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CLSI Veterinary Antimicrobial Susceptibility Testing Subcommittee (VAST)

CLSI
Generic Antimicrobial Agents Working Group

Subcommittee on Veterinary Antimicrobial Susceptibility Testing

June 14-15, 2019

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

CLSI-VAST
Generic Drug Working Group

CLSI
Generic Antimicrobial Agents Working Group

Members (2019):

Cory Langston, Vijay Singu, Virginia Sinnott-Stutzman, Ching Ching Wu, Shabbir Simjee, Lacie Johansen, Sara Lawhon, Virginia Fajt, Mark Papich, John Turnidge, Stefan Schwarz, Marilyn Martinez, Amanda Kreuder, Merran Govendir,

& Tara Bidgood.

CLSI-VAST
Interpretive Categories and Breakpoints for Susceptibility Testing:

- Overall: breakpoints for approximately 182 drug-bug combinations

- Since 2015: 37 new breakpoints; 30 developed by the Generic Drug Working Group

CLSI Veterinary-Specific Breakpoint Additions/Revisions Since 2015*

Antimicrobial Agent	Table	Organism(s)	Animal Species	Body Site	Data Source Presentation
Ampicillin	2A	*Escherichia coli*	Cats	SST, UTI	GWG (January 2018)
Cefovecin	2A	*E. coli*	Cats	UTI	Sponsor (January 2018)
Ampicillin	2A	*E. coli*	Cattle	Metritis	GWG (January 2018)
Cefazolin	2A	*E. coli* *Klebsiella pneumoniae* *Proteus mirabilis*	Dogs	UTI	GWG (January 2017)
Cefovecin	2A	*E. coli* *P. mirabilis*	Dogs	UTI	Sponsor (January 2018)
Cefpodoxime	2A	*E. coli* *K. pneumoniae* *P. mirabilis*	Dogs	UTI	GWG (January 2017)
Cephalexin	2A	*E. coli*	Dogs	SST	GWG (June 2015)
Cephalexin	2A	*E. coli* *K. pneumoniae* *P. mirabilis*	Dogs	UTI	GWG (January 2017)
Piperacillin-tazobactam	2A	*Enterobacteriaceae*	Dogs	SST, UTI	GWG (June 2015)
Doxycycline	2A	*E. coli*	Horses	Resp, SST	GWG (January 2017)
Enrofloxacin	2A	*E. coli*	Horses	Resp, SST	GWG (January 2017)
Minocycline	2A	*E. coli*	Horses	Resp, SST	GWG (January 2018)
Piperacillin-tazobactam	2B	*Pseudomonas aeruginosa*	Dogs	SST, UTI	GWG (June 2015)
Enrofloxacin	2B	*P. aeruginosa*	Horses	Resp, SST	GWG (January 2017)
Ampicillin	2C	*Staphylococcus* spp.	Cats	SST, UTI	GWG (January 2018)
Cefovecin	2C	*Staphylococcus pseudintermedius*	Dogs	SST	Sponsor (January 2018)
Cephalexin	2C	*Staphylococcus aureus* *S. pseudintermedius*	Dogs	SST	GWG (June 2015)
Minocycline	2C	*S. pseudintermedius*	Dogs	SST	GWG (June 2015)
Piperacillin-tazobactam	2C	*Staphylococcus* spp.	Dogs	SST, UTI	GWG (June 2015)
Doxycycline	2C	*S. aureus*	Horses	Resp, SST	GWG (January 2017)
Enrofloxacin	2C	*S. aureus*	Horses	Resp, SST	GWG (January 2017)
Minocycline	2C	*S. aureus*	Horses	Resp, SST	GWG (January 2017)
Ampicillin	2D	*Streptococcus* spp.	Cats	SST, UTI	GWG (January 2018)

CLSI Veterinary-Specific Breakpoint Additions/Revisions Since 2015* (Continued)

Antimicrobial Agent	Table	Organism(s)	Animal Species	Body Site	Data Source Presentation
Cefovecin	2D	*Streptococcus* β-hemolytic group	Dogs	SST	Sponsor (January 2018)
Cephalexin	2D	*Streptococcus* β-hemolytic group	Dogs	SST	GWG (June 2015)
Doxycycline	2D	*Streptococcus equi* subsp. *equi* and *zooepidemicus*	Horses	Resp, SST	GWG (January 2017)
Enrofloxacin	2D	*S. equi* subsp. *equi* and *zooepidemicus*	Horses	Resp, SST	GWG (January 2017)
Minocycline	2D	*Streptococcus* spp.	Horses	Resp, SST	GWG (January 2017)
Ampicillin	2G	*Mannheimia haemolytica*	Cattle	Resp	GWG (January 2018)
Danofloxacin	2G	*M. haemolytica*	Cattle	Resp	Sponsor (January 2016, I and R breakpoints)
Ampicillin	2H	*Pasteurella multocida*	Cats	SST, UTI	GWG (January 2018)
Cefovecin	2H	*P. multocida*	Cats	SST, UTI	Sponsor (January 2018)
Ampicillin	2H	*P. multocida*	Cattle	Resp	GWG (January 2018)
Danofloxacin	2H	*P. multocida*	Cattle	Resp	Sponsor (January 2016, I and R breakpoints)
Ampicillin	2J	*Histophilus somni*	Cattle	Resp	GWG (January 2018)

Abbreviations: GWG, Generic Drug Working Group; I, intermediate; R, resistant; resp, respiratory; SST, skin and soft tissue; UTI, urinary tract infection.

CLSI
Generic Antimicrobial Agents Working Group

Updates from the Generic Drug Working Group

Planned New Breakpoints

CLSI-VAST
Generic Drug Working Group
New Breakpoints

Agent	Species	Status
Chloramphenicol	Dogs, Horses	• … still working on this
Trimethoprim-sulfamethoxazole	Dogs, Cats, Horses	• PK data available • Still need PK-PD targets defined • Difficult to define due to combination product
Rifampin	Dogs, Horses	• PK data available for horses, but scarce for dogs. • PK-PD targets need to be defined.

