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

What is new in EUCAST 2016 – 17

South Africa, May, 2016

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EUCAST Technical Data Coordinator and Webmaster
Sweden

What is new in EUCAST 2016/17?

- New organisms with breakpoints (Addendum 2016)
  - Aerococcus, Kingella, Plesiomonas, Aeromonas
- New agents (including two old) with breakpoints
  - Temocillin, nitroxoline, cephalosporin with inhibitors,
- Consultations
  - colistin, fluoroquinolones, WGS-report (25 June)
- Revision of breakpoints for existing agents
  - Colistin, Fluoroquinolones, Carbapenems (Aminoglycosides, Tigecycline)
- What to do when there are no breakpoints? (SOP 2016)
- Redefining the intermediate category!? (2017)
- Instruction videos (commissioned by WHO)
- Courses, ESCMID Observerships, Collaborative Centres

Species lacking breakpoints

- Aerococcus spp
- Kingella kingae
- Aeromonas
- Plesiomonas
- Nocardia
- Bacillus
- Streptomyces
- Lactobacillus
- Leuconostoc
- …

Species lacking breakpoints

- Aerococcus spp
- Kingella kingae
- Aeromonas
- Plesiomonas
- Nocardia
- Bacillus
- Streptomyces
- Lactobacillus
- Leuconostoc
- …

Aerococcus spp

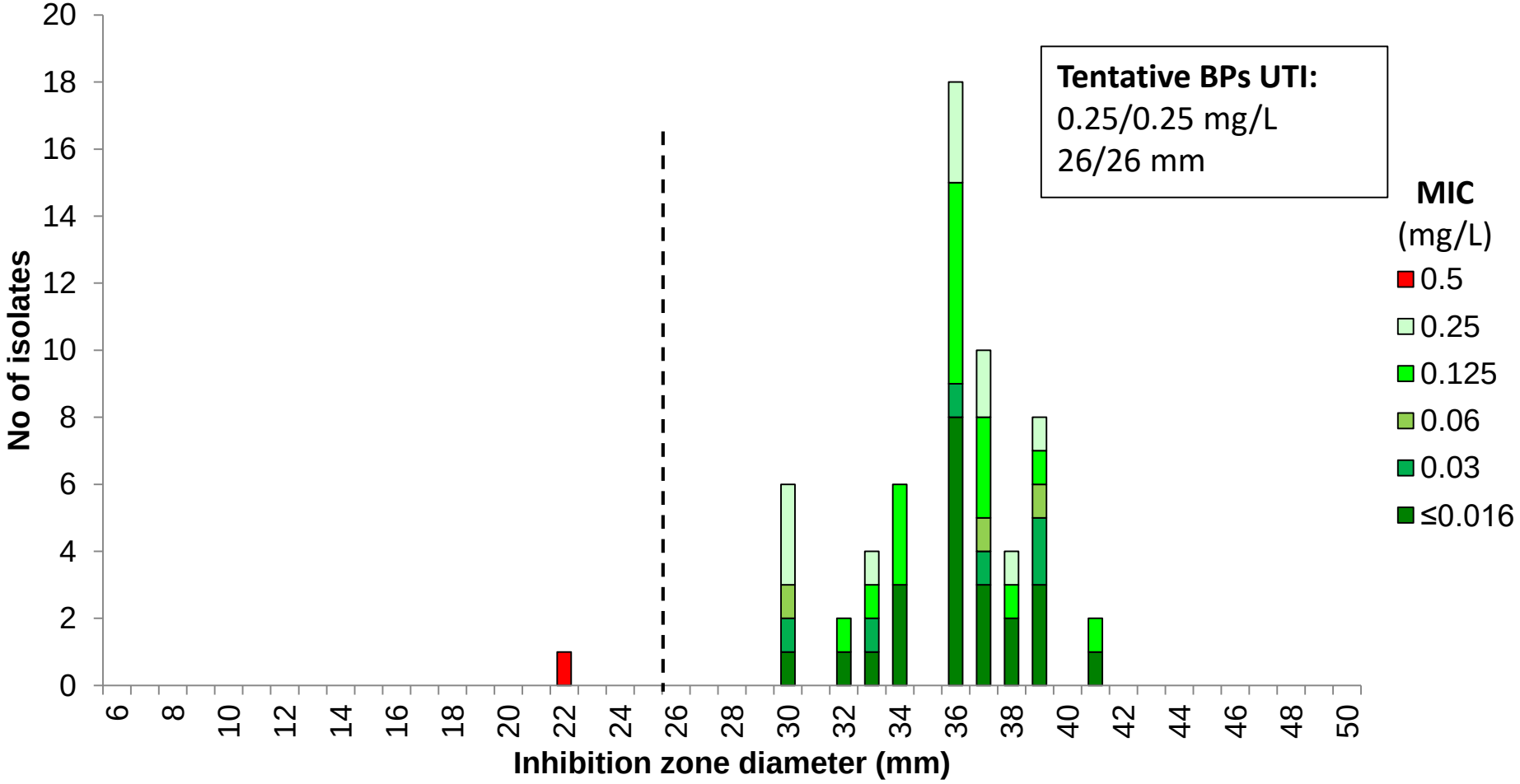
Materials and methods

- *A. urinae* and *A. sangunicola* isolates of different origin
- AST was performed at three laboratories
- Disk diffusion according to EUCAST methods for fastidious organisms
  - MH-F, McFarland 0.5, 5% CO_2
  - 16-20 h incubation
    - With possibility to prolong incubation to 40-44 h when growth is non-sufficient
- MIC determination with BMD (MH-F broth)
  - Agar dilution MICs used for agents with reading difficulties with BMD

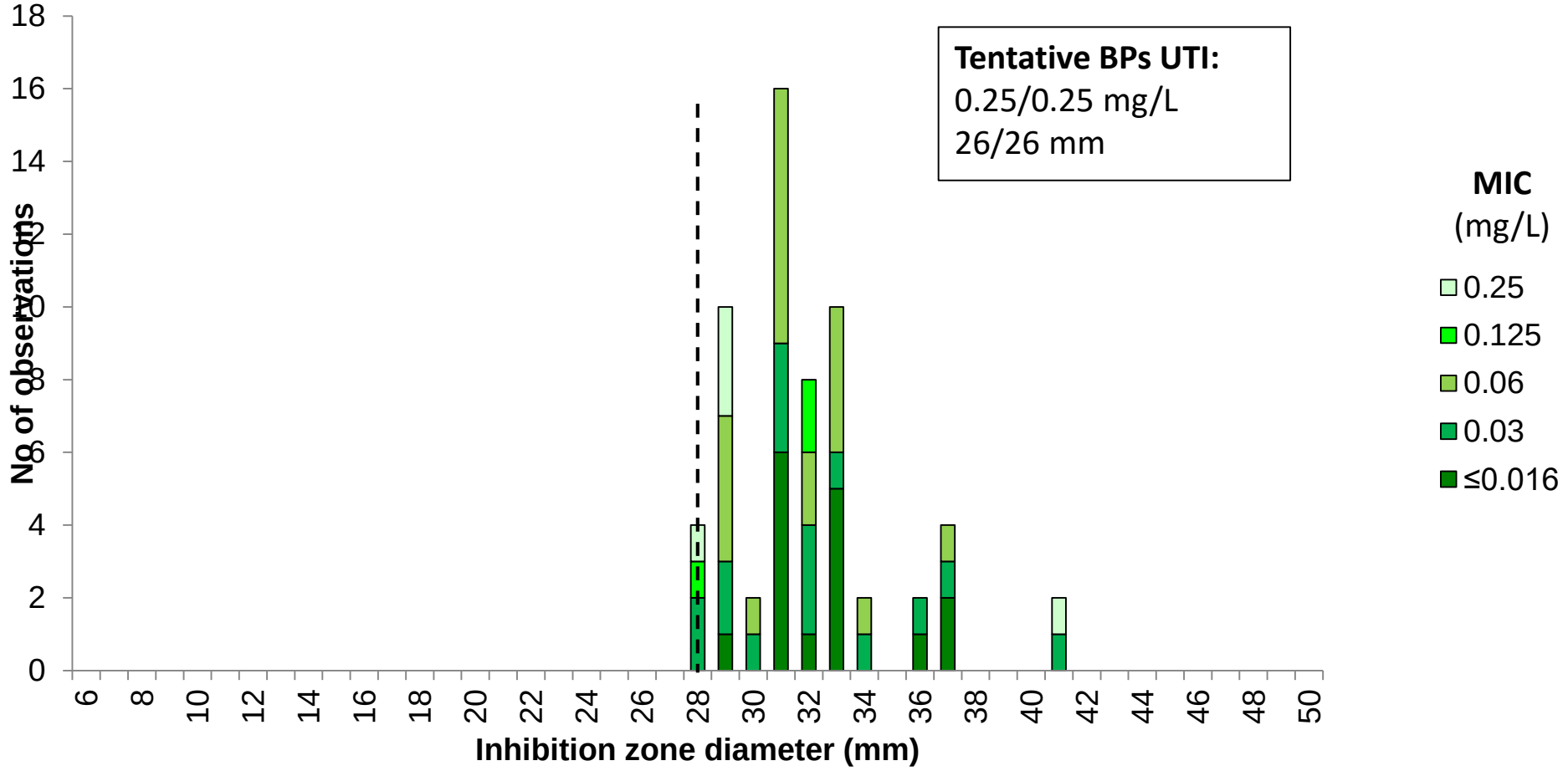
Breakpoints developed for these agents

- UTI
  - Ampicillin / Amoxicillin
  - Ciprofloxacin
  - Levofloxacin
  - Nitrofurantoin
- Systemic infections
  - Benzylpenicillin
  - Meropenem
  - Vancomycin
  - Clindamycin
  - Rifampicin

Ampicillin 2 µg vs. MIC
A. urinae, 30 isolates (60 correlates)



Ampicillin 2 µg vs. MIC
A. sanguinicola, 30 isolates (60 correlates)



