion.
  - Provides expertise through ESCMID Study Groups in special areas (C. difficile, H. pylori, M. tuberculosis, Legionella, Neisseria, etc)
- **ECDC**
  - ECDC networks and experts provide advice on breakpoints in areas of public health (Neisseria, Enteric pathogens, Mycobacterium tuberculosis, etc)
  - EUCAST provides expertise in ECDC projects (EARS-NET, MDR/PDR,…)
- **EMA** - SOP for the determination of breakpoints as part of the process for approval and registration of new compounds (antibacterial and antifungal).
- **National breakpoint committees**
  - Provide expertise for breakpoint setting.
  - Consultation process

EUCAST General Committee in session

- Open meeting
- One meeting per year (during ECCMID)
- One representative per country
- Consultation by email several times per year
- Report on last 12 months and plans for next 12 months.
- Minutes on website (www.eucast.org)

EUCAST Steering Committee in session

- Five 2-day meetings per year
- 11 members (CM, SciS and CDC + BSAC, CA-SFM, CRF, NWGA, SRGA + 3 from GC)
- Decisions by consensus

EUCAST and CLSI – are they different

EUCAST

Systematic review of breakpoints

- Industry consultative role.
- Decision by consensus.
- Five meetings per year.
- EUCAST=EMEA brpt committee.

- Clinical breakpoints and ECOFFs
- Rationale for decisions published
- Documents free of charge (on web)

CLSI

- Industry, the profession, advisory regulators.
- Funded by industry and sales of output.
- Industry part of decision process
- Decision by vote.
- Two meetings per year.
- CLSI technical standing with FDA but breakpoints not accepted by FDA.
- Clinical breakpoints
- Rationale for decisions not published.
- Documents for sale

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Newsfeed – subscribe free of charge!

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Website changes

search term Search

QUICK NAVIGATION

The European Committee on Antimicrobial Susceptibility Testing - EUCAST

EUCAST is a standing committee jointly organized by ESCMID, ECDC and European national breakpoint committees. EUCAST deals with breakpoints and technical aspects of phenotypic in vitro antimicrobial susceptibility testing and functions as the breakpoint committee of EMA and ECDC. EUCAST does not deal with antibiotic policies, surveillance or containment of resistance or infection control. The Steering Committee is the decision making body. It is supported by a General Committee with representatives from European and other countries, FESCI and ISC. The Steering Committee also consults on EUCAST proposals with experts within the fields of infectious diseases and microbiology, pharmaceutical companies and susceptibility testing device manufacturers.

EUCAST has a subcommittee on antifungal susceptibility testing and on methods for detection of resistance mechanisms of clinical and/or epidemiological importance.

Subcommittees on expert rules for antimicrobial susceptibility testing and antimicrobial susceptibility testing of anaerobes have completed their tasks and have been disbanded.

Most antimicrobial MIC breakpoints in Europe have been harmonised by EUCAST. Breakpoints for new agents are set as part of the licensing process for new agents through EMA. EUCAST breakpoints are available in devices for automated susceptibility testing but with some limitations, depending on the system. A disk diffusion susceptibility test method calibrated to EUCAST MIC

EUCAST News

11 Sep 2012
Ceftaroline breakpoints release

12 Aug 2012
Anidulafungin RD updated - er in dosing corrected

03 Aug 2012
Consultation until 14 Sept 2012 Campylobacter breakpoints

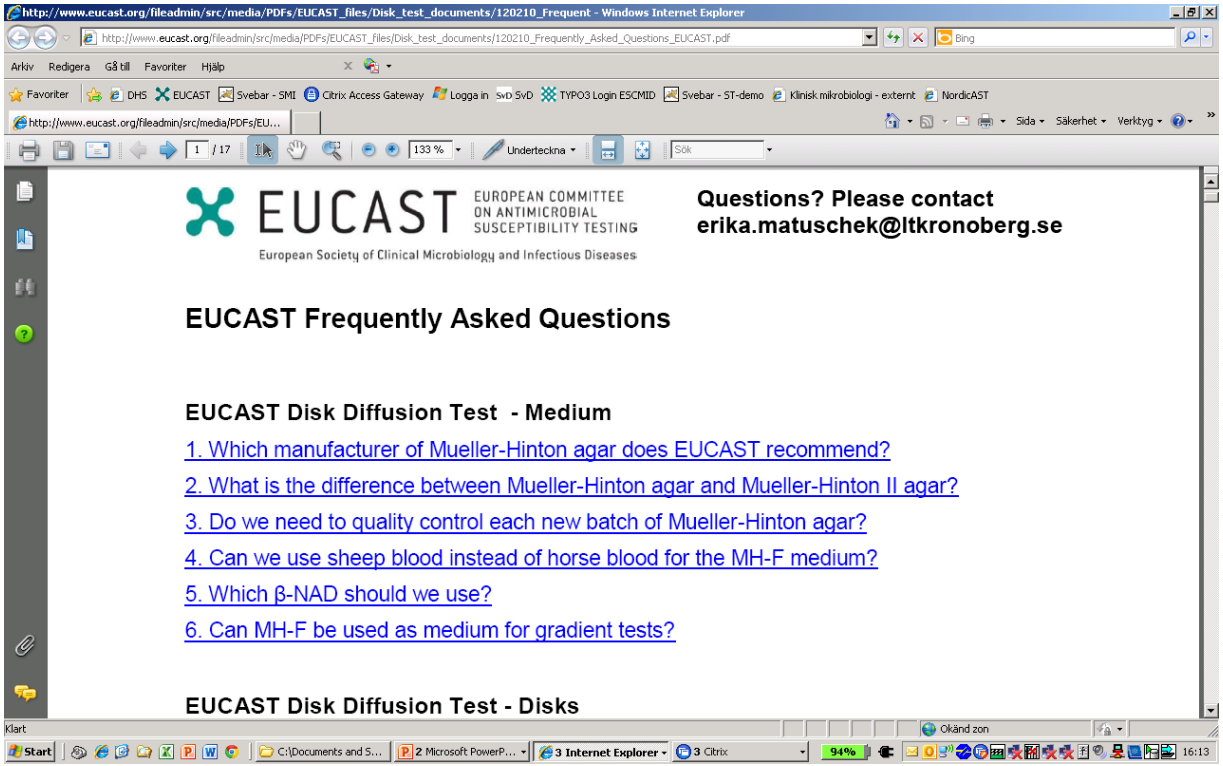
03 Aug 2012
Consultation until 14 Sept 2012 P.multocida breakpoints

30 Jun 2012
QC-tables - updated version Ju 29, 2012

About Newsfeeds

Questions to EUCAST

EUCAST receives between 10 – 20 Qs per week.
Individual replies to all and the FAQ.



EUCAST - breakpoints for new drugs with EMA*

- Daptomycin √
- Tigecycline √
- Doripenem √
- Telavancin √
- Ceftaroline √

- Glycopeptides (one ongoing)
- Cefalosporines (activity against MRSA – one agent ongoing)
- Anti-Mtb (two agents - ongoing)

- Glycopeptide (withdrawn)
- Fluoroquinolone (withdrawn)
- Diaminopyrimidine (withdrawn)

- Extensions of indications (currently none)

***EMA = European Medicines Agency**

EUCAST – recent breakpoints, methods and guidance

- Moraxella catarrhalis (finalized) - 2011
- Helicobacter pylori (finalized) - 2011
- Clostridium difficile (finalized) - 2011
- Listeria monocytogenes (finalized) - 2011
- Campylobacter (finalized) - 2012
- Pasteurella multocida (finalized) - 2012

EUCAST – recent documents

- Expert Rules v 2.0 – CMI 2012
- EUCAST and PK/PD – CMI 2012
- EUCAST AFST - breakpoints and RDs for antifungal agents published (Candidae and Aspergillus).
- Guidance on Stenotrophomons maltophilia 2012
- Guidance on direct AST 2012
- Guidance on systemic breakpoints for oral cephalosporins
- Validation of EUCAST zone diameter breakpoints (many) 2012
- Rationale Documents – now 47

- Breakpoint tables v 3.0 (next week for consultation)

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Stenotrophomonas maltophilia

The organism

Stenotrophomonas maltophilia is a ubiquitous environmental organism. In patients it is most often associated with colonization, but is an occasional cause of infection, particularly in immunocompromised patients and patients with cystic fibrosis.

Antimicrobial resistance

Intrinsic antimicrobial resistance of this organism is a major problem, particularly to aminoglycosides and carbapenems. Multiple efflux pumps and modifications to outer membrane proteins confer variable resistance to a wide range of agents. Chromosomal genes for beta-lactamases affect all beta-lactams including carbapenems. Aminoglycoside acetyl transferase and SmQnr genes (conferring reduced susceptibility to fluoroquinolones) are almost always present (3). In addition, acquired genes may be present conferring resistance to a wide range of agents, including trimethoprim-sulfamethoxazole (co-trimoxazole) (17). Moreover, the formation of biofilms reduces antimicrobial effectiveness.

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Direct antimicrobial susceptibility testing

In direct antimicrobial susceptibility testing the specimen (commonly urines) is used as the source of the inoculum. Tests where positive blood cultures are used as the source of the inoculum are also included as direct tests, although they do not use the specimen directly.

The advantage of direct testing is that results may be available earlier than when the organism is isolated in pure culture before testing and this may have direct patient benefit in terms of early appropriate chemotherapy. There may be additional benefits from the ability to narrow the spectrum of therapy at an early stage.