Generic Drug Working Group
New Breakpoints

Agent	Species	Status
Other 3rd-Generation Cephalosporins?	Dogs, Cats, Horses	✓ Ceftazidime • Cefotaxime (not available?)
Carbapenems	Dogs, Cats	• PK data available • PK-PD targets defined • Presentation planned for 2020
Tylosin	Cattle, Pigs	• Collecting data and PK-PD targets
Amoxicillin, Amoxicillin-Clavulanate	Cat-urine	✓ Studies are planned to collect data (new grant funded)

Table 2A. *Enterobacteriaceae* (Continued)

Test/ Report Group	Body Site	Antimicrobial Agent	Organism	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL			Comments
					S	I	R	S	I	R	
Aminoglycosides/Aminocyclitols (Continued)											
Humans **(10) Warning: For *Salmonella* spp. and *Shigella* spp., aminoglycosides may appear active *in vitro* but are not effective clinically and should not be reported as susceptible.**											
		Amikacin		30 µg	≥17	15–16	≤14	≤16	32	≥64	
		Gentamicin		10 µg	≥15	13–14	≤12	≤4	8	≥16	
		Kanamycin		**30 µg**	**≥18**	**14–17**	**≤13**	**≤16**	**32**	**≥64**	
		Streptomycin		**10 µg**	**≥15**	**12–14**	**≤11**	–	–	–	**(11) There are no MIC breakpoints.**
Penicillins											
Dogs											
A	Skin, soft tissue	Ampicillin	*E. coli*	–	–	–	–	≤0.25	0.5	≥1.0	**(12) Systemic breakpoints were derived from microbiological and PK-PD data. The dosage regimen used for PK-PD analysis of amoxicillin was 22 mg/kg every 12 hours orally.** **(13) Except for lower UTI, *E. coli* and other *Enterobacteriaceae* will test resistant to ampicillin and amoxicillin.**
A	UTI	Ampicillin	*E. coli*	–	–	–	–	≤8	–	–	**(14)** This breakpoint for UTIs was derived from published literature in which orally administered ampicillin 25.6 mg/kg and amoxicillin 11 mg/kg was administered to healthy dogs at 8-hour intervals for 5 consecutive doses and produced urine concentrations in dogs > 300 µg/mL.

Table 2A. *Enterobacteriaceae* (Continued)

Test/ Report Group	Body Site	Antimicrobial Agent	Organism	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL			Comments
					S	I	R	S	I	R	
Penicillins (Continued)											
Cats											
A	Skin, soft tissue, UTI	Ampicillin	*E. coli*	–	–	–	–	≤0.25	0.5	≥1.0	(15) Ampicillin breakpoints were determined from an examination of MIC distribution data and PK-PD analysis of amoxicillin in cats. The dosage regimen used for PK-PD analysis of amoxicillin was 12.5 mg/kg administered every 12 hours orally.
Cattle											

Any others?

Action Items from Past Meetings

January 2019 Action Items

Item #8

“Review other veterinary-specific breakpoints set by the GWG to determine whether other GWG breakpoints for E. coli *should be changed to Enterobacteriaceae, or left as E. coli.”*

Table 2A. *Enterobacteriaceae* (Continued)

Test/ Report Group	Body Site	Antimicrobial Agent	Organism	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL			Comments
					S	I	R	S	I	R	
Aminoglycosides/Aminocyclitols											
Dogs											
A		Amikacin	*E. coli*	–	–	–	–	≤4	8	≥16	**(5)** Breakpoints were derived from microbiological, PK (using accepted clinical doses), and PD data. For dogs, the dose of amikacin modeled was 15 mg/kg, every 24 hours IM, IV, or SC.
A		Gentamicin	*Enterobacteriaceae*	10 µg	≥16	13–15	≤12	≤2	4	≥8	**(6)** Breakpoints were derived from microbiological, PK (using accepted clinical doses), and PD data. For dogs, the dose of gentamicin modeled was 10 mg/kg every 24 hours IM.
Horses (foals)											
A		Amikacin	*E. coli*	–	–	–	–	≤2	4	≥8	**(7)** Breakpoints were derived from microbiological, PK (using accepted clinical doses), and PD data. For foals <11 days of age, the dose of amikacin modeled was 20 mg/kg, every 24 hours IV.
Horses (adults)											
A		Amikacin	*E. coli*	–	–	–	–	≤4	8	≥16	**(8)** Breakpoints were derived from microbiological, PK (using accepted clinical doses), and PD data. For adult horses, the dose of amikacin modeled was 10 mg/kg, every 24 hours, IM or IV.

Penicillins											
Dogs											
A	Skin, soft tissue	Ampicillin	*E. coli*	–	–	–	–	≤0.25	0.5	≥1.0	**(12) Systemic breakpoints were derived from microbiological and PK-PD data. The dosage regimen used for PK-PD analysis of amoxicillin was 22 mg/kg every 12 hours orally.** **(13) Except for lower UTI, *E. coli* and other *Enterobacteriaceae* will test resistant to ampicillin and amoxicillin.**
A	UTI	Ampicillin	*E. coli*	–	–	–	–	≤8	–	–	**(14)** This breakpoint for UTIs was derived from published literature in which orally administered ampicillin 25.6 mg/kg and amoxicillin 11 mg/kg was administered to healthy dogs at 8-hour intervals for 5 consecutive doses and produced urine concentrations in dogs > 300 µg/mL.
Penicillins (Continued)											
Cats											
A	**Skin, soft tissue, UTI**	**Ampicillin**	***E. coli***	–	–	–	–	**≤0.25**	**0.5**	**≥1.0**	**(15) Ampicillin breakpoints were determined from an examination of MIC distribution data and PK-PD analysis of amoxicillin in cats. The dosage regimen used for PK-PD analysis of amoxicillin was 12.5 mg/kg administered every 12 hours orally.**
Cattle											
A	**Metritis**	**Ampicillin**	***E. coli***	–	–	–	–	**≤0.25**	**0.5**	**≥1.0**	**(16) Breakpoints were derived from microbiological and PK-PD data. The dose of ampicillin trihydrate used to derive this breakpoint was 11 mg/kg every 24 hours IM.**

Group	Site	Agent	Organism	Content	S	I	R	S	I	R	Comments
β-Lactam Combination Agents											
Dogs											
A	Skin, soft tissue	Amoxicillin-clavulanate	*E. coli*	–	–	–	–	≤0.25/0.12	0.5/0.25	≥1/0.5	**(19)** Amoxicillin-clavulanate breakpoints were determined from an examination of MIC distribution data, efficacy data, and PK-PD analysis of amoxicillin in dogs. The dosage regimen used for PK-PD analysis of amoxicillin was 11 mg/kg administered every 12 hours orally. **(20) With the exception of isolates from UTIs, *E. coli* and other *Enterobacteriaceae* should be reported as resistant to ampicillin, amoxicillin, and amoxicillin-clavulanate because the drug concentrations achieved according to the labeled dosing regimen are not high enough to reach the therapeutic target. For uncomplicated UTIs, see comment (21).**

β-Lactam Combination Agents (Continued)											
Cats											
A	Skin, soft tissue, UTI	Amoxicillin-clavulanate	*E. coli*	–	–	–	–	≤0.25/0.12	0.5/0.25	≥1/0.5	**(23)** Amoxicillin-clavulanate breakpoints were determined from an examination of MIC distribution **data**, efficacy data, and PK-PD analysis of amoxicillin in cats at a dosage of 12.5 mg/kg (amoxicillin) administered every 12 hours orally.
Humans											