South Africa 2016

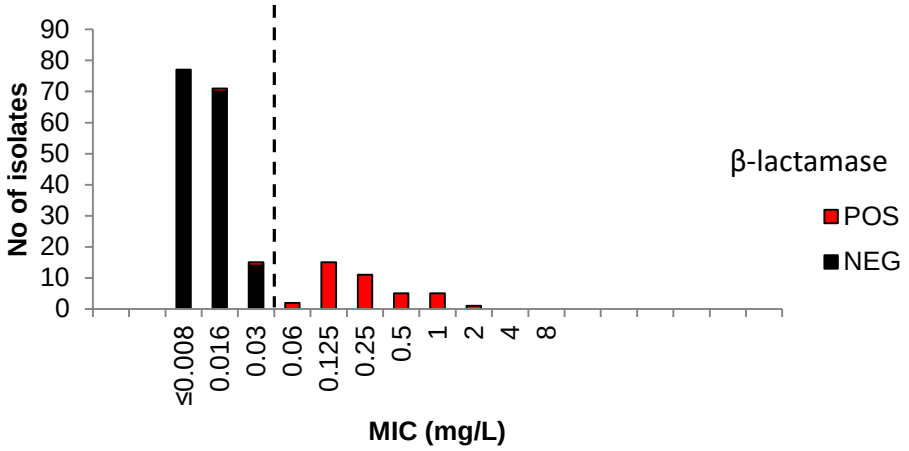
Kingella kingae

Materials and methods

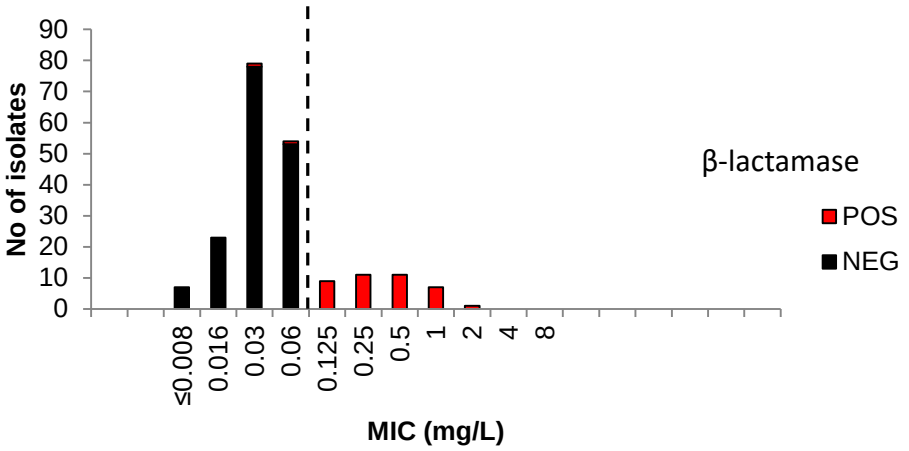
- International collection of *Kingella kingae* (202 clinical isolates supplied by Pablo Yagupsky)
  - AST with EUCAST methods
  - Disk diffusion according to EUCAST methods for fastidious organisms (159 isolates)
    - MH-F, McFarland 0.5, 5% CO_2
    - 16-20 h incubation
      - Prolong incubation to 40-44 h when growth is non-sufficient
    - Media from two manufacturers
    - 3 readers
  - BMD with MH-F broth (202 isolates)

Penicillins

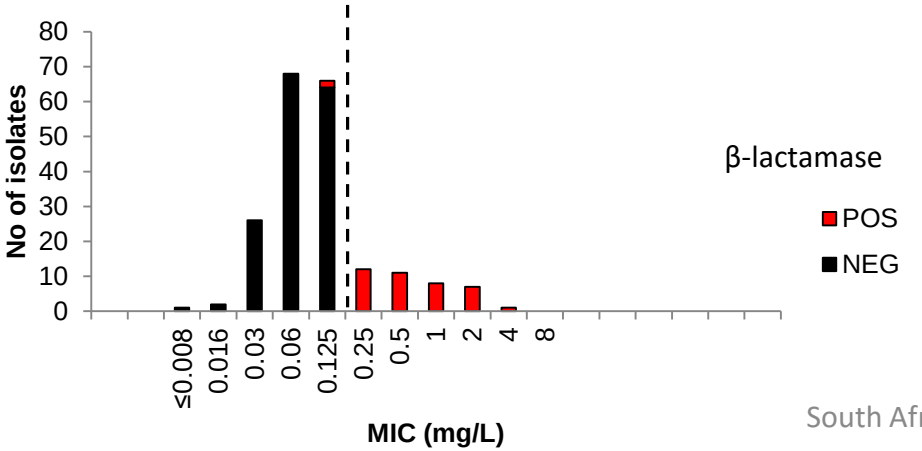
Benzylpenicillin MIC vs. β-lactamase
***Kingella kingae*, 202 clinical isolates**



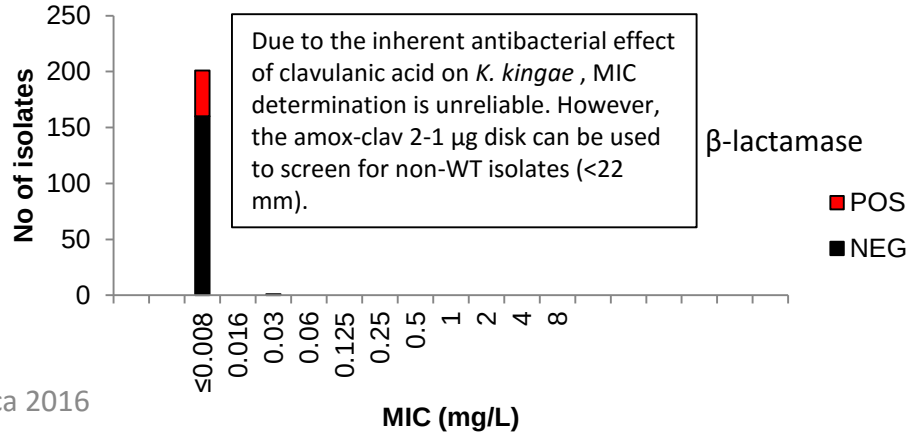
Ampicillin MIC vs. β-lactamase
***Kingella kingae*, 202 clinical isolates**



Amoxicillin MIC vs. β-lactamase
***Kingella kingae*, 202 clinical isolates**

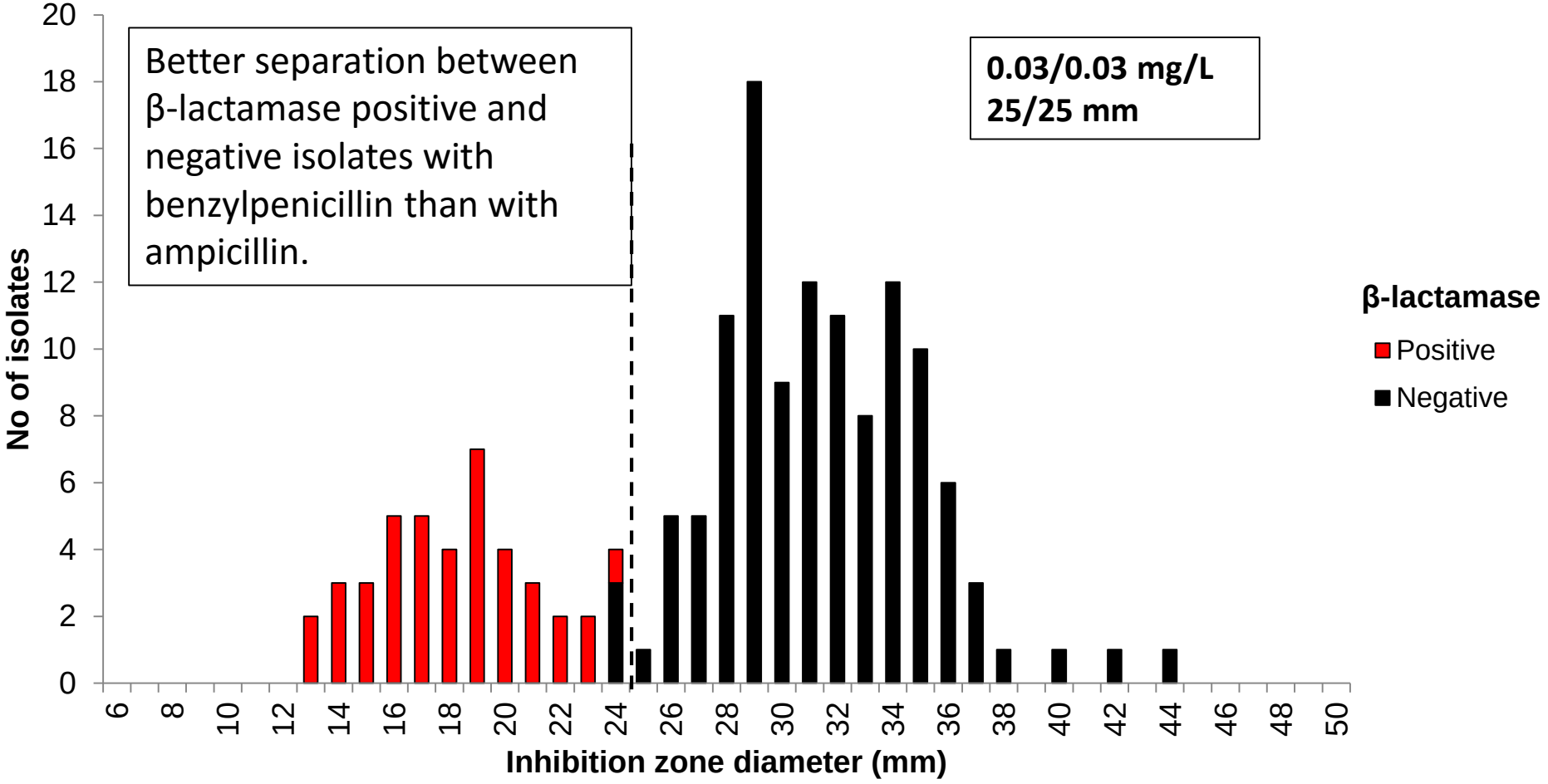


Amoxicillin-clavulanic acid MIC vs. β-lactamase
***Kingella kingae*, 202 clinical isolates**