The main disadvantage is that the inoculum cannot be effectively controlled. Also there may be mixed cultures and there may be pH variations or substances in the specimens that affect results (e.g. antimicrobial agents in urine, antimicrobial absorption materials in blood cultures). These problems may result in less reliable results than with pure cultures. EUCAST does not recommend primary susceptibility testing and any laboratory using this approach must take responsibility for ensuring that results are reliable. The following should be noted:

1. There are currently no validated methods for processing specimens to ensure that the correct inoculum is achieved.
2. Tests should be repeated on pure cultures as needed and the correlation of direct and secondary tests should be monitored so that the reliability of direct tests can be assessed.
3. In disk diffusion tests, if the inoculum is visibly light, do not report susceptible results as zone diameters may be increased leading to resistant isolates appearing susceptible.

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Why do EUCAST have no systemic breakpoints for Enterobacteriaceae with oral cephalosporins?

There have been multiple questions from clinicians, particularly those working in orthopaedics, who have "successfully used oral cephalosporins for prophylaxis and to treat Enterobacteriaceae infections for many years". They ask what has changed and why these agents are now considered inappropriate.

In EUCAST rationale documents it is stated that Enterobacteriaceae are inappropriate targets in sites other than uncomplicated urinary tract infection, but there is no further explanation. In early EUCAST discussions oral cephalosporins were originally considered inappropriate for treatment of infections in other sites than the urinary tract infection for several reasons:

1. Comparison of free drug pharmacokinetics with MICs alone indicates that inadequate concentrations are achieved for most agents and are borderline at best (see table).

2. The relevant pharmacodynamic relationship indicative of activity of cephalosporins is T>MIC and the target %*f*T>MIC is 40-50%. Approximate calculations based on common dosages indicate that activity is inadequate for all agents (see table). It should be emphasized that the figures in the table are based on pharmacokinetic parameter values for the mean of the population. Monte Carlo simulations would show that the %*f*T>MIC values are even less than those in the table for half the population treated.

3. Evidence of successful clinical use is anecdotal and may be unrelated to specific Enterobacteriaceae isolates, which are rare in orthopaedic infection and often in

EUCAST – what to expect in 2013

- Corynebacteria (ongoing) - 2013
- Pseudomonas non-aeruginosa (ongoing) - 2013
- Neisseria gonorrhoeae disk diffusion ? - 2013/14
- Actinomyces (ongoing) - 2013
- New drugs with EMA - 2013/14
- C.difficile – disk diffusion test - 2013
- Topical agents – ECOFFs in lieu of breakpoints - 2013
- Disk diffusion testing of (some) anaerobes - 2013/14

- New **subcommittee** ”on detection of resistance mechanisms of clinical and/or epidemiological importance” – final report 2013.
- Development of **flowchart algorithms** for AST in clinical laboratories.
- Next **breakpoint table** (v 3.0) released 5 Dec and 1 Jan, 2013
- Global **colistin** Breakpoints – joint initiative between EUCAST and CLSI.

EUCAST breakpoint table

	A	B	C	D	E	F	G	H
44								
45	**Carbapenems**	**MIC breakpoint**		**Disk**	**Zone diameter**		**Notes**	
46		**S ≤**	**R>**	**content**	**S ≥**	**R<**	Numbers for comments on MIC breakpoints	
47								
48	**Doripenem**							
49	**Ertapenem**							
50	**Imipenem**[1]							
51	**Meropenem**							
52								
53								
54	**Monobactams**							
55								
56								
57	**Aztreonam**[1]						d by most ESBLs and other hat produce ESBLs appear ontrol purposes laboratories	
58								
59								
60	**Fluoroquinolones**							
61								
62								
63	**Ciprofloxacin**[1]						ponse in systemic infections g/L). The available data relate *onella* species.	
64	**Levofloxacin**							
65	**Moxifloxacin**	0.5	1	**5**	20	17		
66	**Nalidixic acid (screen)**	Note[2]	Note[2]	**30**	16[A]	16[A]	**2/A.** Nalidixic acid may be used to screen for fluoroquinolone resistance in Enterobacteriaceae. The zone diameter breakpoint correlates to an MIC value of 16 mg/L in most Enterobacteriaceae. If *Salmonella* spp. are resistant report resistant to all fluoroquinolones. If other Enterobacteriaceae are resistant, then test the agent in question.	
67	**Norfloxacin**	0.5	1	**10**	22	19		
68	**Ofloxacin**	0.5	1	**5**	22	19		
69								
70								
71	**Aminoglycosides**[1]	**MIC breakpoint**		**Disk**	**Zone diameter**		**Notes**	
72		**S ≤**	**R>**	**content**	**S ≥**	**R<**	Numbers for comments on MIC breakpoints	
73							**1.** Aminoglycoside breakpoints are based on once-daily administration of high aminoglycoside dosages. Most often aminoglycosides are given in combination with beta-lactam agents.	
74	**Amikacin**	8	16	**30**	16	13		
75	**Gentamicin**	2	4	**10**	17	14		
76	**Netilmicin**	2	4	**10**	15	12		
77	**Tobramycin**	2	4	**10**	15	12		
78								
79								
80	**Glycopeptides**	**MIC breakpoint**		**Disk**	**Zone diameter**		**Notes**	
81		**S ≤**	**R>**	**content**	**S ≥**	**R<**	Numbers for comments on MIC breakpoints	

The intermediate column is not spelled out!

Example *E. coli* with Imipenem:

S ≤ 2 mg/L
R >8 mg/L
} Intermediate = 4-8 mg/L

S ≥21 mm
R <15 mm
} Intermediate = 15-20 mm

Links in EUCAST breakpoint table

Click on antibiotic for **Rationale Document**

Click on MIC breakpoint for **MIC distributions**

Click on zone breakpoint for **zone diameter distributions**

	Carbapenems						
45							
46							
47							
48	Doripenem						
49	Ertapenem						
50	Imipenem[1]						
51	Meropenem						
52							
53							
54	**Monobactams**	**MIC breakpoint**		**Disk**	**Zone diameter**		**Notes**
55		**S ≤**	**R>**	**content**	**S ≥**	**R<**	Numbers for comments on MI
56							
57	Aztreonam[1]	1	8	**30**	25	21	**1**. The aztreonam breakpoints for Er clinically important beta-lactamases susceptible or intermediate with the may want to use a test which speci
58							
59							
60	**Fluoroquinolones**	**MIC breakpoint**		**Dis**			
61		**S ≤**	**R>**				
62							
63	Ciprofloxacin[1]	0.5		**5**			
64	Levofloxacin	1	2	**5**			
65	Moxifloxacin	0.5	1	**5**			
66	**Nalidixic acid (screen)**	Note[2]	Note[2]	**30**			resistant to all fluoroquinolones. If other Enterobac
67	Norfloxacin	0.5	1	**10**	22	19	
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72		**S ≤**	**R>**	**conten**		**R<**	Numbers for comments on MIC breakpoints
73							**1**. Aminoglycoside breakpoints are based on once-d aminoglycosides are given in combination with beta
74	Amikacin	8	16			13	
75	Gentamicin	2					
76	Netilmicin	2					
77	Tobramycin	2					
78							
79							
80	**Glycopeptides**	**MIC bre**					
81		**S ≤**					

Ciprofloxacin	Rationale for the EUCAST clinical breakpoints, version 1.9	22nd August 2007

Introduction

The fluoroquinolones comprise a class of agents derived from nalidixic acid and developed since the 1960s. The early fluoroquinolones had a limited spectrum of antibacterial activity, mainly against Gram-negative pathogens. The newer fluoroquinolone agents have enhanced intrinsic activity against Gram-positive organisms and anaerobes and improved pharmacokinetic characteristics in comparison with preceding derivatives. Emergence of resistance is mainly due to mutations in the QRDR region where phenotypic resistance arises as a result of stepwise mutations. Microorganisms with one mutation may exhibit elevated fluoroquinolone MICs that are sometimes difficult to distinguish from wild-type MIC distributions. Other low level resistance mechanisms include increased activity of efflux pumps, Qnr proteins (capable of protecting DNA gyrase from quinolones) and inactivating enzymes.

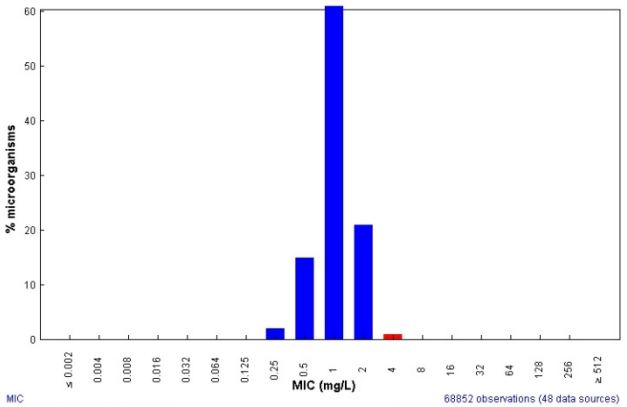
EUCAST has defined clinical breakpoints for the fluoroquinolones ciprofloxacin (CIP), levofloxacin (LEV), moxifloxacin (MOX), norfloxacin (NOR) and ofloxacin (OFL). They are with few exceptions available in all European countries. Older fluoroquinolones which are available only in few countries or in topical preparations have not been addressed.