Dogs											
A	**Skin, soft tissue**	**Cephalexin**	***E. coli***	**–**	**–**	**–**	**–**	**≤2**	**4**	**≥8**	**(25) Cephalexin breakpoints were determined from an examination of MIC distribution data, efficacy data, and PK-PD analysis of cephalexin in dogs. The dosage regimen used for PK-PD analysis of cephalexin was 25 mg/kg administered every 12 hours orally.**

Dogs (Continued)											
A	**UTI**	**Cephalexin**	***E. coli*** ***Klebsiella pneumoniae*** ***Proteus mirabilis***	**–**	**–**	**–**	**–**	**≤16**	**–**	**≥32**	**(26) Cefazolin and cephalexin may be tested when used for treatment of uncomplicated UTIs caused by *E. coli, K. pneumoniae,* or *P. mirabilis.* Cefpodoxime may be tested individually because some isolates may be susceptible to this**
A	Skin, soft tissue	Cefazolin	*E. coli*	–	–	–	–	≤2	4	≥8	(27) Cefazolin breakpoints were determined from an examination of MIC distribution **data** and PK-PD analysis of cefazolin. The dosage regimen used for PK-PD analysis of cefazolin was 25 mg/kg administered every 6 hours IV in horses and dogs.
A	**UTI**	**Cefazolin**	***E. coli***	**–**	**–**	**–**	**–**	**≤16**	**–**	**≥32**	**See comment (26).**

Fluoroquinolones[d]											
Dogs											
A	Skin, soft tissue, UTI	Difloxacin	*Enterobacteriaceae*	10 µg	≥21	18–20	≤17	≤0.5	1–2	≥4	
A	Skin, soft tissue, respiratory, UTI	Enrofloxacin	*Enterobacteriaceae*	5 µg	≥23	17–22	≤16	≤0.5	1–2	≥4	
A	Skin, soft tissue, UTI	Marbofloxacin	*Enterobacteriaceae*	5 µg	≥20	15–19	≤14	≤1	2	≥4	
Cats											
A	Skin, soft tissue	Enrofloxacin	*Enterobacteriaceae*	5 µg	≥23	17–22	≤16	≤0.5	1–2	≥4	
A	Skin, soft tissue	Marbofloxacin	*Enterobacteriaceae*	5 µg	≥20	15–19	≤14	≤1	2	≥4	
A	Skin, soft tissue	Orbifloxacin	*Enterobacteriaceae*	10 µg	≥23	18–22	≤17	≤1	2–4	≥8	
A	Skin, respiratory	Pradofloxacin	*E. coli*	5 µg	≥24	20–23	≤19	≤0.25	0.5–1	≥2	**(33) Pradofloxacin breakpoints were determined using a dose of 3 mg/kg once daily of an oral tablet or 5 mg/kg once daily of an oral suspension for cats.**
Horses											

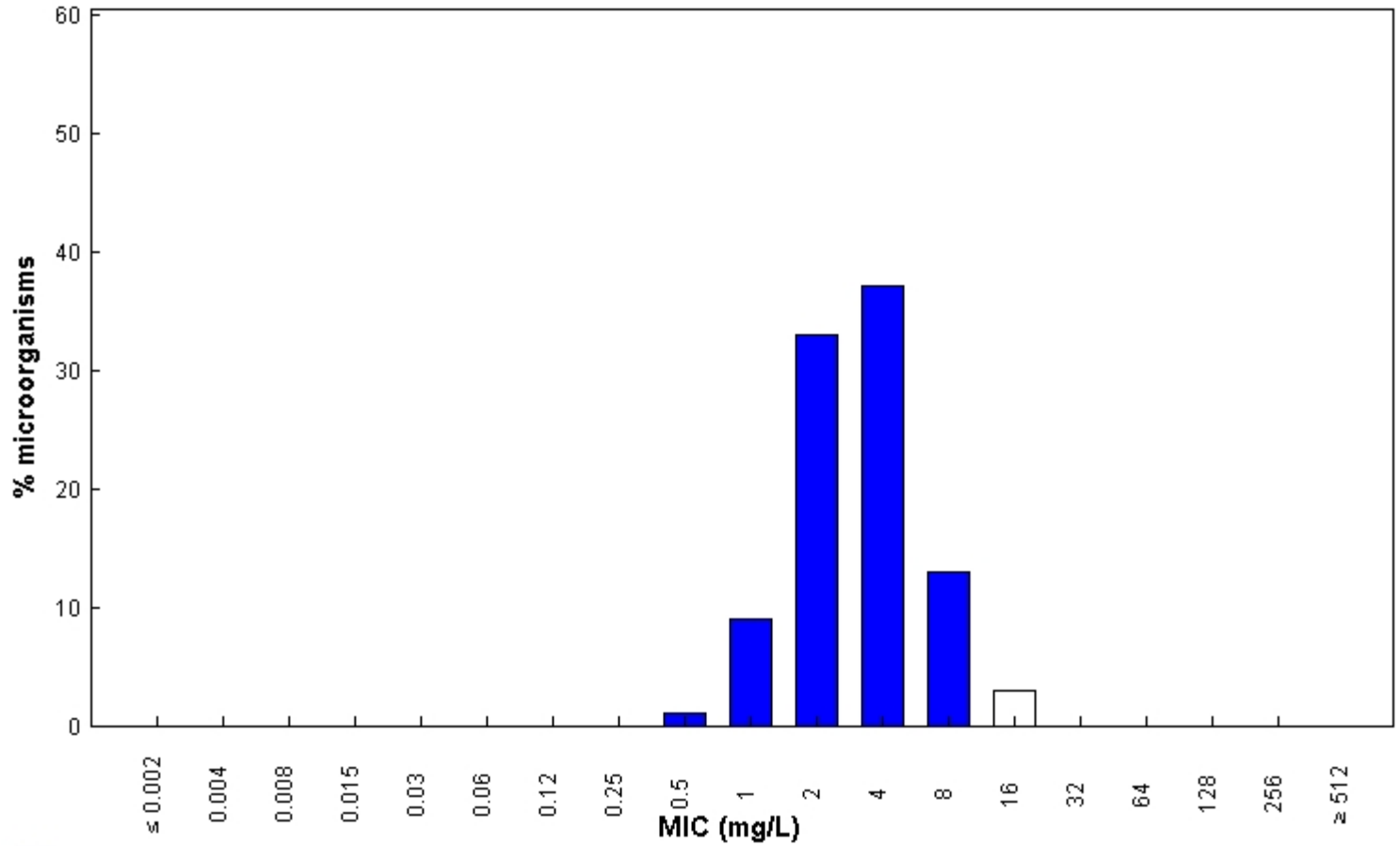
										an oral suspension for cats.
Horses										
A	Skin, soft tissue, respiratory	Enrofloxacin	*E. coli*	–	–	–	–	≤0.12	0.25	≥0.5	(34) Enrofloxacin breakpoints were determined from an examination of MIC distribution data and PK-PD analysis of enrofloxacin, after administration of enrofloxacin at a dose of 7.5 mg/kg every 24 hours orally.