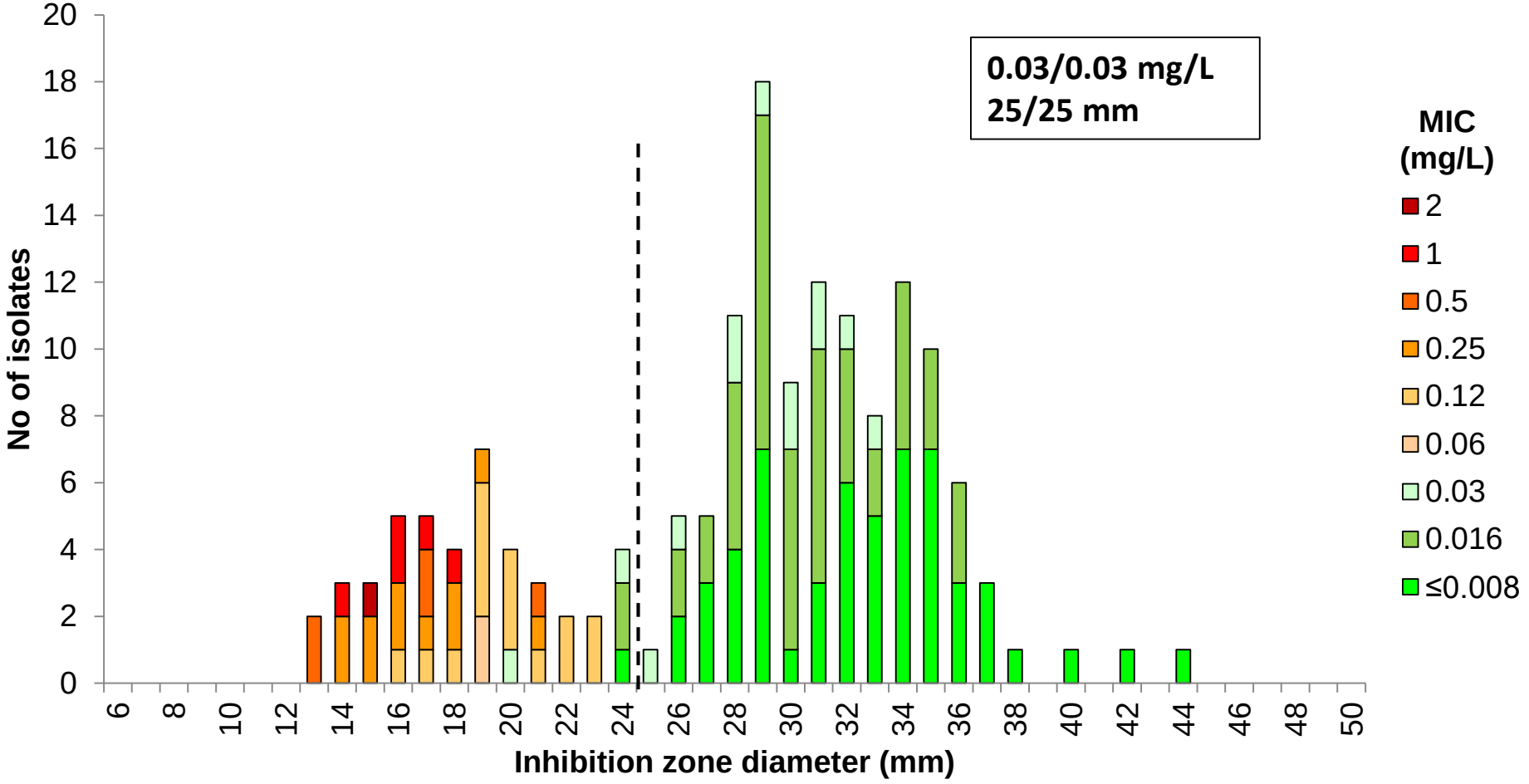


South Africa 2016

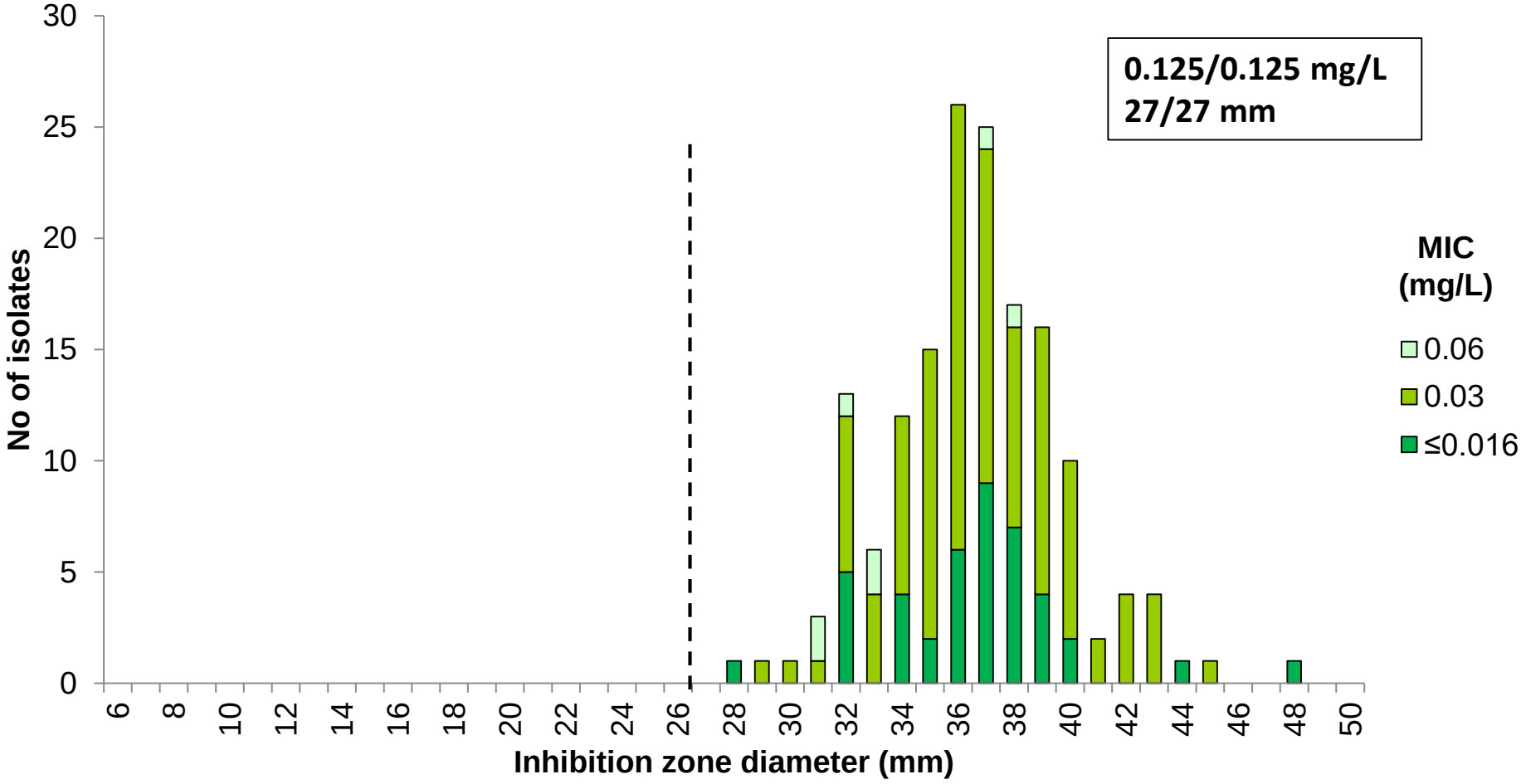
Benzylpenicillin 1 unit vs. β-lactamase
Kingella kingae, 159 clinical isolates



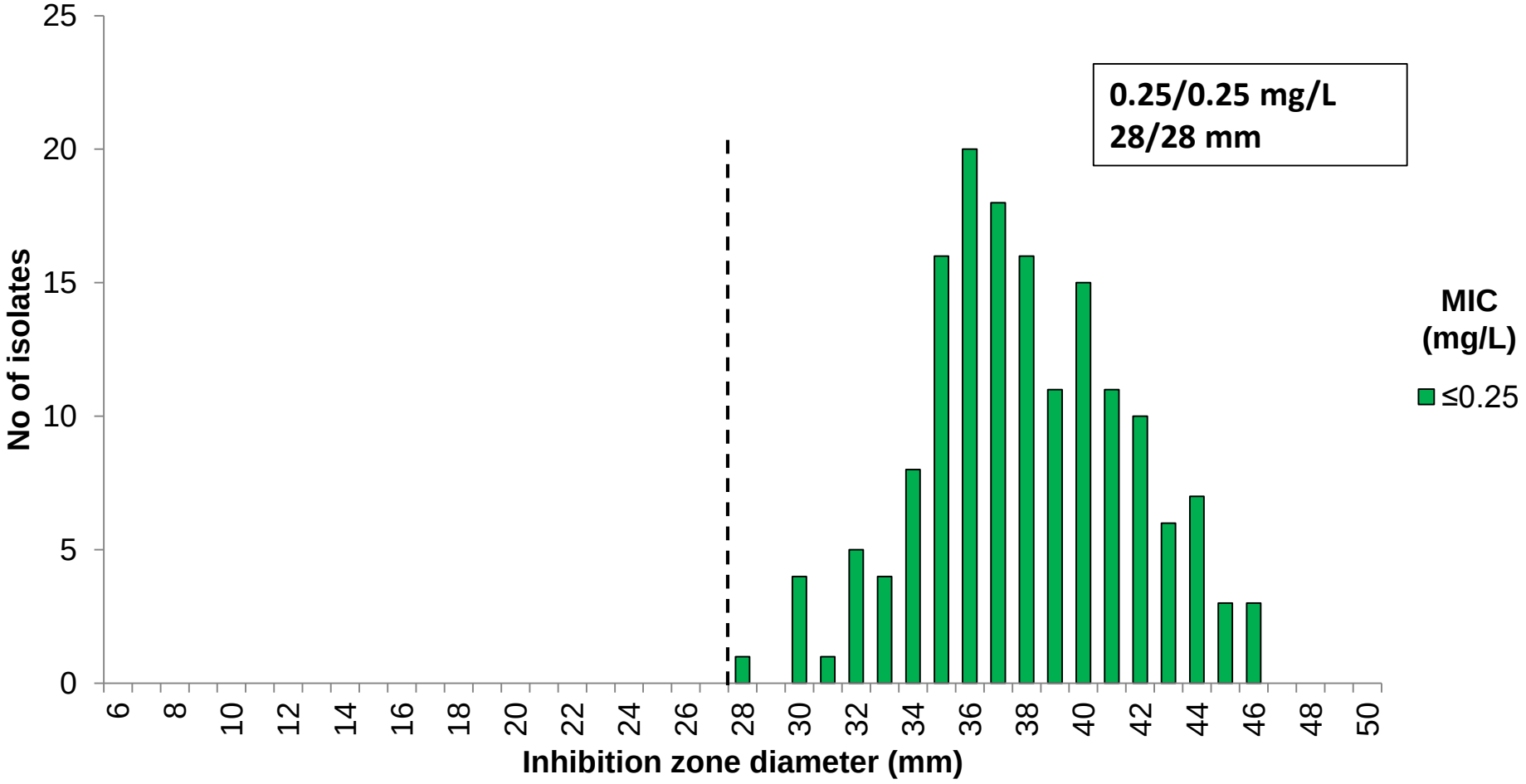
Benzylpenicillin 1 unit vs. MIC
Kingella kingae, 159 clinical isolates