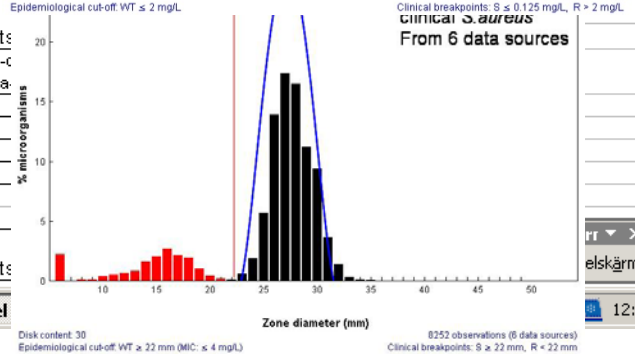
Some fluoroquinolones are available for both oral and intravenous therapy while others are available for oral therapy only. This is reflected in the breakpoints.

Ciprofloxacin is used to treat complicated and uncomplicated urinary tract infections, acute and chronic bacterial prostatitis, gonorrhoea, lower respiratory tract infections, acute sinusitis, skin and skin structure infections, bone and joint infections, complicated intra-abdominal infections and blood stream infections, mainly involving Gram-negative organisms including *Pseudomonas aeruginosa*. It is also used in infectious diarrhoea caused by susceptible bacteria when antibacterial therapy is indicated. Other than in cystic fibrosis patients its use in paediatric patients is still a matter of debate.

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose (mg)	500 x 2 oral 400 x 2 iv	500 x 2 oral 200 x 2 iv	250 x 2 oral 200 x 2 iv	500 x 2 oral 200 x 2 iv	250-500 x 2 oral 400 x 2 iv	500 x 2 oral 400 x 2 iv
Maximum dose schedule (mg)	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 2 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv
Available formulations	oral, iv	oral, iv	oral, iv	oral, iv	oral, iv	oral, iv

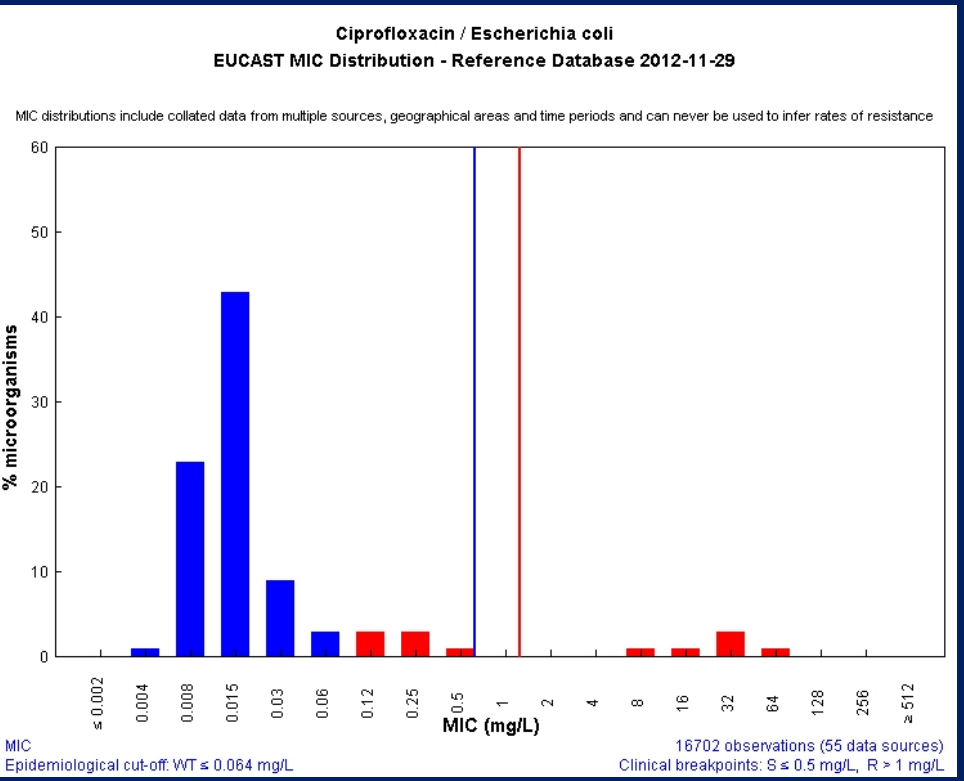


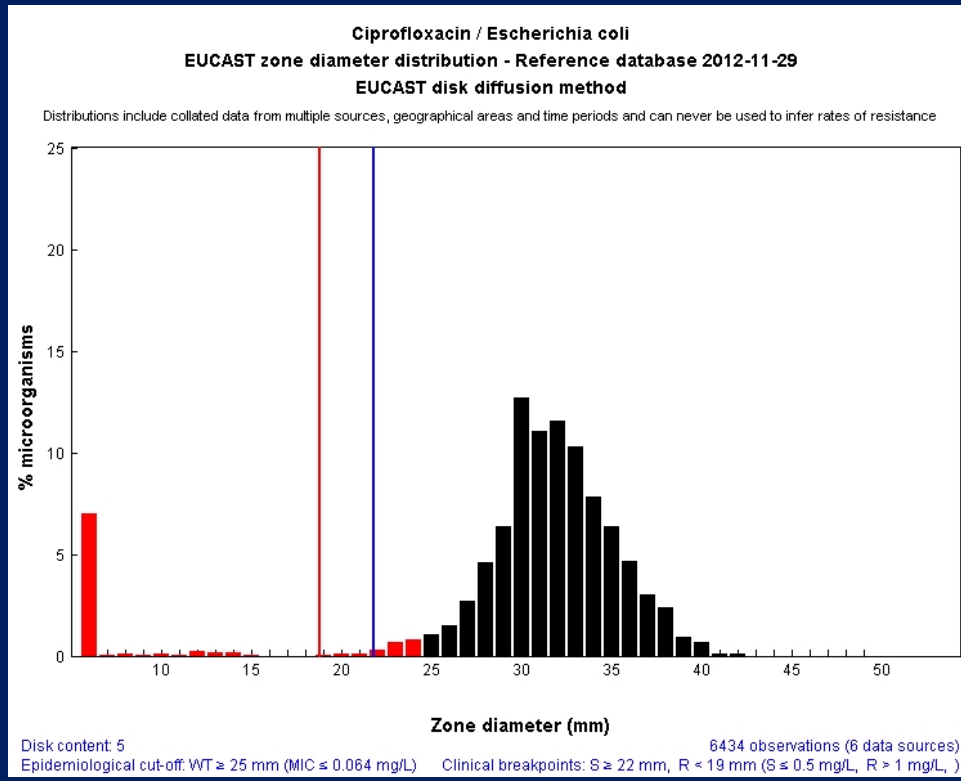


Calibration of zone diameter breakpoints to EUCAST breakpoints

Distribution of MICs and zone diameters

Agent, species and test system agreed.