Tetracyclines										
Horses										
A	Respiratory, skin, soft tissue	Doxycycline	*E. coli*	–	–	–	–	≤0.12	0.25	≥0.5	(40) Doxycycline breakpoints were derived from microbiological and PK-PD analysis using a clinical dose of 20 mg/kg, orally, twice daily to horses, and PD data. (41) Do not test tetracycline as a surrogate for doxycycline and minocycline in horses.
A	Respiratory, skin, soft tissue	Minocycline	*E. coli*	–	–	–	–	≤0.12	0.25	≥0.5	(42) Minocycline breakpoints were derived from microbiological and PK-PD analysis using a clinical dose of 5 mg/kg, orally, twice daily to horses, and PD data. See comment (41).

Amikacin / Proteus mirabilis

International MIC Distribution - Reference Database 2019-06-13

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): 8 mg/L

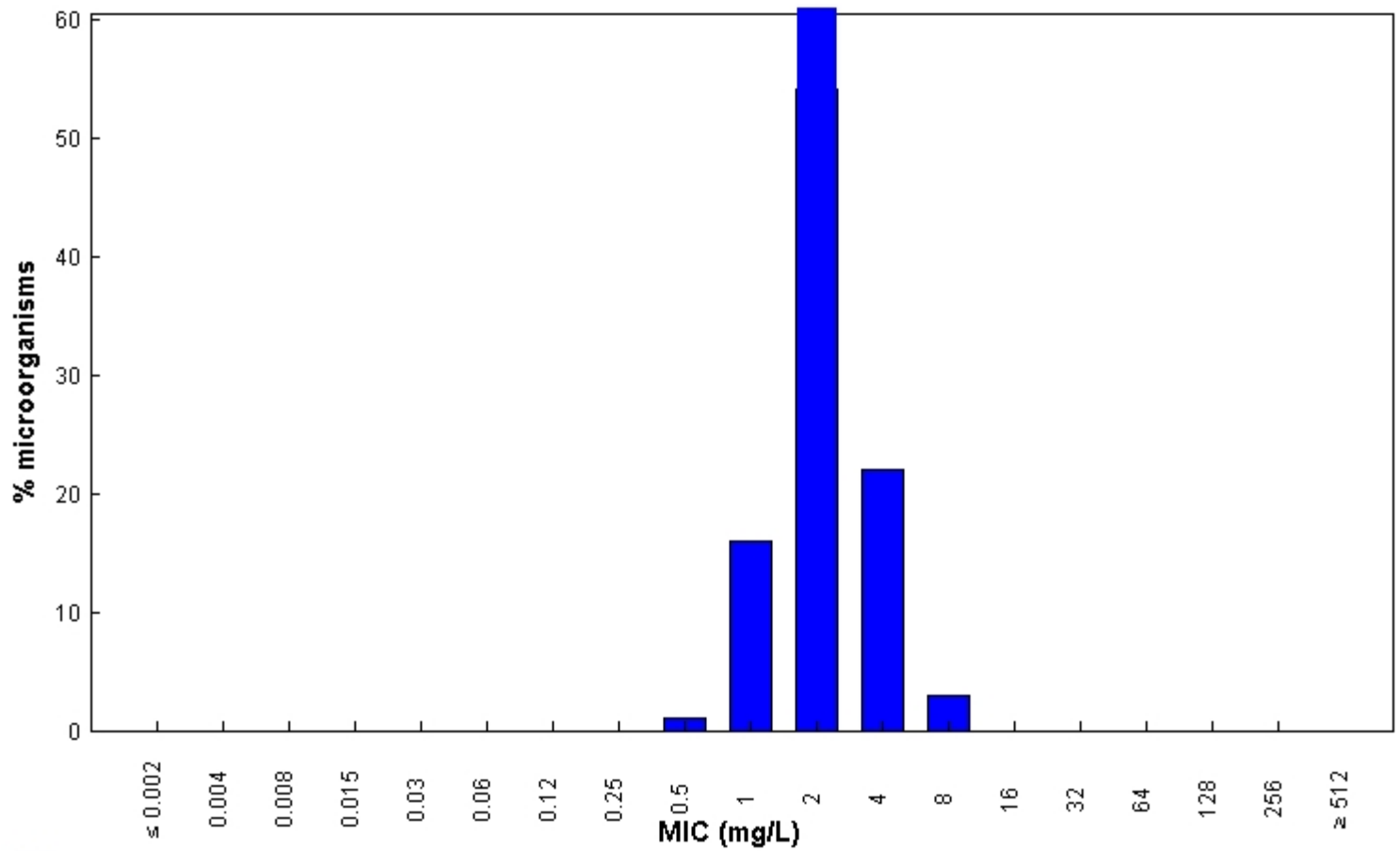
Wildtype (WT) organisms: ≤ 8 mg/L

4007 observations (7 data sources)