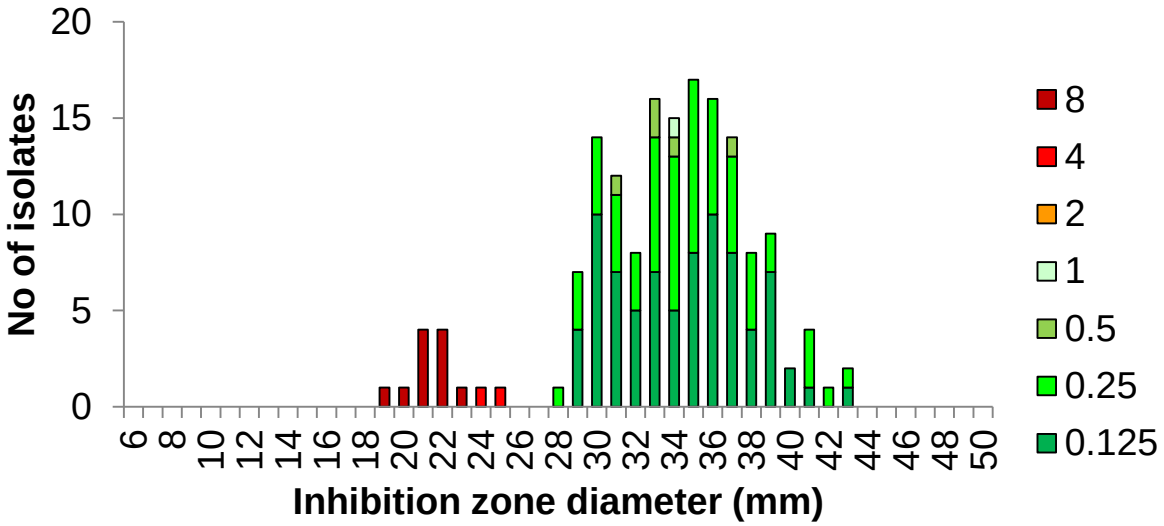
Cefotaxime 5 µg vs. MIC
Kingella kingae, 159 clinical isolates



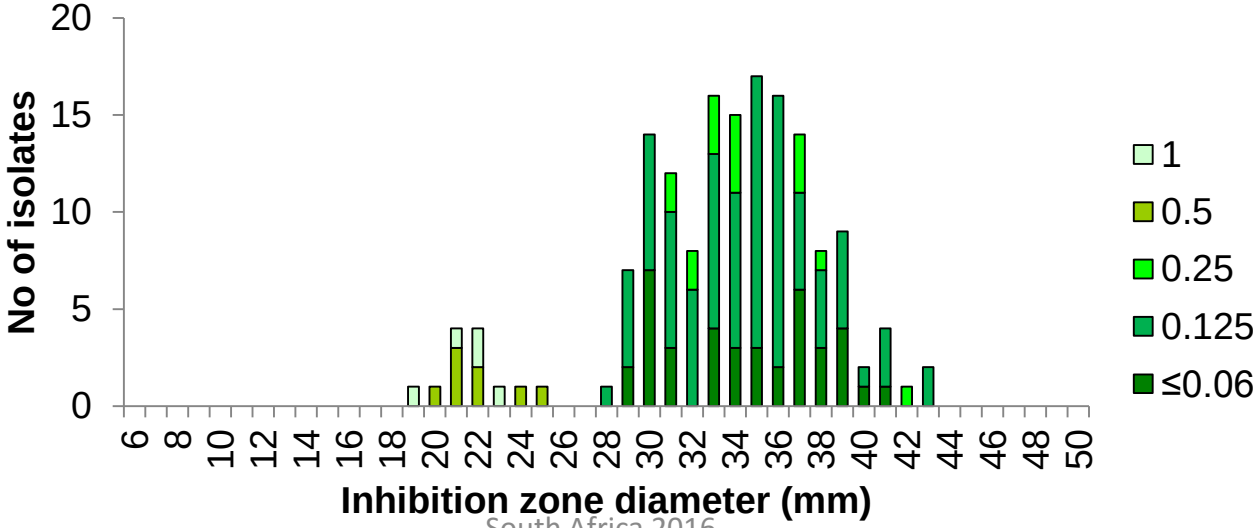
Ciprofloxacin 5 µg vs. MIC
Kingella kingae, 159 clinical isolates



Tetracycline 30 µg vs. MIC
Kingella kingae, 159 clinical isolates



Tetracycline 30 µg vs. Doxycycline MIC
Kingella kingae, 159 clinical isolates



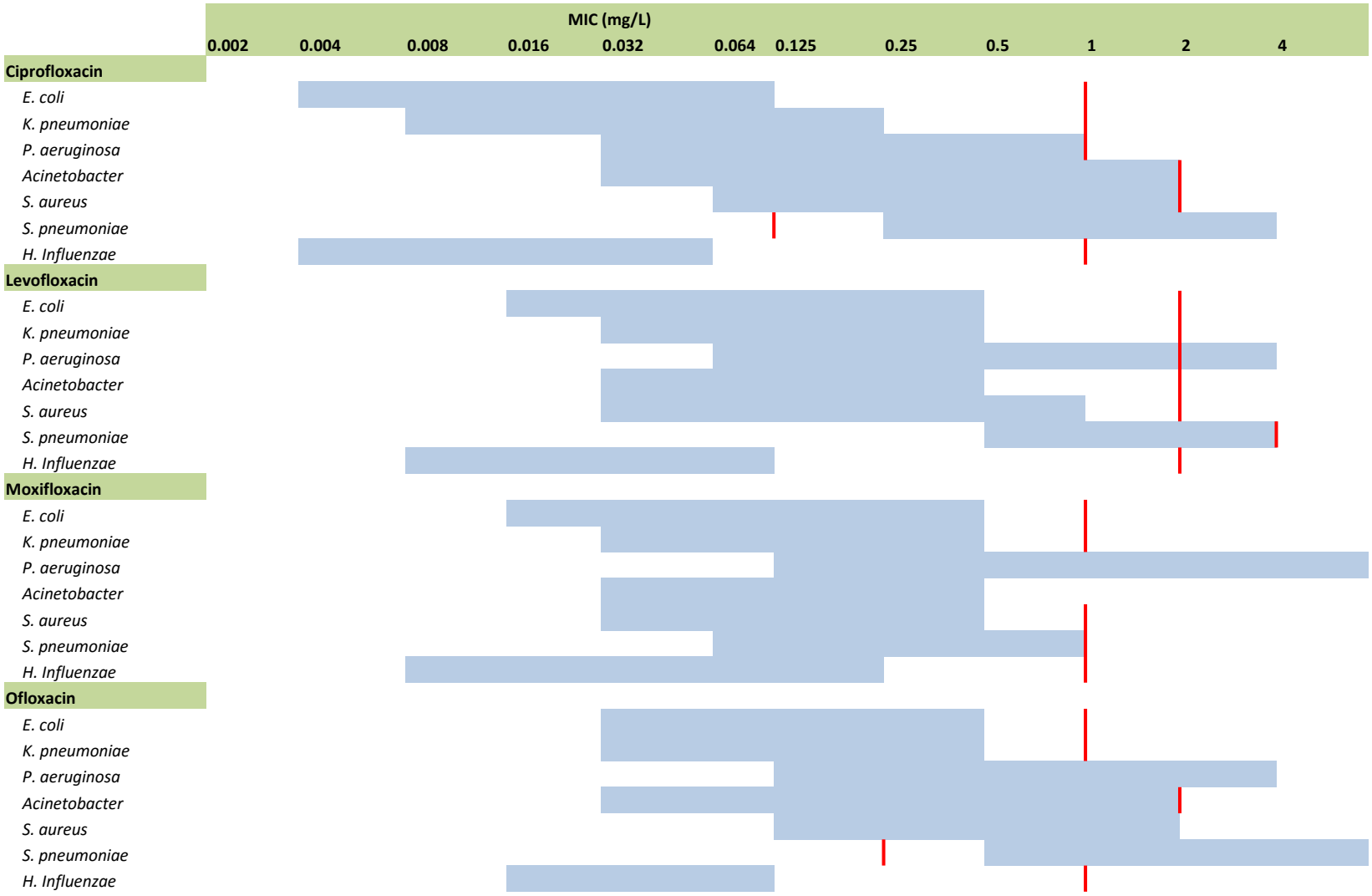
EUCAST review process

Currently under review

- Fluoroquinolones 2016
- Carbapenems 2016
- Colistin 2016

- Aminoglycosides 2016/17

Fluoroquinolones wild-type distributions



South Africa 2016

Proposed new ciprofloxacin breakpoints

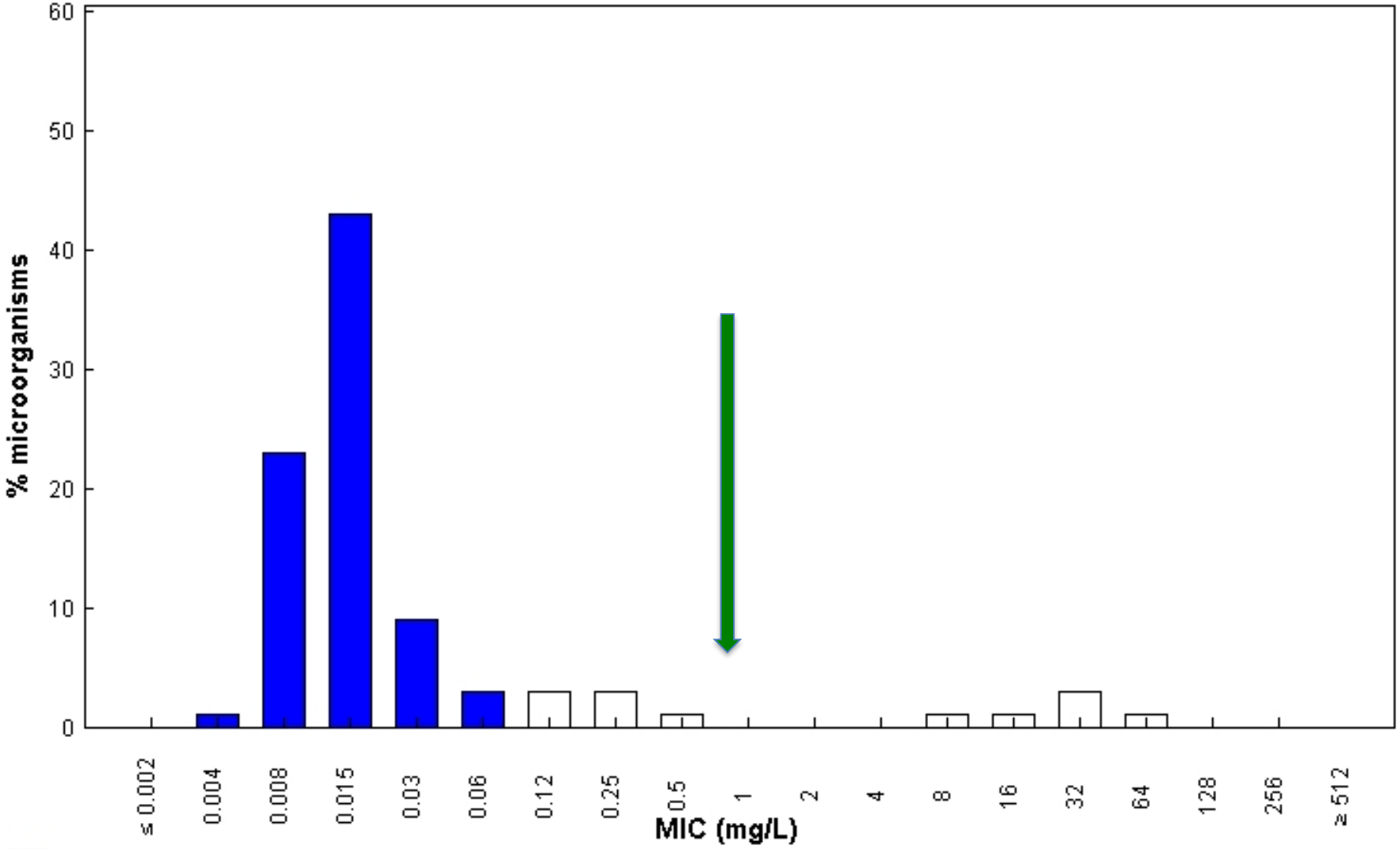
S≤X / R>Y mg/L

Species	Old breakpoints	ECOFF	New breakpoints
Enterobacteriaceae	0.5/1	0.06	0.25/0.5
P. aeruginosa	0.5/1	0.5	0.5/0.5 (HD)
Acinetobacter	1/1	1	1/1 (HD)
S. pneumoniae	0.12/2	2	-
S. aureus	1/1	1	1/1 (HD)
H. influenzae	0.5/0.5	0.06	0.06/0.06