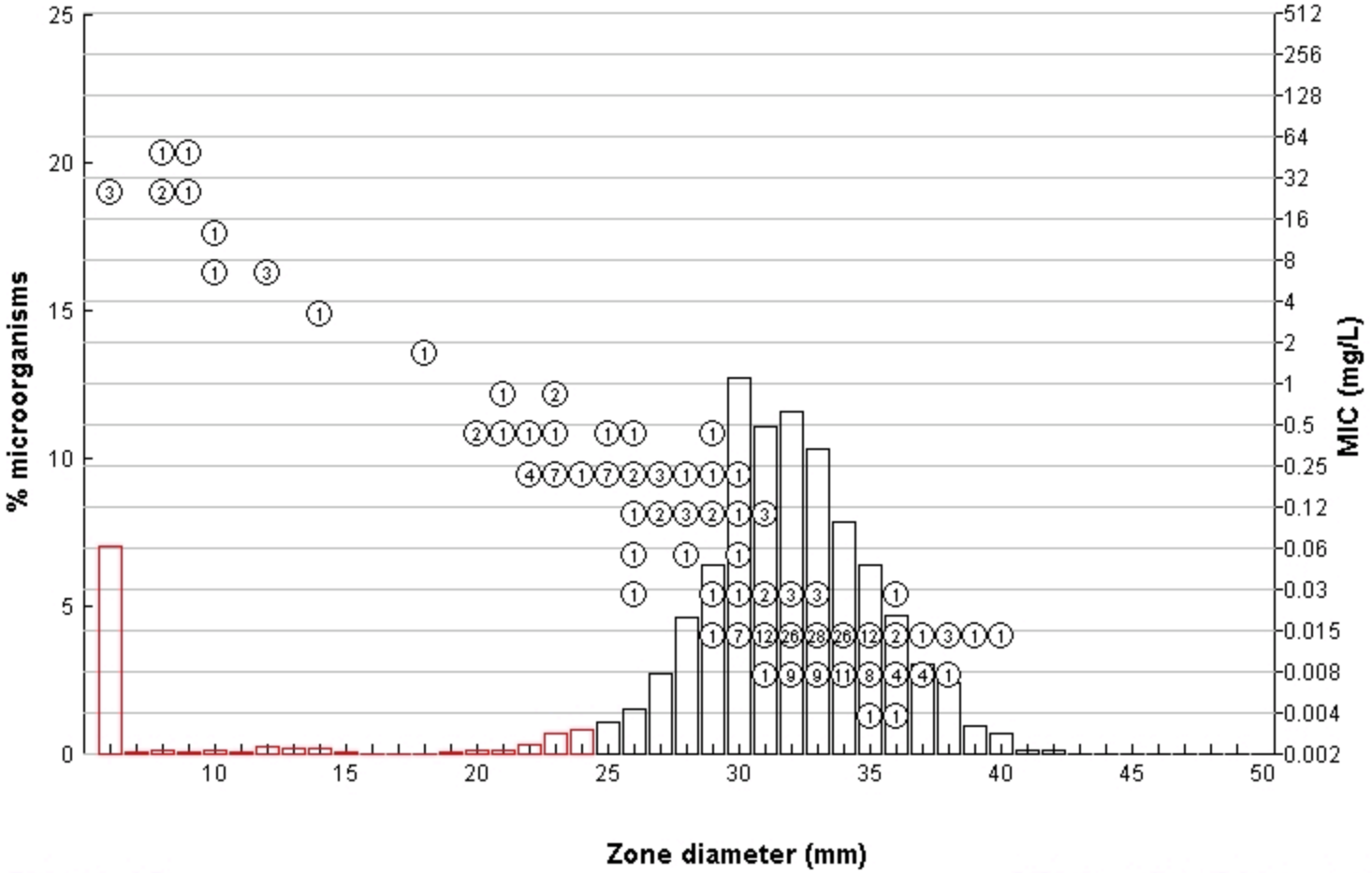


Ciprofloxacin / Escherichia coli

EUCAST zone diameter distribution - Reference database 2012-11-29

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



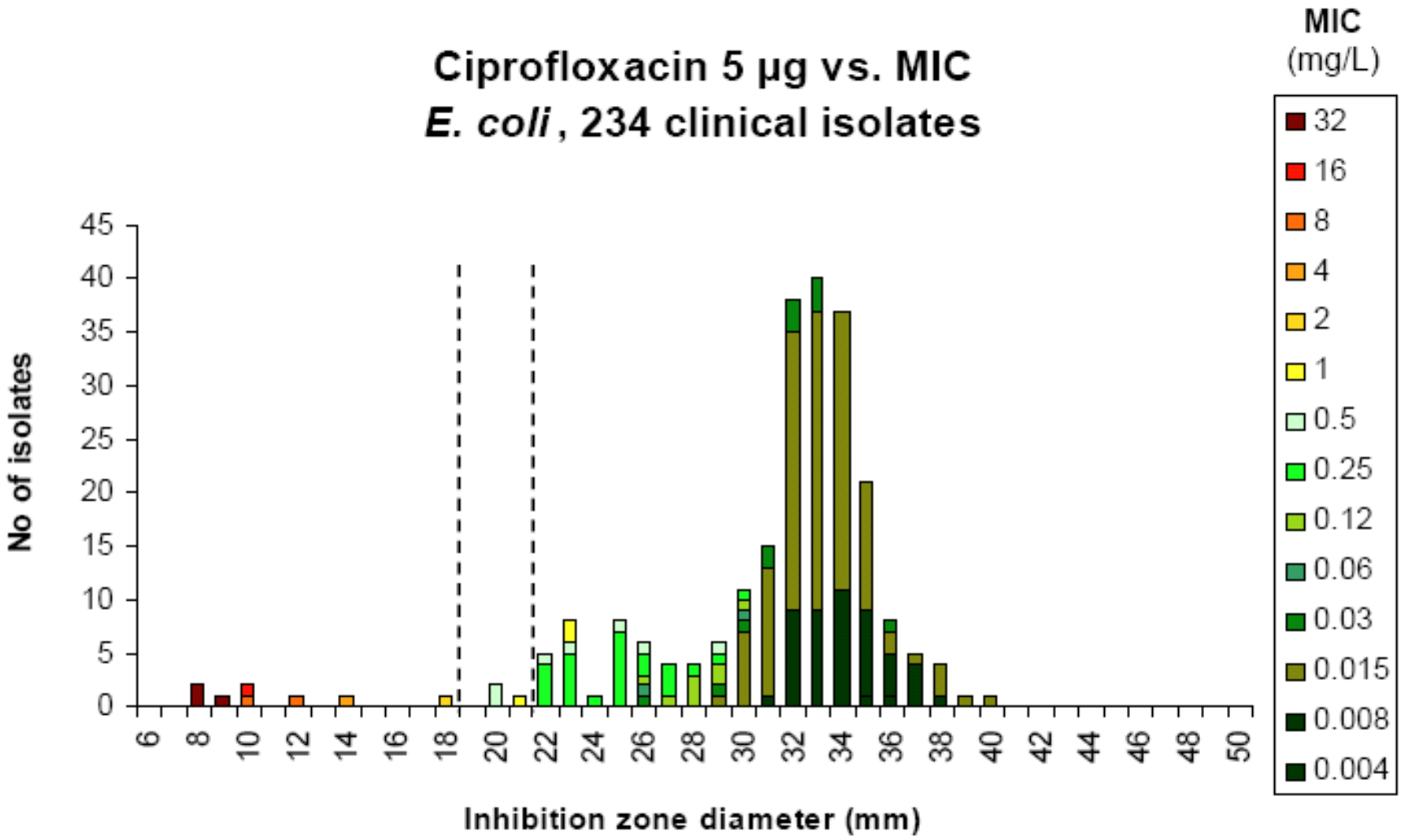
Disk content: 5

6434 observations (6 data sources)

Epidemiological cut-off: WT ≥ 25 mm (MIC ≤ 0.064 mg/L)

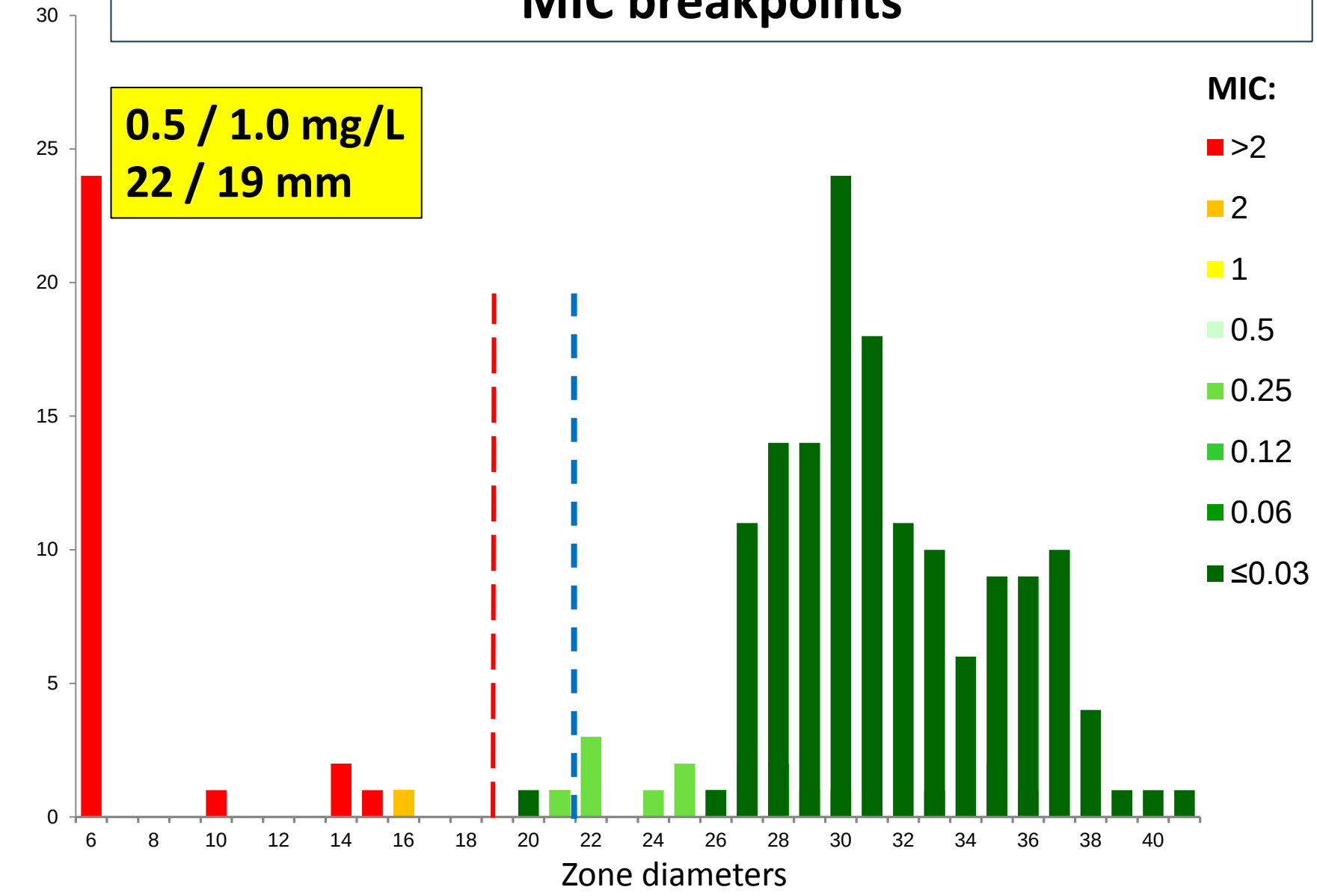
Clinical breakpoints: S ≥ 22 mm, R < 19 mm (S ≤ 0.5 mg/L, R > 1 mg/L,)