Amikacin / Escherichia coli

International MIC Distribution - Reference Database 2019-06-13

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): 8 mg/L

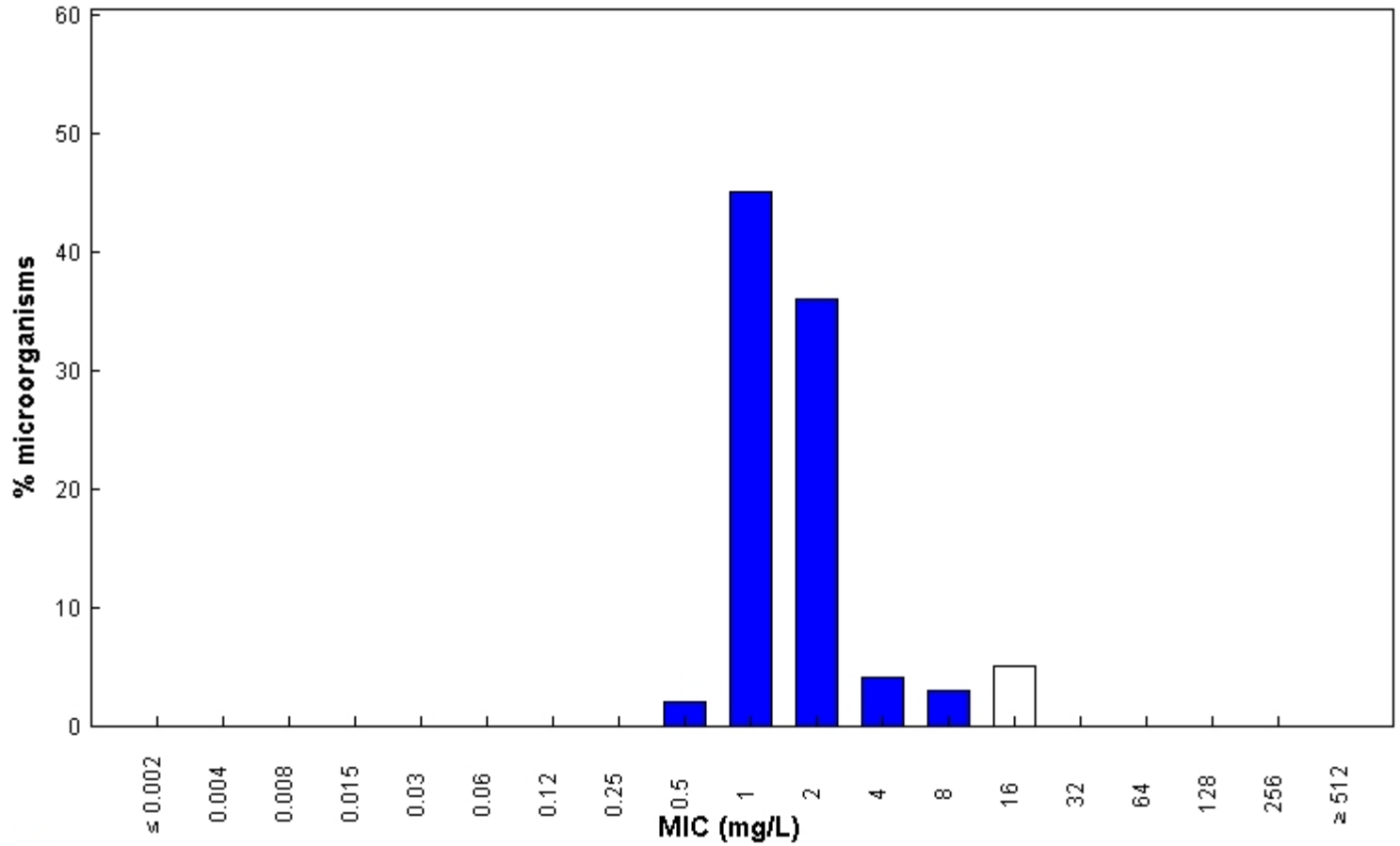
Wildtype (WT) organisms: ≤ 8 mg/L

28672 observations (22 data sources)

Amikacin / Klebsiella pneumoniae

International MIC Distribution - Reference Database 2019-06-13

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): 8 mg/L

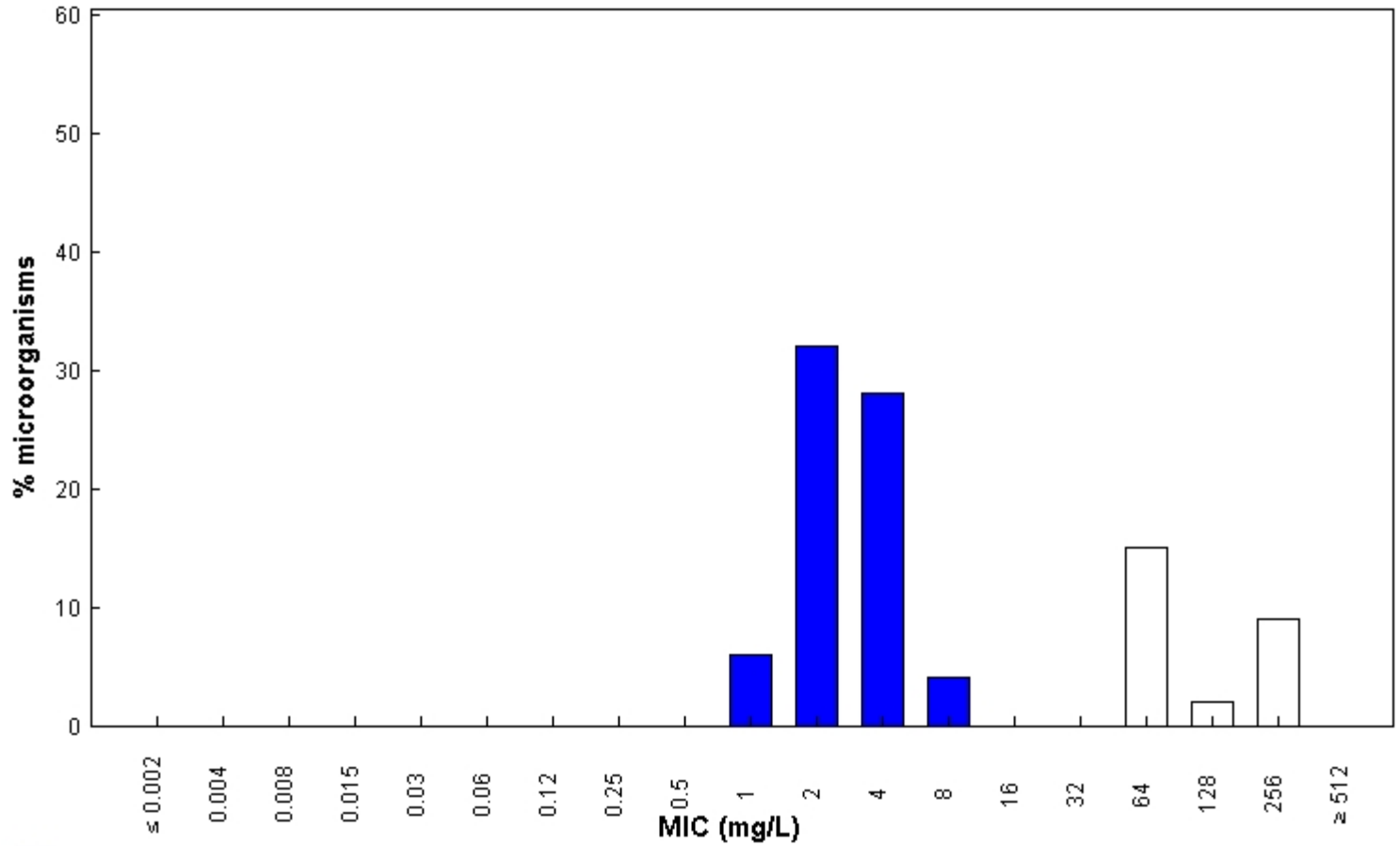
Wildtype (WT) organisms: ≤ 8 mg/L

11045 observations (5 data sources)