Ciprofloxacin / Escherichia coli

International MIC Distribution - Reference Database 2016-05-14

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



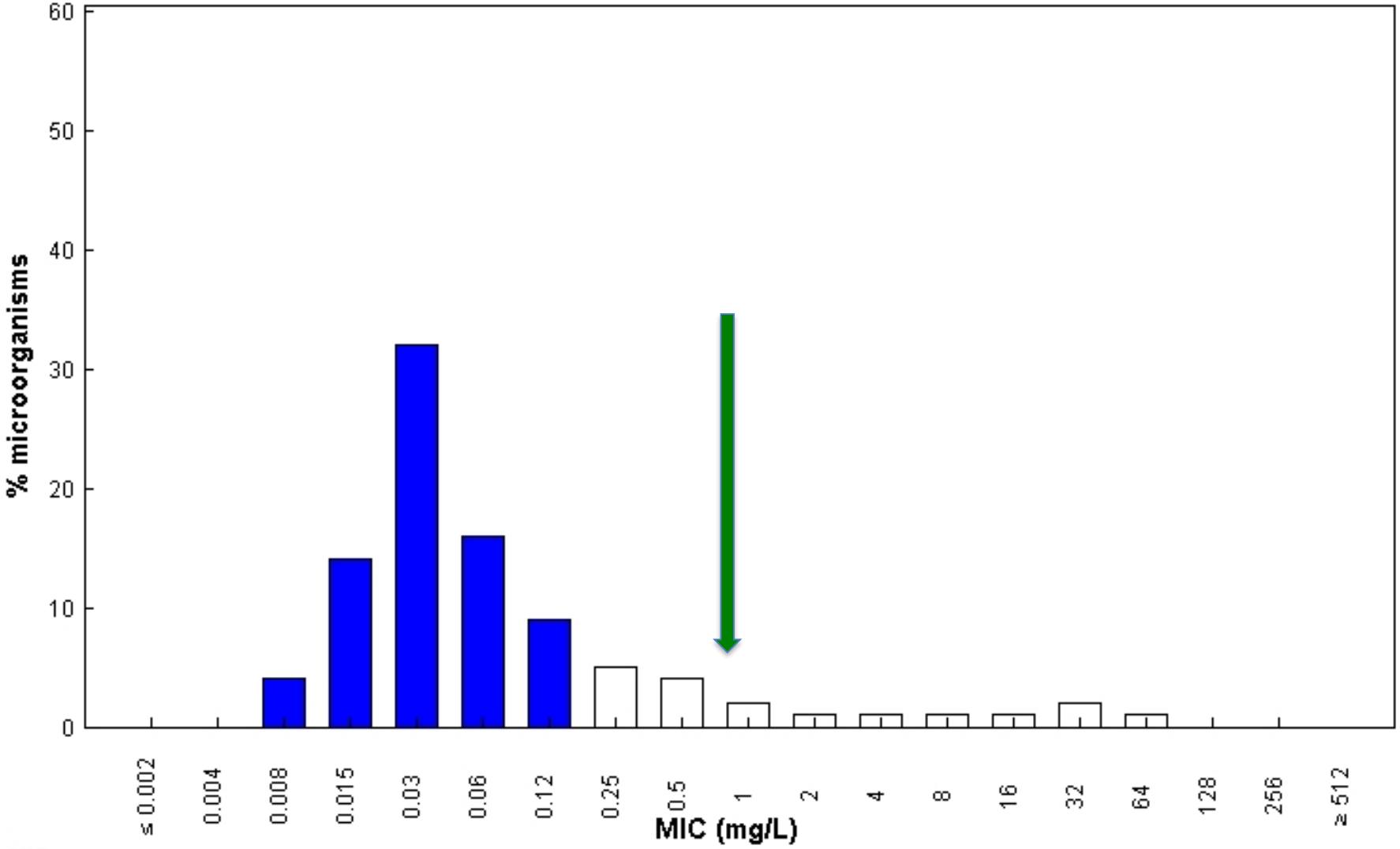
MIC
Epidemiological cut-off (ECOFF): 0.064 mg/L
Wildtype (WT) organisms: ≤ 0.064 mg/L

16702 observations (55 data sources)

Ciprofloxacin / Klebsiella pneumoniae

International MIC Distribution - Reference Database 2016-05-14

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



MIC

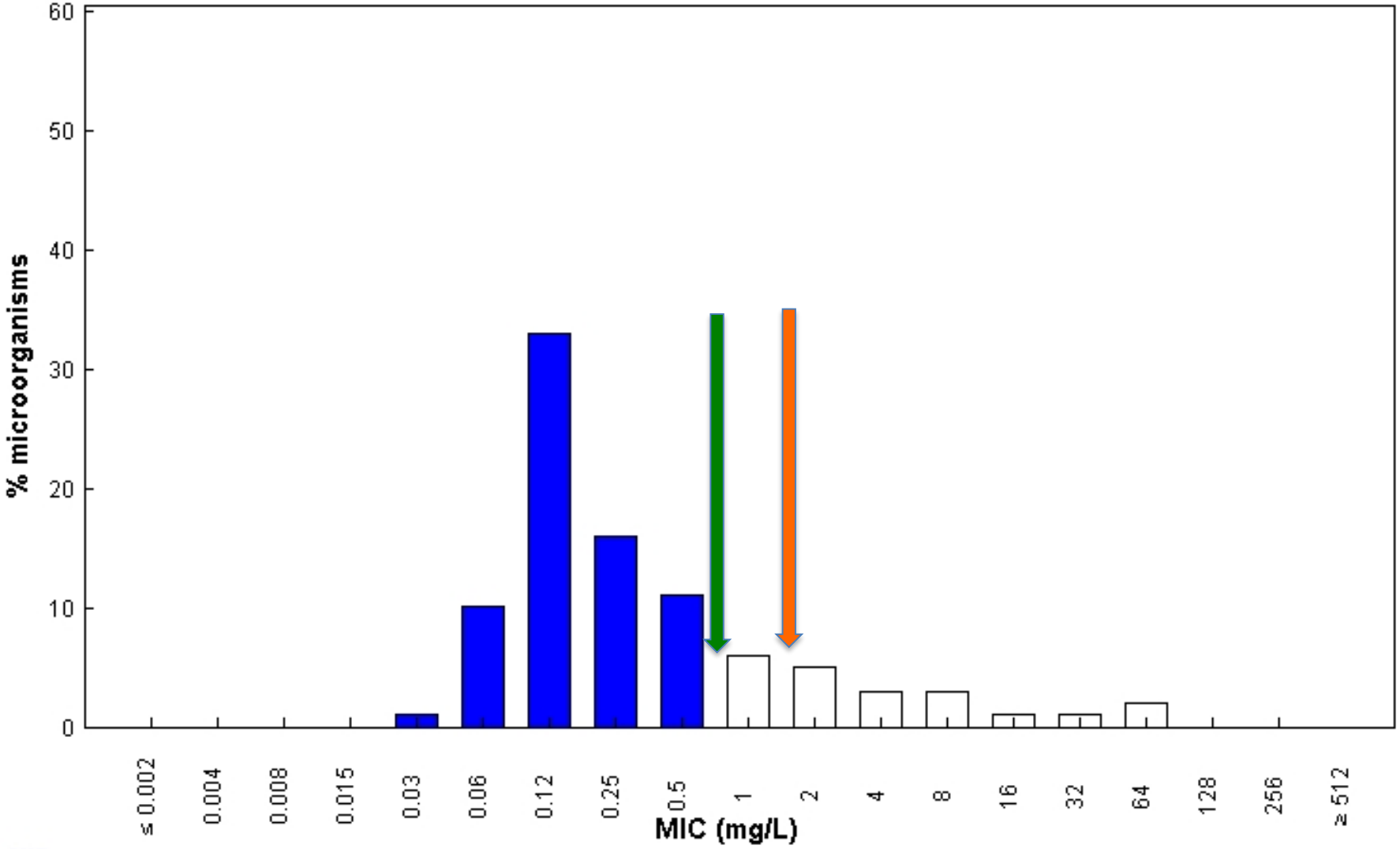
Epidemiological cut-off (ECOFF): 0.125 mg/L

Wildtype (WT) organisms: ≤ 0.125 mg/L

5905 observations (71 data sources)

Ciprofloxacin / Pseudomonas aeruginosa
International MIC Distribution - Reference Database 2016-05-14

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): 0.5 mg/L
Wildtype (WT) organisms: ≤ 0.5 mg/L

27967 observations (82 data sources)

Proposed modified carbapenem breakpoints

- not ready for consultation yet.