Ciprofloxacin 5 µg vs. MIC
E. coli, 234 clinical isolates



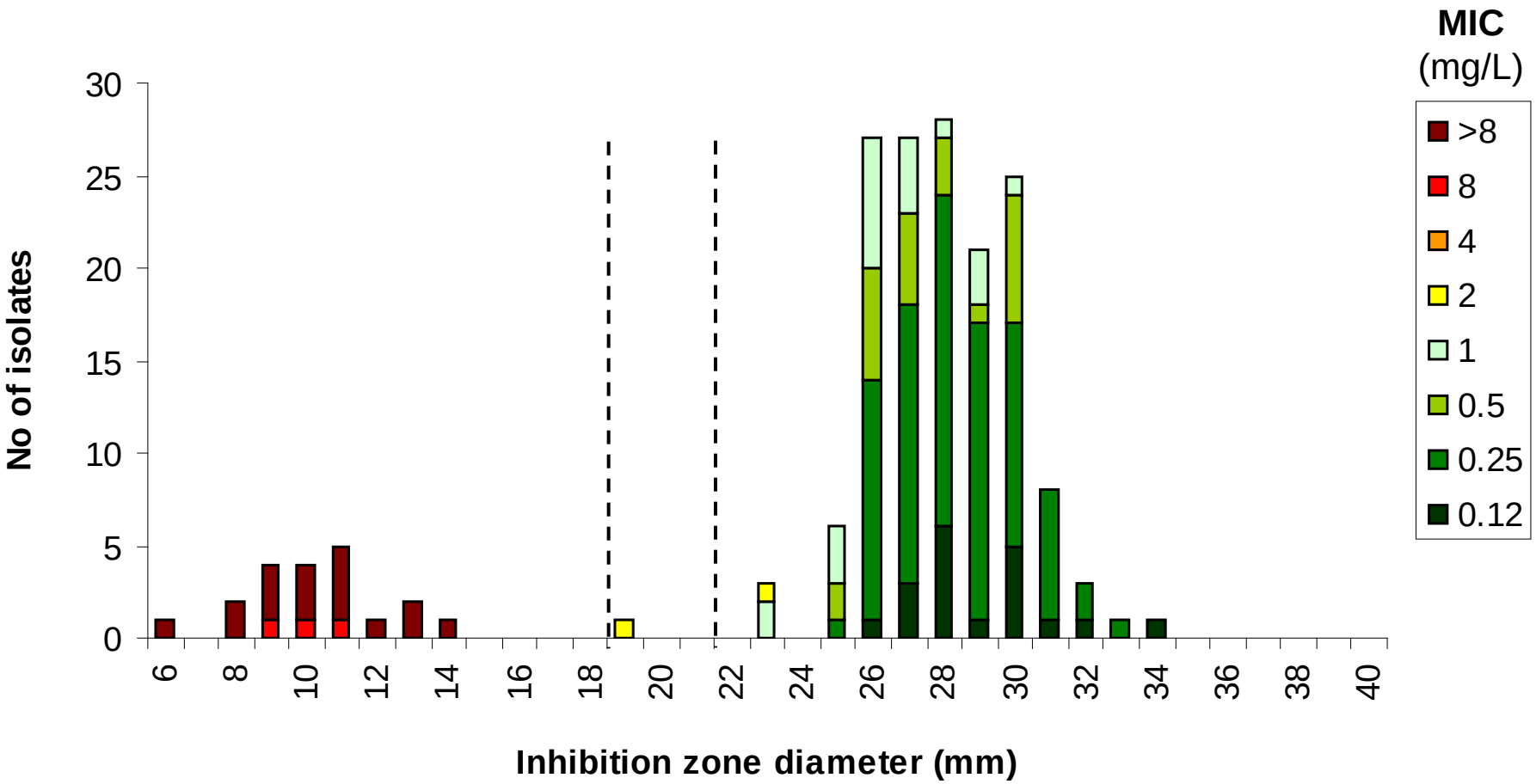
Breakpoints		**ECOFF**
MIC	S≤0.5, R>1 mg/L	WT≤0.06 mg/L
Zone diameter	S≥22, R<19 mm	

Calibrating zone diameter breakpoints to clinical MIC breakpoints



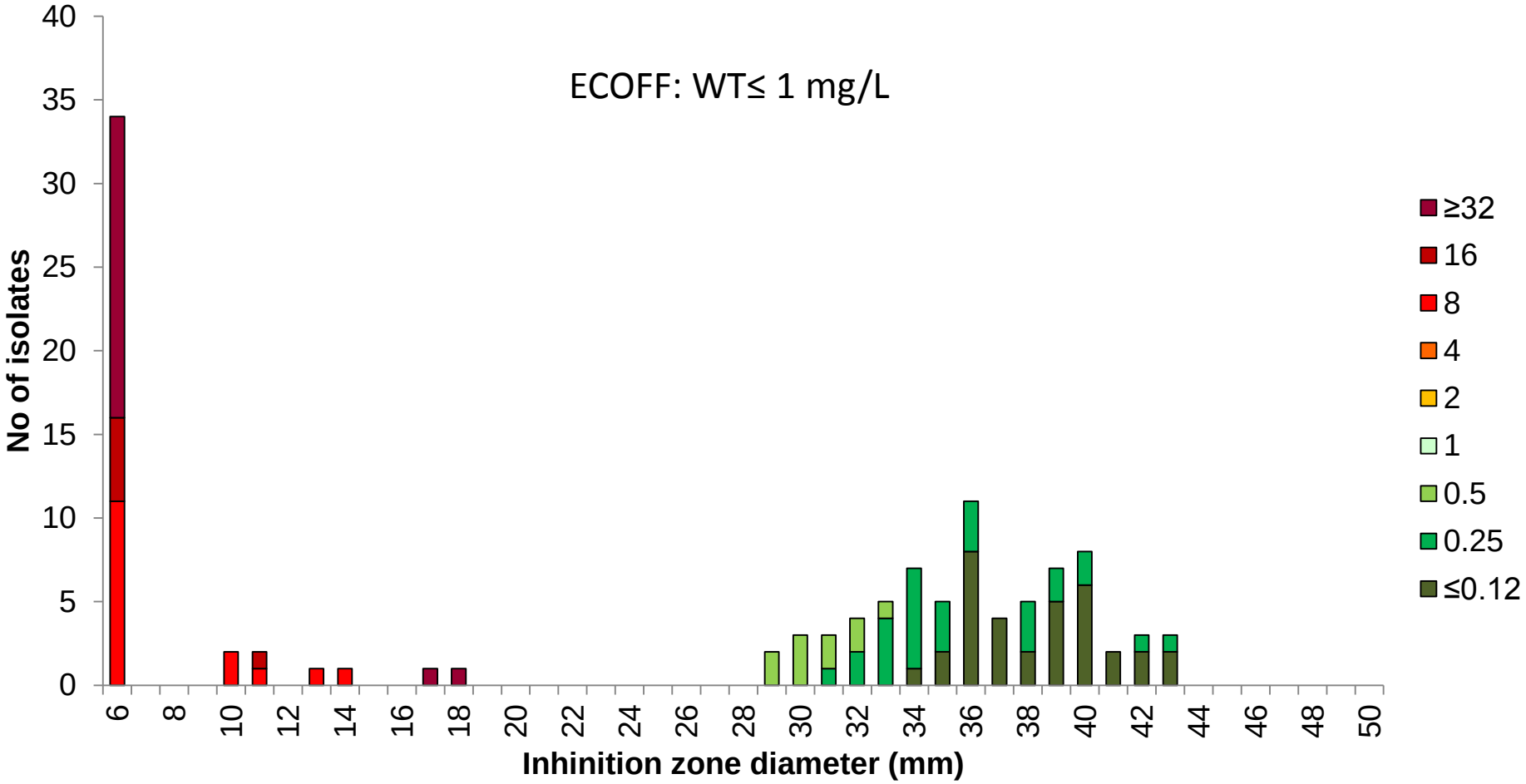
Ciprofloxacin MICs and zone diameters vs. Enterobacteriaceae