Ampicillin / Escherichia coli

International MIC Distribution - Reference Database 2019-06-13

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



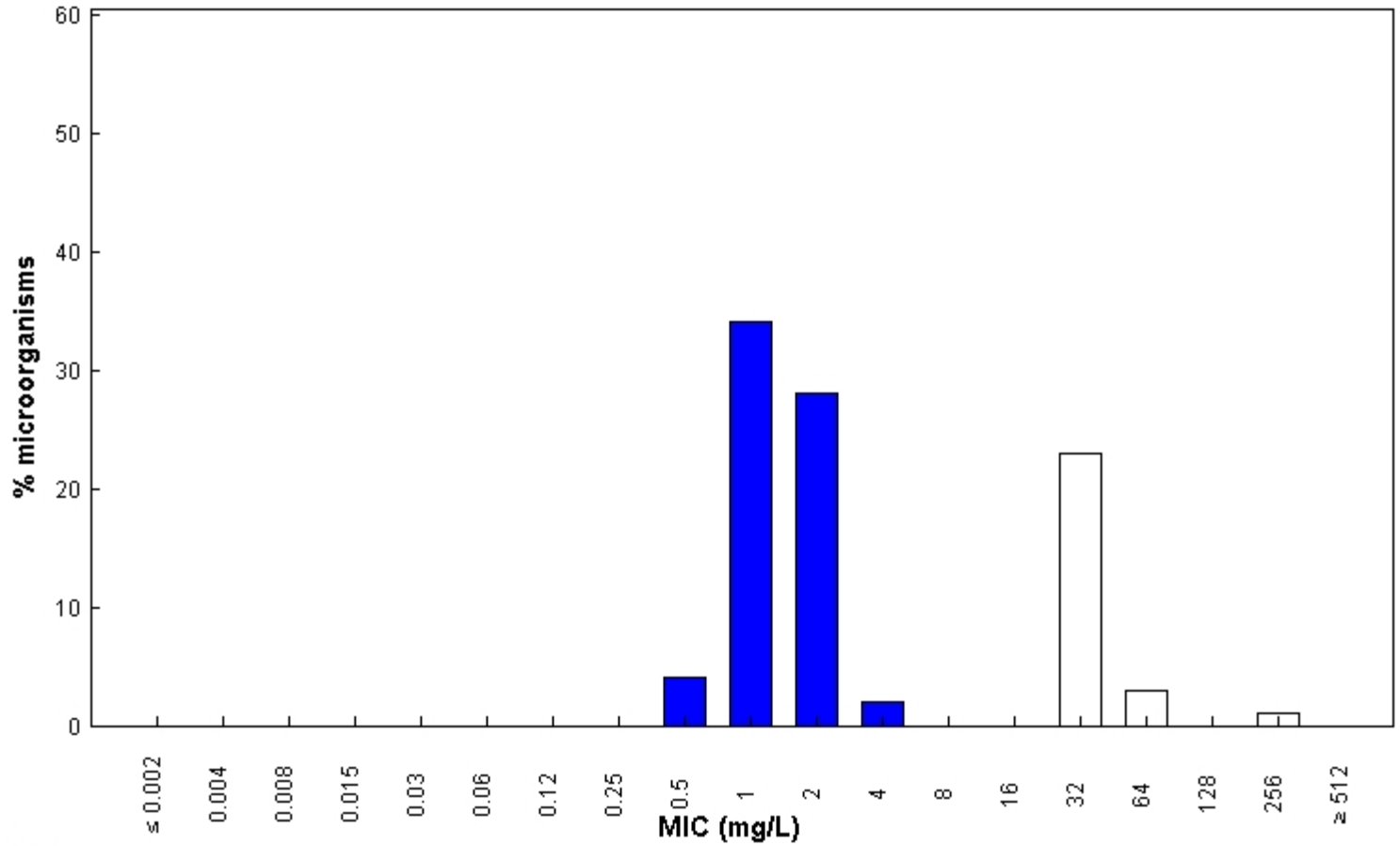
MIC
Epidemiological cut-off (ECOFF): 8 mg/L
Wildtype (WT) organisms: ≤ 8 mg/L

73390 observations (52 data sources)