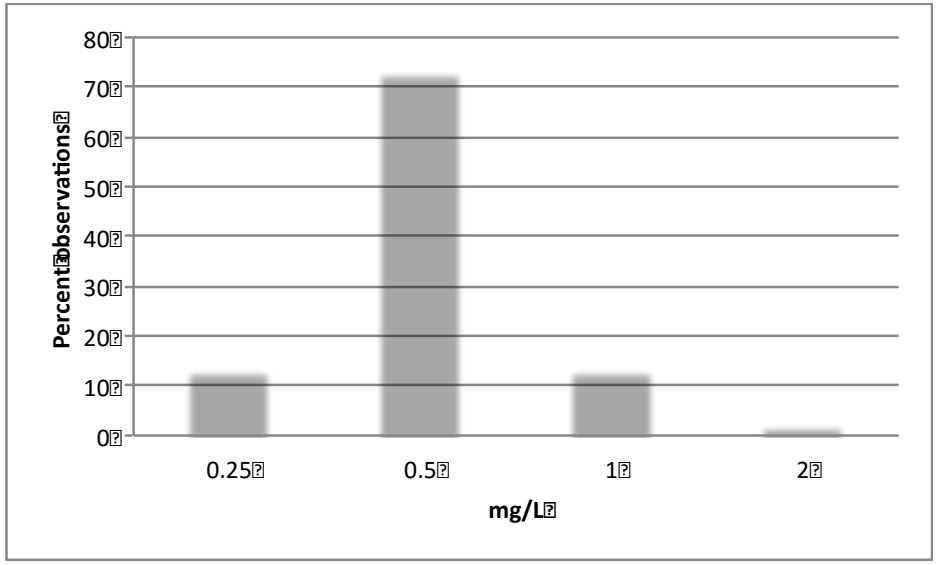
Proposed new carbapenem breakpoints

S≤X / R>Y mg/L

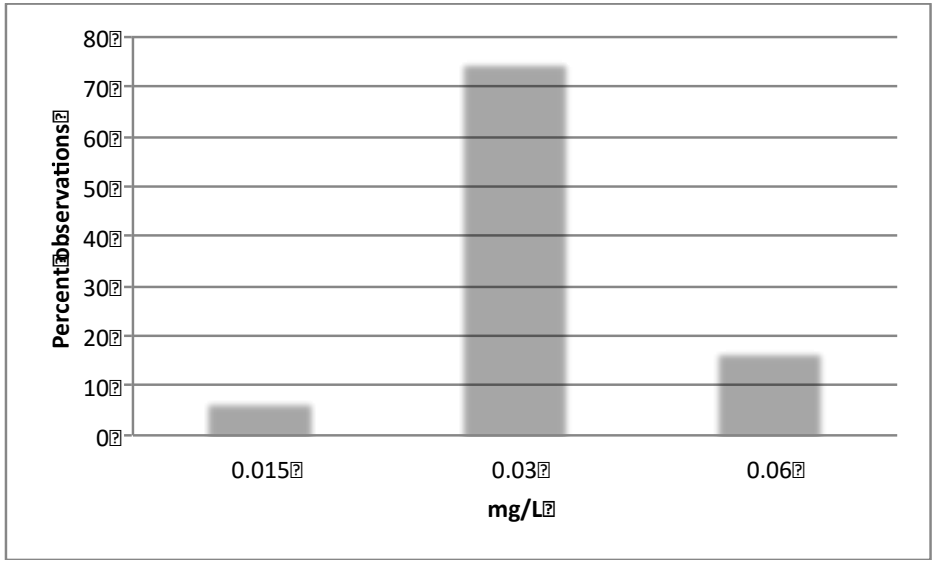
Anti-microbial	Entero-bacteriaceae	*P. aeruginosa*	*Acineto-bacter*
Ertapenem	0.5/0.5 (1)	-	-
Imipenem	2/4 (8)	4/4 (8)	2/4 (8)
Meropenem	2/4 (8)	2/4 (8)	2/4 (8)
Doripenem	1/1 (2)	1/1 (2)	1/1 (2)

Reproducibility of broth microdilution

K. pneumoniae



E. coli



JMI Laboratories (courtesy of Prof R. Jones)

Screening for carbapenem resistance in Enterobacteriaceae

- It is important to get the detection cut-off right!

- The clinical breakpoint is not suitable!

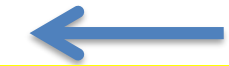
EUCAST advise on carbapenemase detection.

Notes

Numbered notes relate to general comments and/or MIC breakpoints.
Lettered notes relate to the disk diffusion method.

1. The carbapenem breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including the majority of carbapenemases). Some isolates that produce carbapenemase are categorised as susceptible with these breakpoints and should be reported as tested, *i.e.* the presence or absence of a carbapenemase does not in itself influence the categorisation of susceptibility. Carbapenemase detection and characterisation are recommended for public health and infection control purposes.

Carbapenem	MIC (mg/L)	
	S/I breakpoint	Screening cut-off
Meropenem[1]	≤2	>0.12
Imipenem[3]	≤2	>1
Ertapenem[4]	≤0.5	>0.12



Poor sensitivity

Poor specificity

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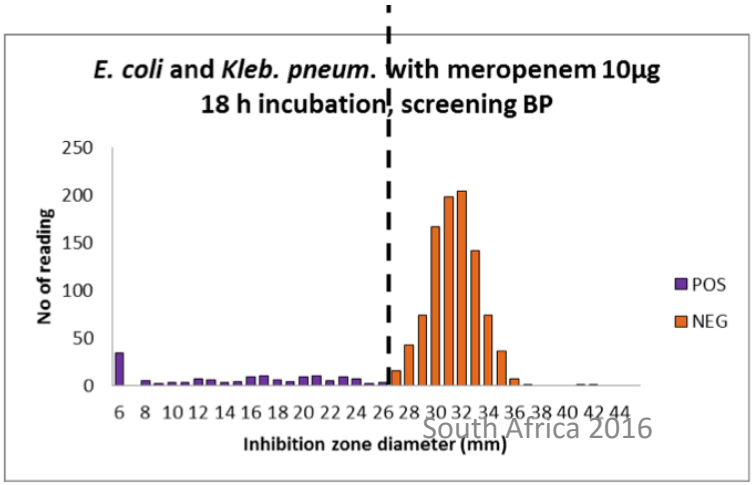
Screening for carbapenem resistance in Enterobacteriaceae

- It is important to adher to the recommended methodology.

6 hours

8 hours

18 hours
Standard method

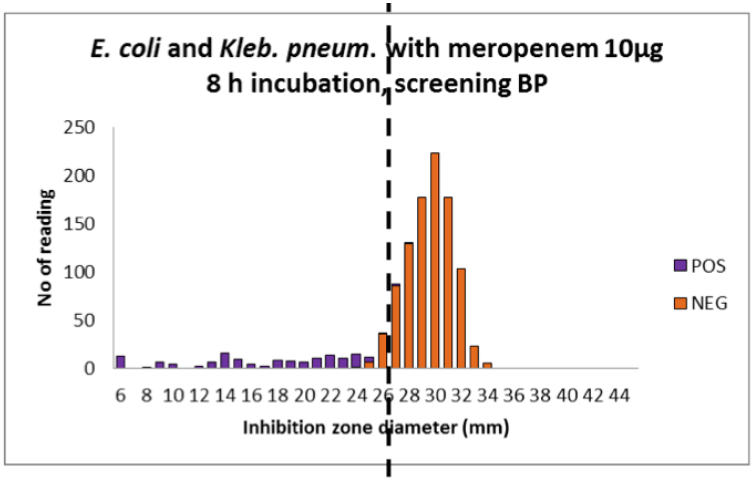


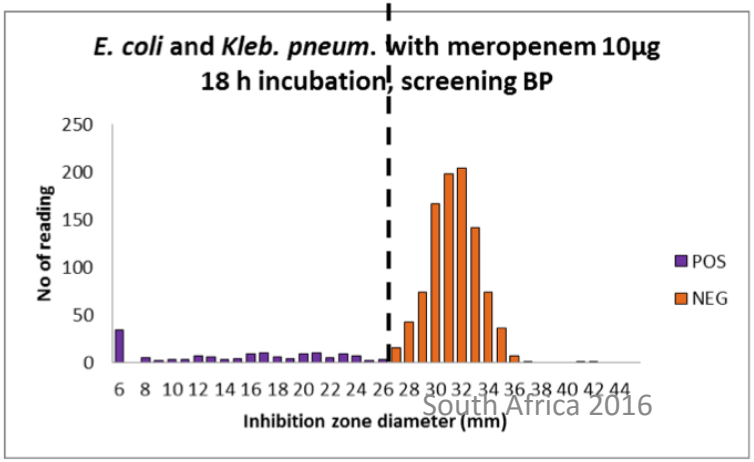
Screening for carbapenem resistance using the EUCAST recommended screening breakpoint:
Suspect carbapenem resistance when zone <25 mm (or if OXA48 are abundant, <27 mm.

6 hours

8 hours

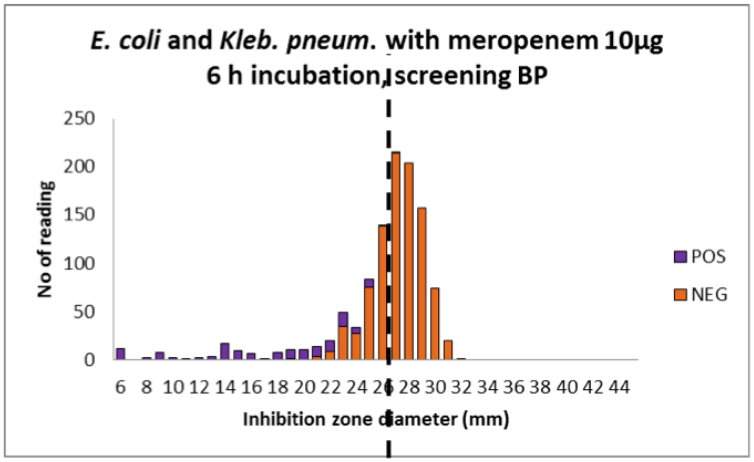
18 hours
Standard method



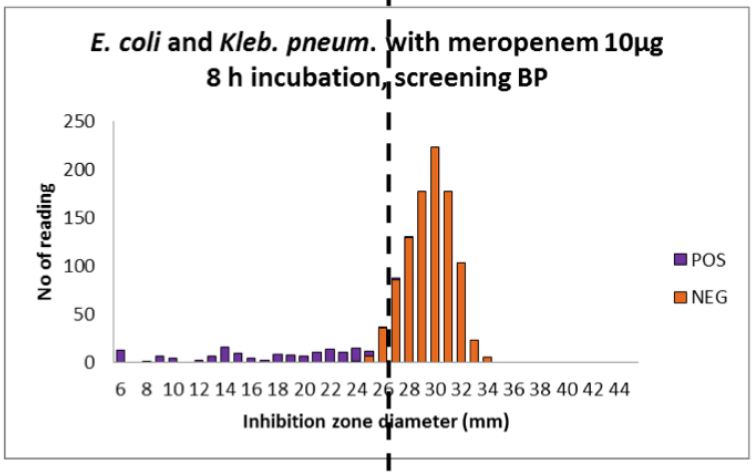


Screening for carbapenem resistance using the EUCAST recommended screening breakpoint:
Suspect carbapenem resistance when zone <25 mm (or if OXA48 are abundant, <27 mm.