Tetracycline 30 µg vs. MIC
S. aureus , 172 clinical isolates



Breakpoints		**ECOFF**
MIC	S≤1, R>2 mg/L	WT≤1 mg/L
Zone diameter	S≥22, R<19 mm	

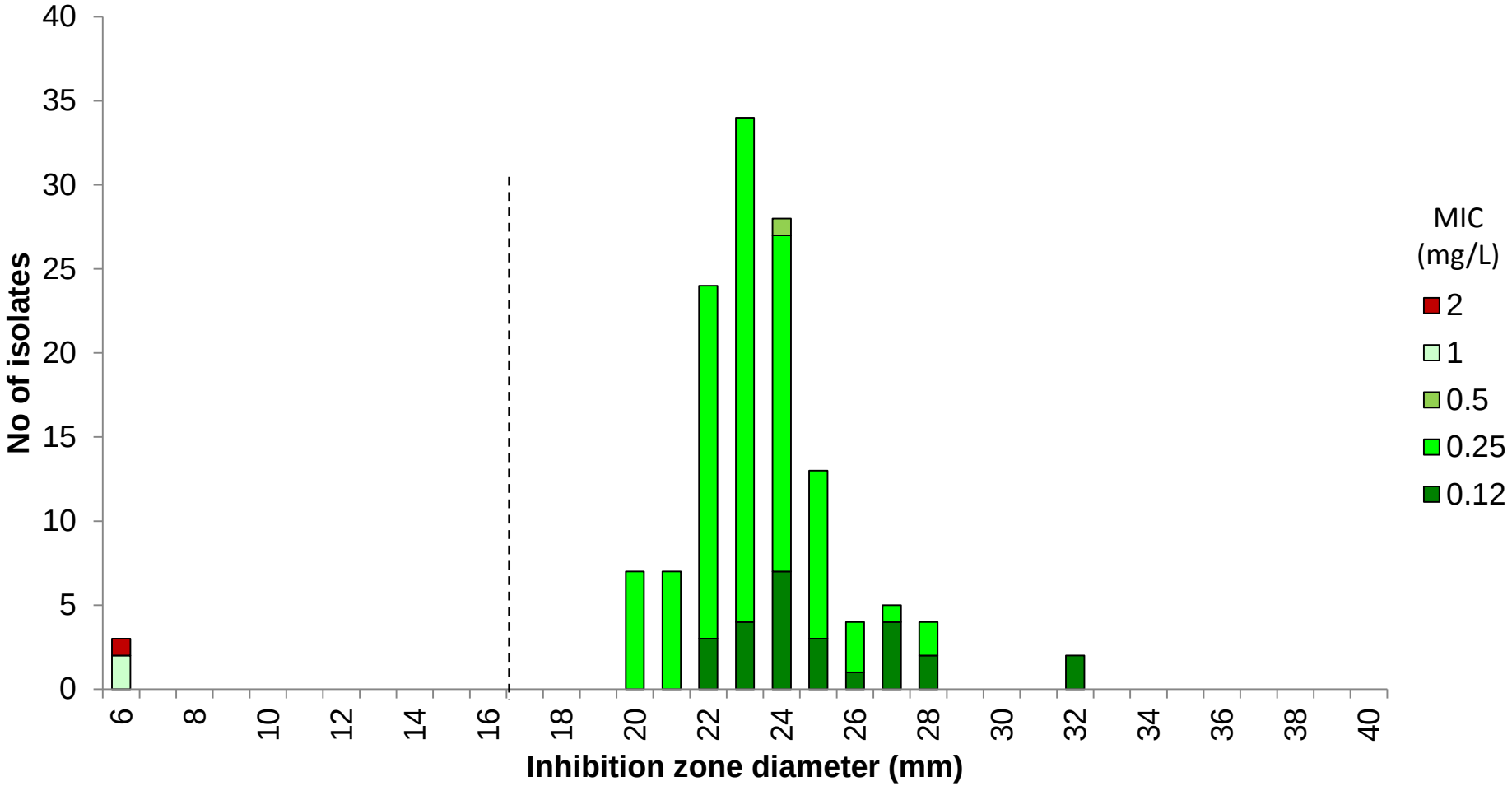
Ciprofloxacin 5 µg vs. MIC, *Campylobacter jejuni* and *coli*
57 clinical isolates tested in duplicate



NL and FI isolates read in Växjö.

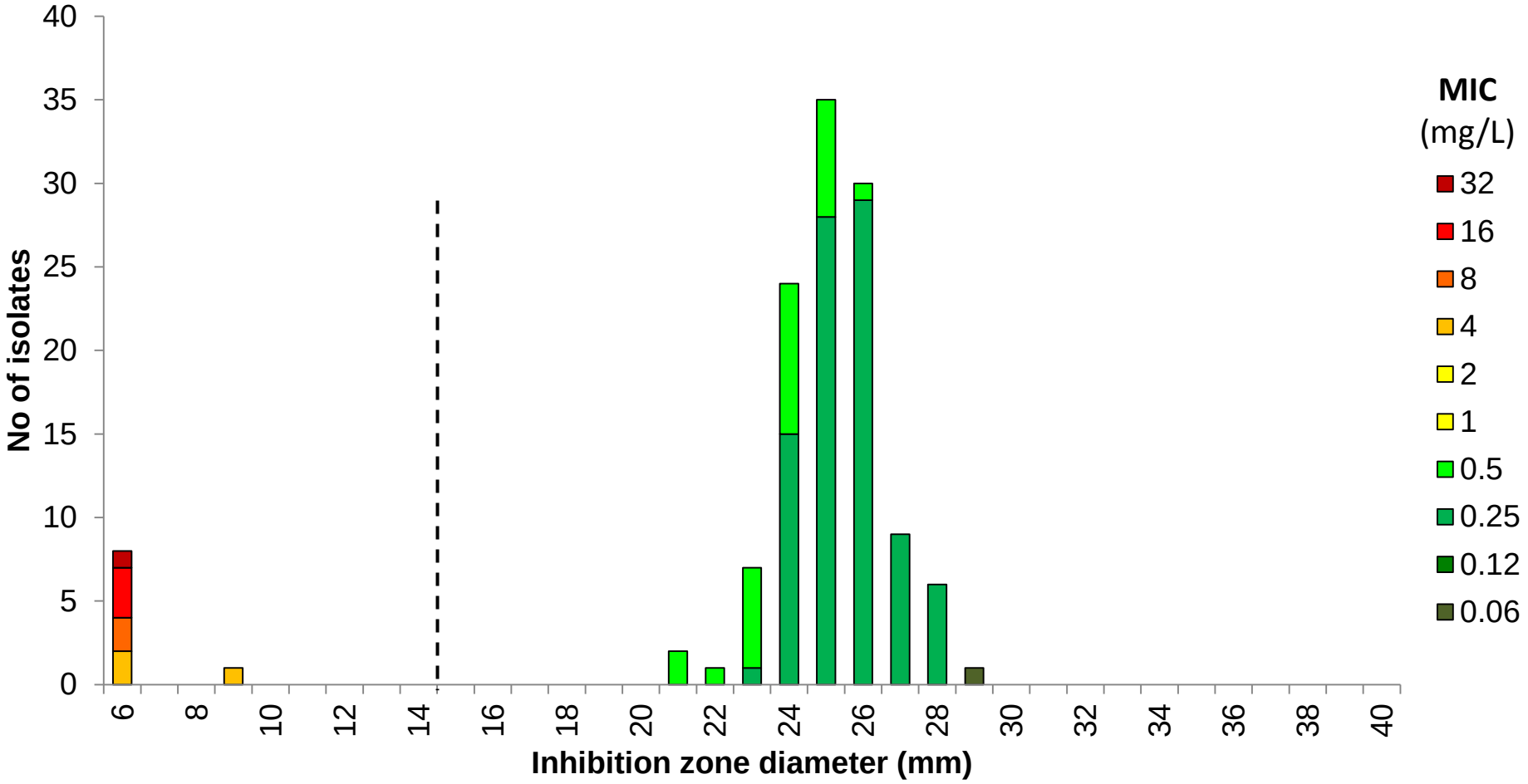
All isolates tested in duplicate on in-house MH-F plates from Oxoid and BBL MH.

Ampicillin 2 µg vs. MIC
Pasteurella multocida, 131 clinical isolates



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

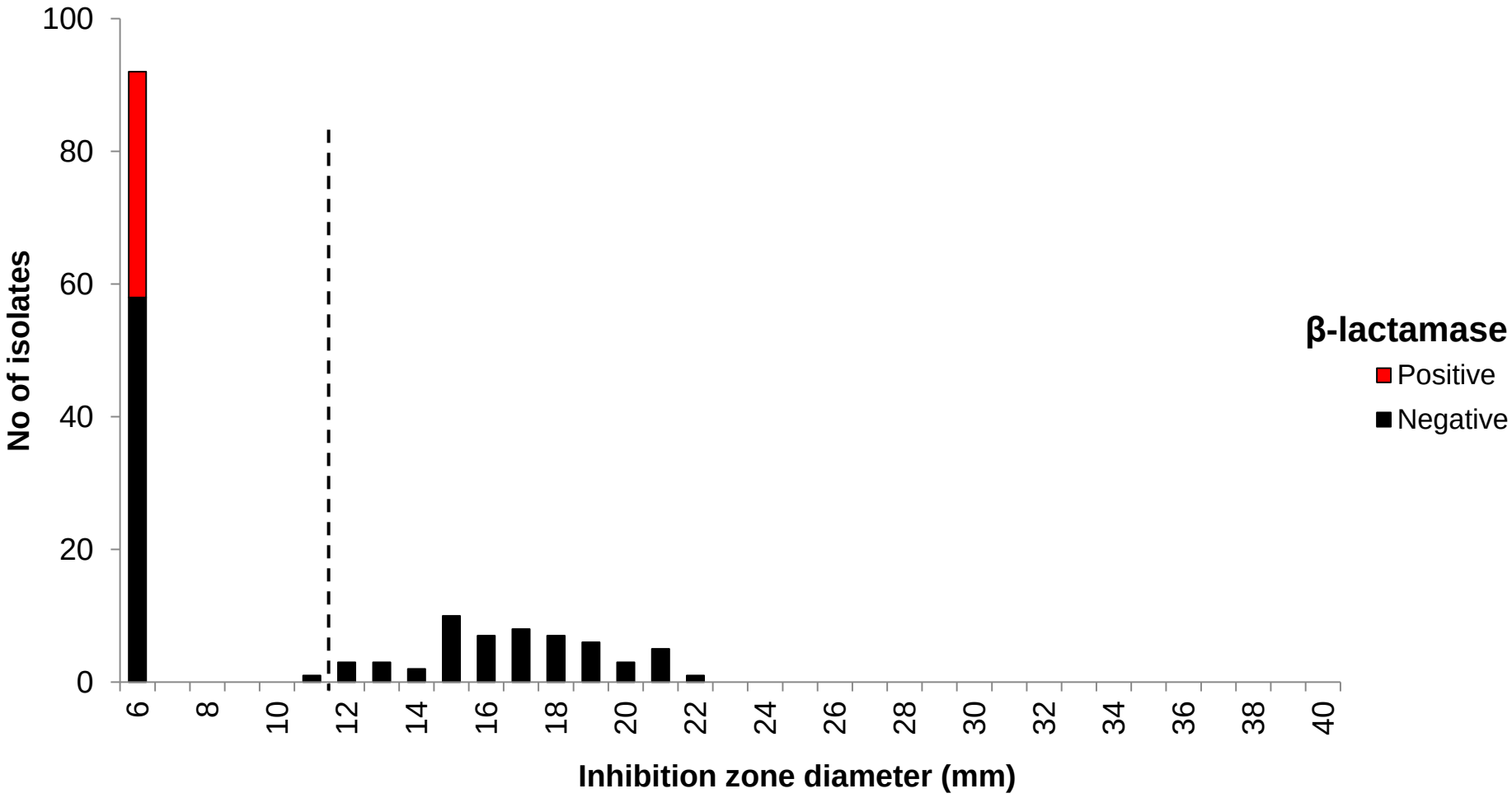
Ampicillin 2 µg vs. MIC
S. saprophyticus, 124 clinical isolates