Ampicillin / Proteus mirabilis

International MIC Distribution - Reference Database 2019-06-13

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): 8 mg/L

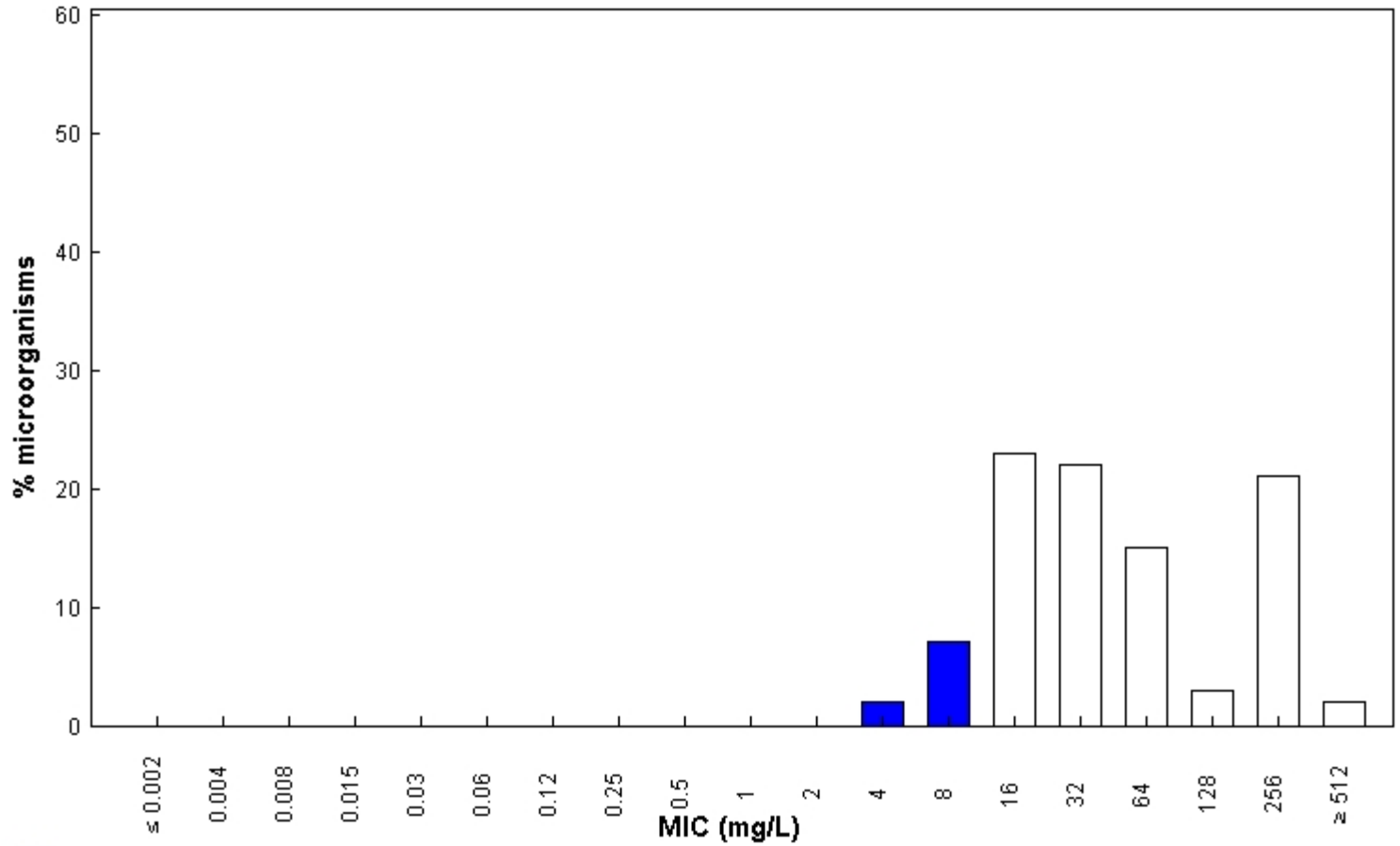
Wildtype (WT) organisms: ≤ 8 mg/L

4544 observations (8 data sources)

Ampicillin / Klebsiella pneumoniae

International MIC Distribution - Reference Database 2019-06-13

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): 8 mg/L

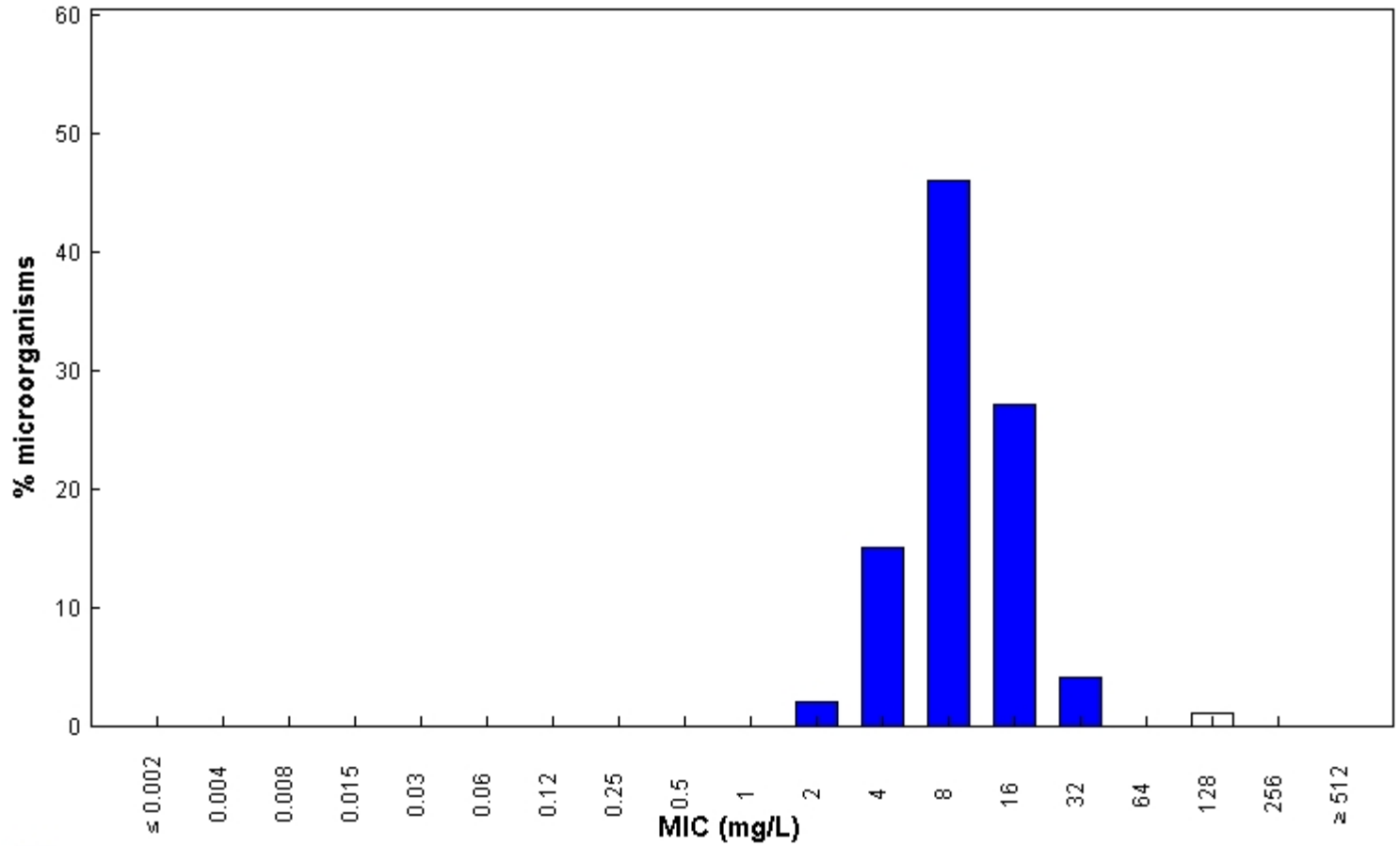
Wildtype (WT) organisms: ≤ 8 mg/L

3948 observations (8 data sources)