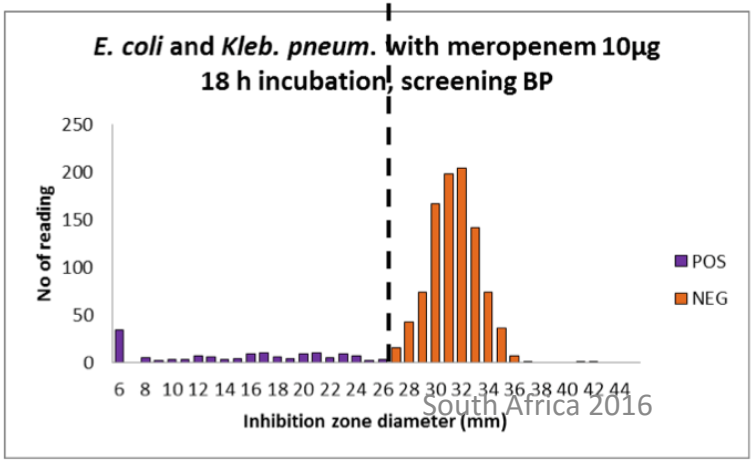
6 hours



8 hours



18 hours
Standard method



Screening for carbapenem resistance using the EUCAST recommended screening breakpoint:
Suspect carbapenem resistance when zone <25 mm (or if OXA48 are abundant, <27 mm.

Screening for carbapenem resistance in Enterobacteriaceae

- It is important to adhere to the recommended methodology.

- It is tempting to read plates early, and they can be read at 6 or 8 h, BUT then you must use a different breakpoint.

Colistin – methods and breakpoints reviewed by joint EUCAST/CLSI subcommittee

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

Consultation on proposal to reduce colistin breakpoints for *Pseudomonas aeruginosa* to susceptible ≤2 mg/L, resistant > 2 mg/L

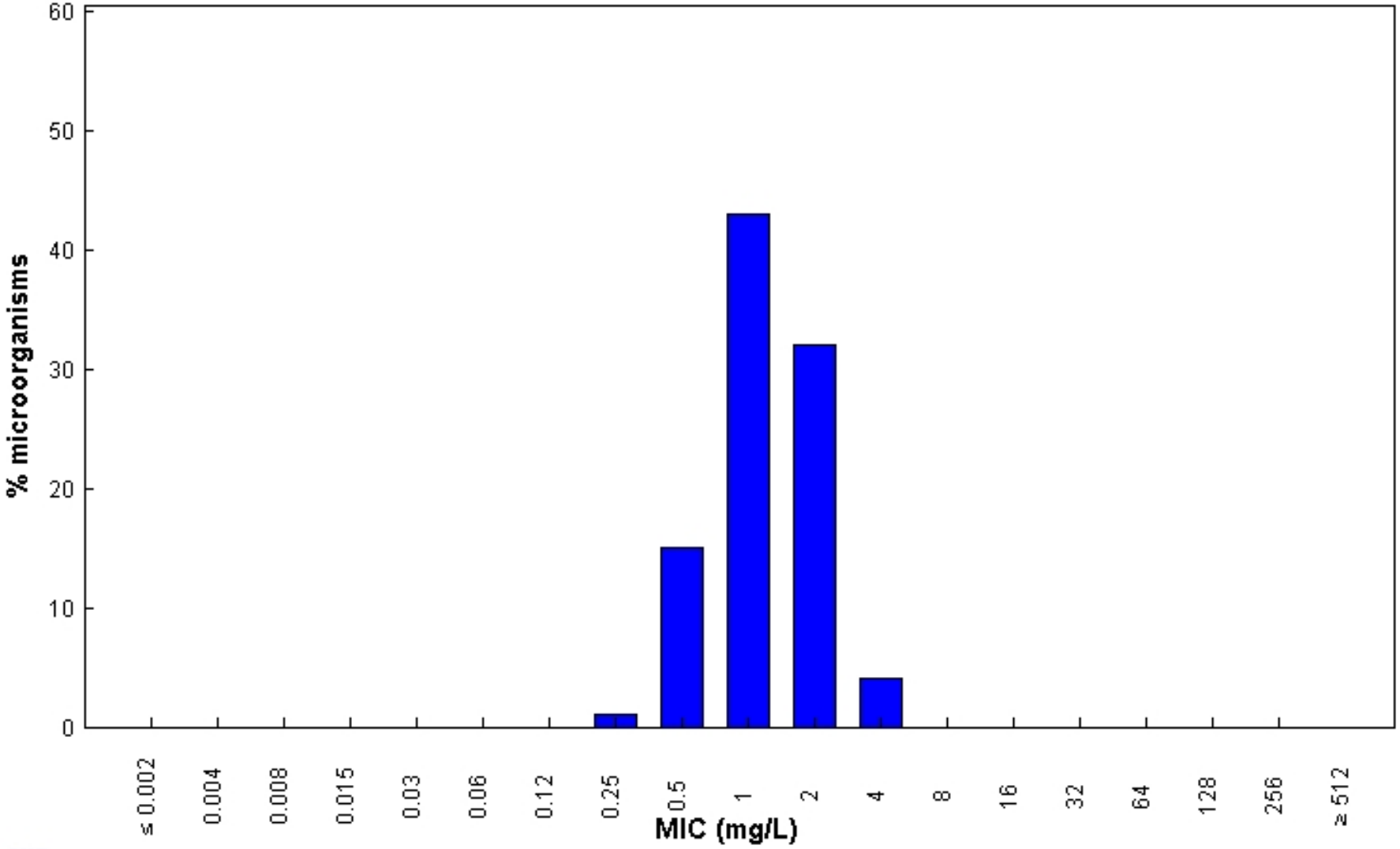
Detailed below are proposals to reduce colistin breakpoints for *Pseudomonas aeruginosa* from susceptible ≤4 mg/L, resistant >4 mg/L to susceptible ≤2 mg/L, resistant >2 mg/L. The proposals are open for comment by 24 June 2016.

Please send comments, with supporting data or references where appropriate, to the EUCAST Scientific Secretary (derek.brown222@btinternet.com). Please use the accompanying form for your comments.

Colistin / Pseudomonas aeruginosa

International MIC Distribution - Reference Database 2016-05-14

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): 4 mg/L

Wildtype (WT) organisms: ≤ 4 mg/L

6579 observations (19 data sources)

Colistin MIC distributions and ECOFFs

Antimicrobial: **Colistin** (Method: **MIC**)

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

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Acinetobacter baumannii	0	0	0	0	0	0	0	0	33	163	108	0	0	1	1	0	0	0	0	ND
Citrobacter freundii	0	0	0	0	0	0	0	2	4	3	0	0	0	0	0	0	0	0	0	ND
Citrobacter koseri	0	0	0	0	0	0	5	8	3	0	0	0	0	0	0	0	0	0	0	ND
Enterobacter aerogenes	0	0	0	0	0	4	4	55	150	44	10	3	3	3	0	0	4	0	0	2.0
Enterobacter cloacae	0	0	0	0	0	0	16	255	398	76	15	6	9	17	23	8	22	2	2	2.0
Escherichia coli	0	0	0	0	0	2	231	2058	2776	874	74	16	14	5	8	2	30	0	0	2.0
Klebsiella pneumoniae	0	0	0	0	0	0	24	451	1220	411	36	17	14	35	14	5	9	0	1	2.0
Pseudomonas aeruginosa	0	0	0	0	1	6	24	114	1051	2872	2118	287	30	48	7	3	12	0	6	4.0
Raoultella ornithinolytica (Klebs. oxytoca)	0	0	0	0	0	16	10	143	406	192	22	6	1	10	2	1	2	0	1	2.0
Salmonella dublin	0	0	0	0	0	0	0	0	0	24	30	108	65	1	0	0	0	0	0	ND
Salmonella enteritidis	0	0	0	0	0	0	0	0	0	1	3	11	15	0	0	0	0	0	0	ND

Ac-

Consultation on Colistin

13 May – 24 June

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Comments on proposals to reduce colistin breakpoints for *Pseudomonas* spp. to susceptible ≤2 mg/L, resistant >2 mg/L, May 2016

Please send any comments on these proposals, with supporting data or references where appropriate, to the EUCAST Scientific Secretary (derek.brown222@btinternet.com) before 24th June 2016. Please use this form for your comments.

Comment from (name, contact details)	Comments
	Please add lines if required.

Colistin project

- A collection of wild type and non-wild type isolates with low and high MICs
- *E.coli, K.pneumoniae, Ps. aeruginosa* and *Acinetobacter* spp.

- BMD + Two Gradient tests + Disk diffusion

Whole Genome Sequencing

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

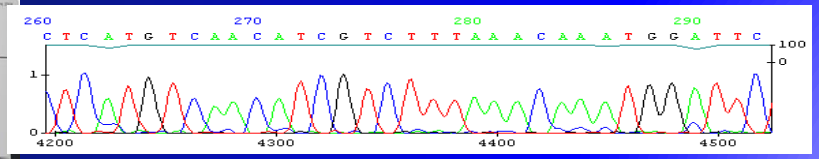
European Society of Clinical Microbiology and Infectious Diseases

Consultation on Report from the EUCAST Subcommittee on the Role of Whole Genome Sequencing (WGS) in Antimicrobial Susceptibility Testing of Bacteria

The report is open for comment by 24 June 2016. Please send comments, with supporting data or references where appropriate, to the EUCAST Scientific Secretary (derek.brown222@btinternet.com). Please use the accompanying form for your comments.

What can WGS offer ?

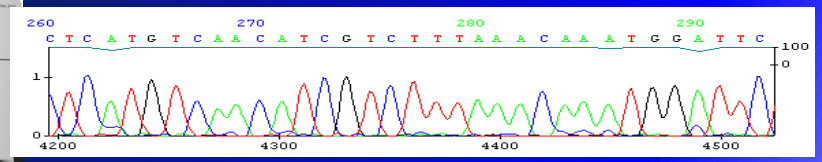
	Phenotypic AST	WGS-based AST
Measures susceptibility	✓	X
Resistance mechanisms	✓ (limited)	✓✓✓
ECOFF (WT vs. non-WT)	✓	✓
Clinical resistance (S vs. R)	✓	**?** (must be inferred)
Additional data	X	✓✓✓
Suitable speed	✓(most) X (e.g. TB)	X (most) ✓(e.g. TB)
Cost	✓	X



WGS / NGS – what does it offer?

- Characterizing resistance genes/mechanisms
- Predicting antimicrobial resistance as a phenomenon – mostly good correlation to ECOFFs
- Identifying virulence genes
- Typing (like / unlike)

- Predict clinical antimicrobial susceptibility ??



Courtesy Neil Woodford

EUCAST / WHO video tutorials

A change in the EUCAST definitions of the **intermediate** category is under discussion.

- a proposal is undergoing public consultation

EUCAST is exploring how to make the definition of INTERMEDIATE unambiguous.

The proposal is not to remove the INTERMEDIATE category!

Intermediate - current definition

(1) A micro-organism is defined as intermediate by a level of antimicrobial agent activity associated with **uncertain therapeutic** effect.