Breakpoints

Zone diameter S≥15, R<15 mm

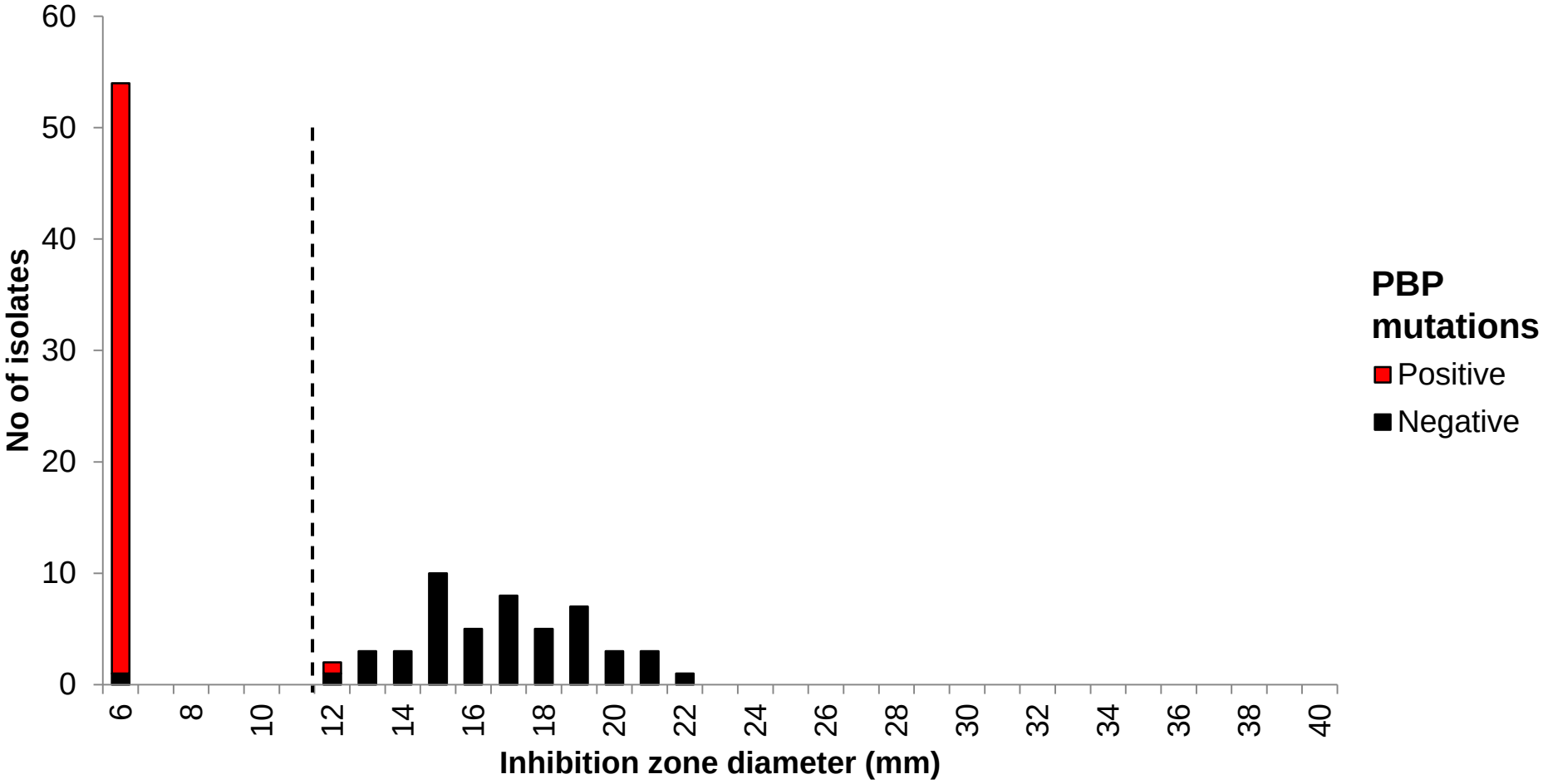
Benzylpenicillin 1 unit vs. β-lactamase
H. influenzae, 148 clinical isolates



Breakpoints

Benzylpenicillin zone diameter (screen) S≥12, R<12 mm

Benzylpenicillin 1 unit vs. PBP mutations
H. influenzae, 104 β-lactamase negative clinical isolates



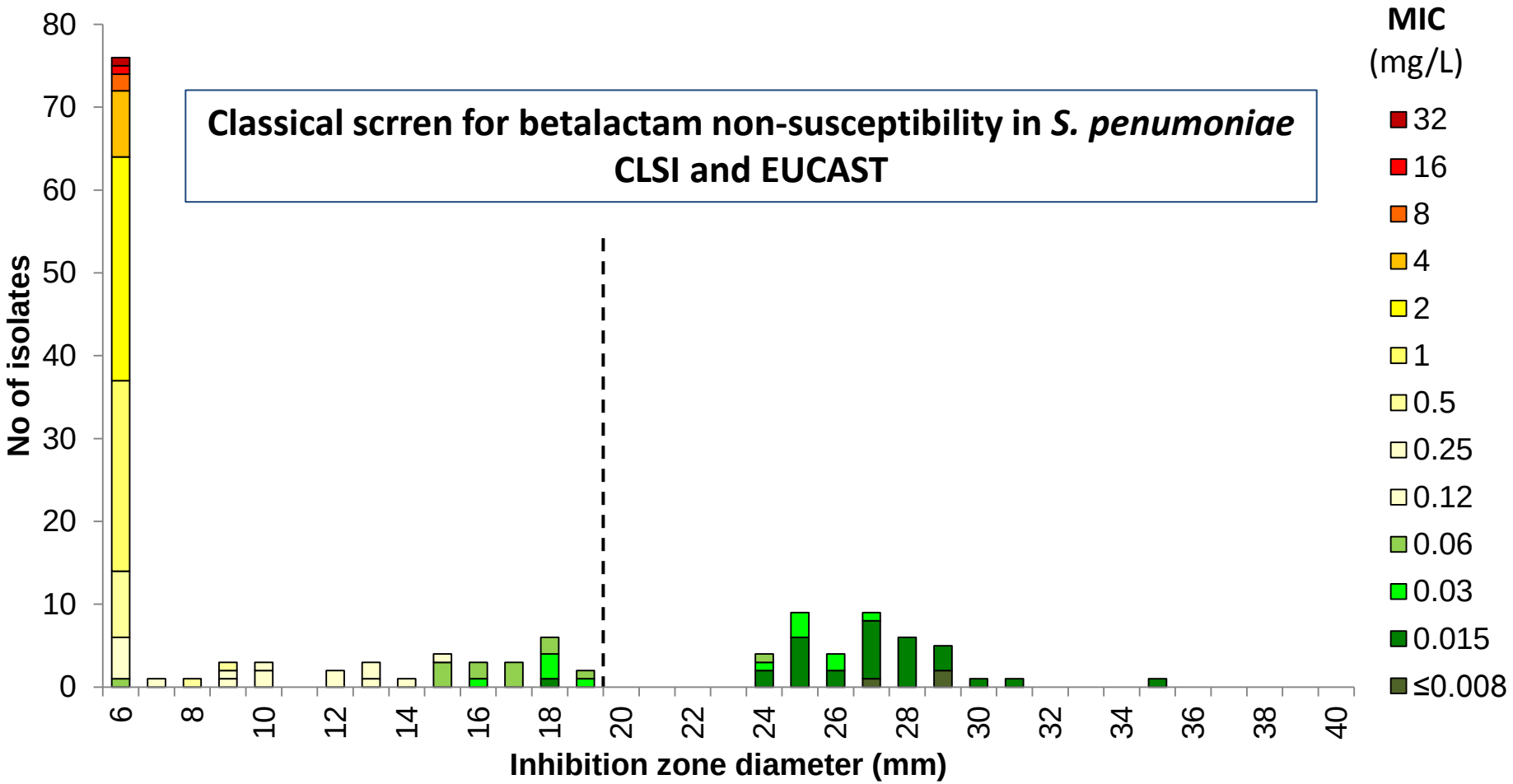
Breakpoints

Benzylpenicillin zone diameter (screen) S≥12, R<12 mm

Screening for betalactam resistance in *S. pneumoniae*

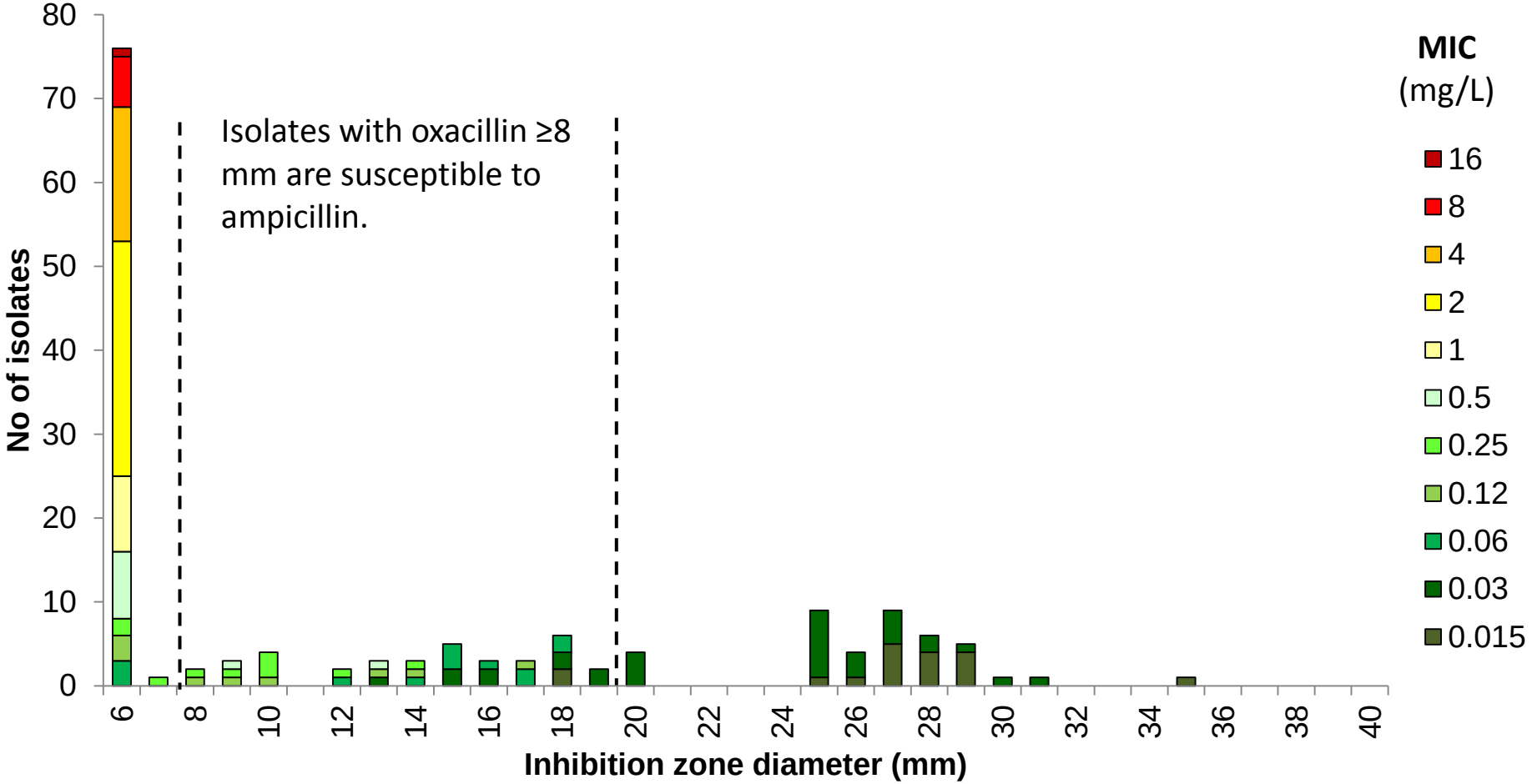
EUCAST
EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Oxacillin 1 µg vs. Benzylpenicillin MIC
S. pneumoniae, 148 clinical isolates



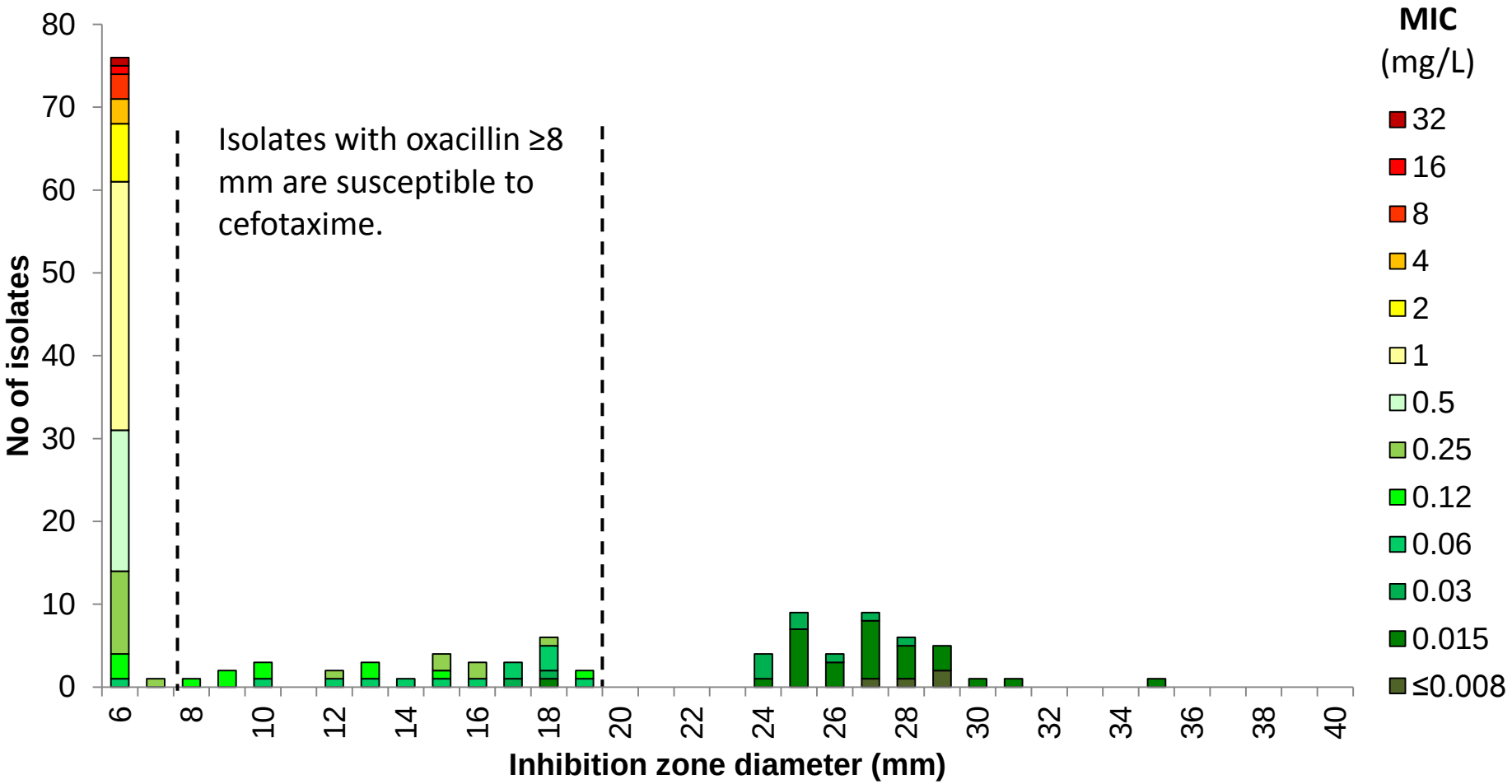
Breakpoints		**ECOFF**
Benzylpenicillin MIC	S≤0.06, R>2 mg/L	WT≤0.06 mg/L
Oxacillin zone diameter (screen)	S≥20, R<20 mm	

Oxacillin 1 µg vs. Ampicillin MIC
S. pneumoniae, 153 clinical isolates



Breakpoints		**ECOFF**
Ampicillin MIC	S≤0.5, R>2 mg/L	WT≤0.06 mg/L
Oxacillin zone diameter (screen)	S≥20, R<20 mm	

Oxacillin 1 µg vs. Cefotaxime MIC
S. pneumoniae, 147 clinical isolates



Breakpoints		**ECOFF**
Cefotaxime MIC	S≤0.5, R>2 mg/L	WT≤0.06 mg/L
Oxacillin zone diameter (screen)	Cefotaxime S ≥ 8 mm	

Screening for beta-lactam resistance in *S. pneumoniae*

Flowchart

Oxacillin 1 µg disk Zone diameter (mm)	**Antimicrobial agent**	**Further testing and/or interpretation**
≥ 20 mm	All beta-lactam agents for which clinical breakpoints are listed (inlcuding those with "Note")	Report susceptible irrespective of clinical indication.
< 20 mm*	Benzylpenicillin (meningitis) and phenoxymethylpenicillin (all indications)	Report resistant.
	Benzylpenicillin (for infections other than meningitis)	Test by an MIC method for the agent considered for clinical use and interpret according to the clinical breakpoints.
	Ampicillin and amoxicillin (without and with beta-lactamase inhibitor), cefepime, cefotaxime and ceftriaxone	**Oxacillin zone diameter ≥ 8 mm**: Report susceptible.
		Oxacillin zone diameter < 8 mm: determine the MIC of the beta-lactam agent intended for clinical use but for ampicillin, amoxicillin and piperacillin (without and with beta-lactamase inhibitor) infer susceptibility from the MIC of ampicillin.
	Other beta-lactam agents	Test by an MIC method for the agent considered for clinical use and interpret according to the clinical breakpoints.

Countries are encouraged to form National AST Committees (NAC).

NAC

A document describing a prototype NAC is available on website.

NAC

- **Nationa antimicrobial susceptibility testing committee**
  - Strategy at national level
  - Implementation of breakpoints and methods
  - Education (national workshops, websites)
  - Liaison and consultation with EUCAST (chairman or scientific secretary GC representative)
  - Liaison with groups involved in AMR-surveillance (ECDC, EARSS, ….).
  - QA
- Antimicrobial Policies
- Antimicrobial Resistance Surveillance
- Antimicrobial Consumption and Policies

National AST Committee (NAC) Sept 2012

Countries not on the map: Australia Iceland Israel