(2) ap… co…

(3) un…

Three definitions rolled into one but the report does not say which applies!

…in interpretations.

A micro-organism is categorized as intermediate (I) by applying the appropriate breakpoints in a defined phenotypic test system

These breakpoints may be altered with legitimate changes in circumstances

The EUCAST process for setting breakpoints

is closely related to the dose/dosage/dosing, mode of administration and PK/PD

Where EUCAST has an INTERMEDIATE category there is a defined “standard” and “high” dose.

See the EUCAST breakpoint table.

Dosages	EUCAST Clinical Breakpoint Table v. 6.0, valid from 2016-01-01	
EUCAST breakpoints are based on the following dosages (see section 8 in Rationale Documents).		
Penicillins	**Standard dose**	**High dose**
Benzylpenicillin	600 mg x 4 iv	2.4 g x 6 iv
Ampicillin	500 mg -1 g x 3-4 iv	1 - 2 g x 4-6 iv
Ampicillin-sulbactam		
Amoxicillin	500 mg x 3 iv Oral dosage under discussion	2 g x 6 iv Oral dosage under discussion
Amoxicillin-clavulanic acid	500 mg x 3 iv Oral dosage under discussion	2 g x 6 iv Oral dosage under discussion
Piperacillin	4 g x 3 iv	4 g x 4 iv
Piperacillin-tazobactam	4 g x 3 iv	4 g x 4 iv
Ticarcillin	3 g x 4 iv	3 g x 6 iv
Ticarcillin-clavulanic acid	3 g x 4 iv	3 g x 6 iv
Phenoxymethylpenicillin		
Oxacillin		
Cloxacillin		
Dicloxacillin		
Flucloxacillin		
Mecillinam	200 - 400 mg x 3 oral	None
Cephalosporins	**Standard dose**	**High dose**
Cefaclor		
Cefadroxil	500 mg x 2 oral	1 g x 2 oral
Cefalexin		
Cefazolin		
Cefepime	2 g x 2 iv	2 g x 3 iv
Cefixime		
Cefotaxime	1 g x 3 iv	2 g x 3 iv
Cefoxitin		
Cefpodoxime		
Ceftaroline	600 mg x 2 iv over 1 hour	None
Ceftazidime	1 g x 3 iv	2 g x 3 iv

Solution to the Intermediate dilemma?

Under development and discussion.

New consultation to follow.

AST - when there is no breakpoint?

- The breakpoint is “IE”
- The breakpoint is “—”
- The agent is not in the table
- The species is not in the table

Breakpoint table indicates “IE” or “-”

“IE”: insufficient evidence

- there is a lack of clinical evidence to suggest a clinical breakpoint.
- report an MIC and a comment

“-”: intrinsic resistance

- whatever evidence is available suggests that the agent is ineffective irrespective of dose
- do not test, report “R” if a report is needed.

The agent is not in the table

1. Older agent – limited interest
2. New agent – under development

- Ad 1. Ask EUCAST what they plan?
  - Surrogate agent (test another macrolide?)
  - Perform MIC – compare with MIC database
- Ad 2. Check with company, EUCAST, Medicines agency

The species is not in the table

1. Rare species – possibly under development
2. Reliable AST difficult or not possible

- Ad 1. Ask EUCAST to name a surrogate species with which to compare?
  - Perform MIC – compare with MIC database on species or related species;
- Ad 2. Beware – MIC-testing will “always” yield a result, but in this case of doubtful relevance.
  - fosfomycin (agar dilution only), caspofungin
  - Stenotrophomonas, Burkholderia

Not infrequently -

There are species and agents not mentioned in EUCAST tables but present in CLSI tables.

Ask CLSI whether or not they take responsibility for the breakpoint in question!

When there are no breakpoints…

- Do not report “S”, “I” or “R”
  - These are susceptibility categories based on evidence for or against favorable clinical outcome.
- Report an MIC with a comment or only a comment
  - MIC value + comment
  - MIC + PK/PD cut off value + comment
  - MIC value + WT/NWT + comment
  - comment

Other EUCAST activities

- Postgraduate courses
- ECCMID Workshops – presentations available on ESCMID website
- EUCAST Projects – we invite you to sign up as a EUCAST Network Laboratory and participate in AST projects.
- EUCAST Observerships – we invite ESCMID members to visit with one (or both) of the EUCAST Development Labs (Växjö/Copenhagen) for 3 - 5 days. ESCMID supports this with 1000 – 2000 EUR.

Profession & Career

Awards & Grants

Collaborative Centres & Observerships

- About Collaborative Centres (ECCs)
- ECC search
- Register Collaborative Centre
- About Observerships
- ECDC Observerships
- WHO Observerships
- Apply Observership

Educational activities

Mentorships

Parity Commission

PA Workshops

Trainee Association of ESCMID

Speciality training

Jobs in CM & ID

EU Partner Search

EU calls & other funding

ESCMID Collaborative Centres (ECCs) and Observerships

Observerships are funded opportunities for members to spend one day to one month at an ESCMID Collaborative Centre. These are ID and/or CM centres of excellence in Europe of which there are now over 80.

About Collaborative Centres (ECCs)

The ECCs are clinical microbiology and/or infectious disease centres of excellence in Europe and beyond. They attract and welcome ESCMID members from abroad to ...

ECC search

Search our over 80 Collaborative Centres to find a Centre for your Observership.

Register Collaborative Centre

To sign up your institute for ESCMID Collaborative Centre status, apply anytime using this

Virulence and Resistance in Staphylococcus aureus: 2016 State of the Art
28 June - 1 July 2016, Lyon, France

Medical Biofilm Techniques 2016
22 - 25 August 2016, Lyngby, Denmark

Status Quo of Brain Infections 2016
4 - 7 September 2016, Izmir, Turkey

Antimicrobial Stewardship in Veterinary Medicine
11 - 12 September 2016, Gothenburg, Sweden

Antimicrobial Susceptibility Testing and Surveillance: from Laboratory to Clinic. A EUCAST, ESGARS and EPASG Perspective
20 - 23 September 2016, Bochum, Germany

Management of Infections in Septic Shock Patients
22 - 23 September 2016, Istanbul, Turkey

Infectious Diseases in Pregnant Women, Fetuses and Newborns
25 - 29 September 2016, Bertinoro, Italy

SIGN UP

Upcoming Registration Deadlines

20 May 2016
Individualized Medicine in Infectious Diseases: a Practical Approach
Tübingen, Germany

20 May 2016
Virulence and Resistance in Staphylococcus aureus: 2016 State of the Art
Lyon, France

Upcoming Grant Application Deadlines

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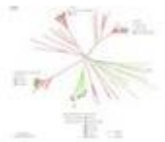
ECCMID

ESCMID-ASM antibiotic drug development conference 21 – 23 Sept 2016

Save the date: ESCMID-ASM conference on ***Drug Development*** to meet the challenge of AMR, Vienna, 21 - 23/09/2016





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Thank you

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

Why are there no daptomycin breakpoints for *Enterococcus* spp.?

DB

Daptomycin and *Enterococcus* spp.

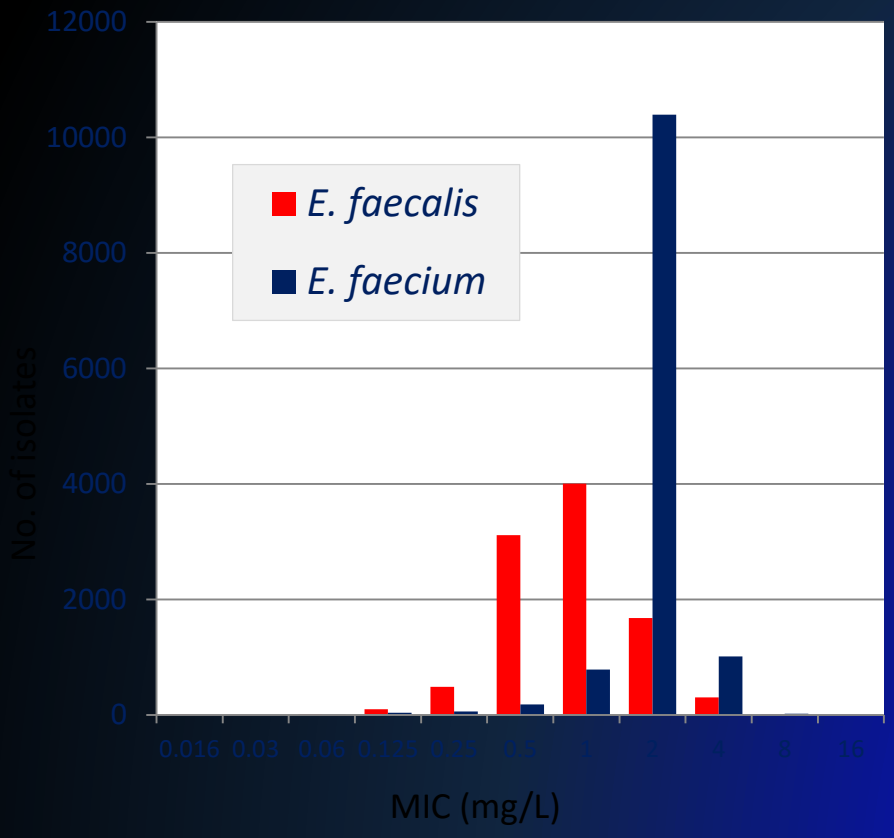
- Daptomycin marketing approval in EU for:
  - adult cSSTI (4 mg/kg/day)
  - *S. aureus* right-sided endocarditis (6 mg/kg/day)

- Staphylococci and streptococcus groups A, B, C, G
  - daptomycin MIC breakpoints - S ≤ 1 mg/L, R > 1 mg/L

- No EUCAST daptomycin breakpoints for enterococci
  - Insufficient evidence (IE) to set PK-PD and *Enterococcus* spp. breakpoints

Daptomycin and enterococci

Daptomycin MIC distributions



Monte Carlo simulation with licensed daptomycin dose (4 mg/kg/day)

Daptomycin MIC (mg/L)	% target attainment with an AUC/MIC target of		
	373 (-1 SD)	438 (mean)	503 (+1 SD)
<0.25	100.0	100.0	100.0
0.5	100.0	100.0	100.0
1	96.8	77.2	42.9
2	0	0	0
≥4	0	0	0

A. MacGowan (upublished)

Daptomycin and *Enterococcus* spp.

- Serious infections caused by wild type *Enterococcus* spp. (daptomycin MIC≤4 mg/L) are unlikely to be successfully treated with licensed dosages of daptomycin (4 mg/kg/day)

- Breakpoints for *Enterococcus* spp. would be inappropriate

- If daptomycin MICs ≤4 mg/L, infections may be successfully treated with high doses (at least 8 mg/kg/day) of daptomycin