Cefalothin / Escherichia coli

International MIC Distribution - Reference Database 2019-06-13

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



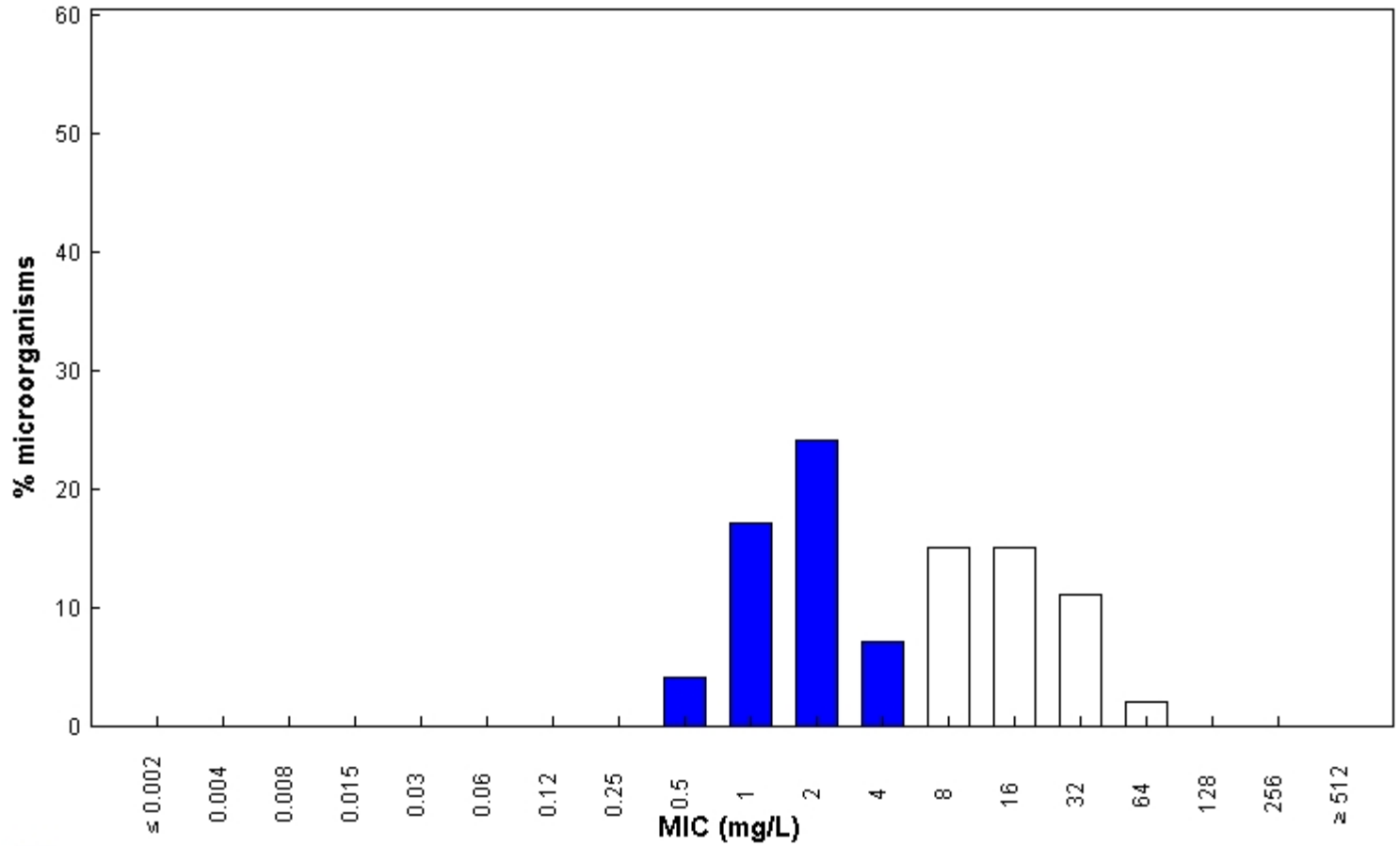
MIC
Epidemiological cut-off (ECOFF): 32 mg/L
Wildtype (WT) organisms: ≤ 32 mg/L

3861 observations (14 data sources)

Doxycycline / Escherichia coli

International MIC Distribution - Reference Database 2019-06-13

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

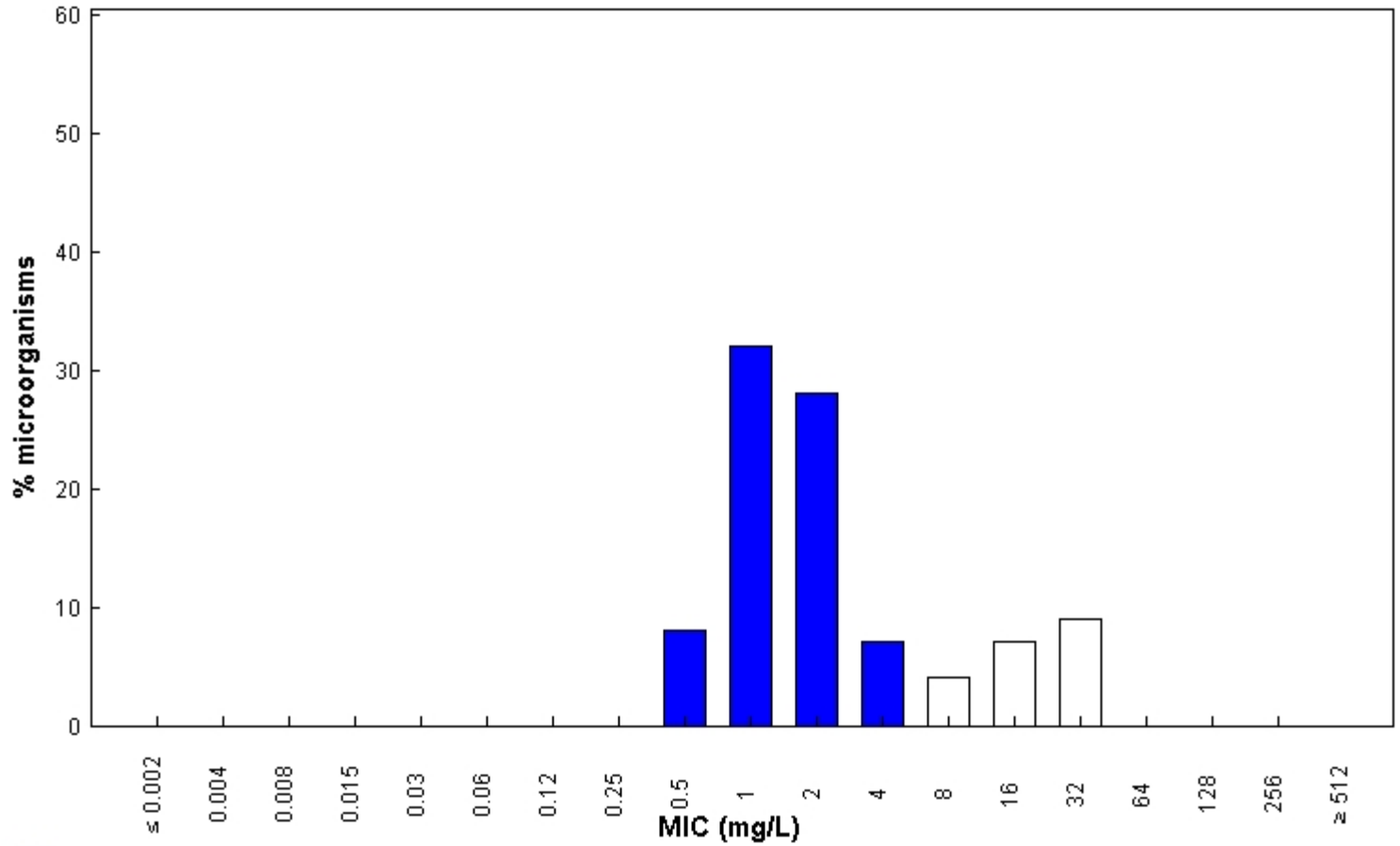
Wildtype (WT) organisms: ≤ 4 mg/L

5028 observations (17 data sources)

Doxycycline / Klebsiella pneumoniae

International MIC Distribution - Reference Database 2019-06-13

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



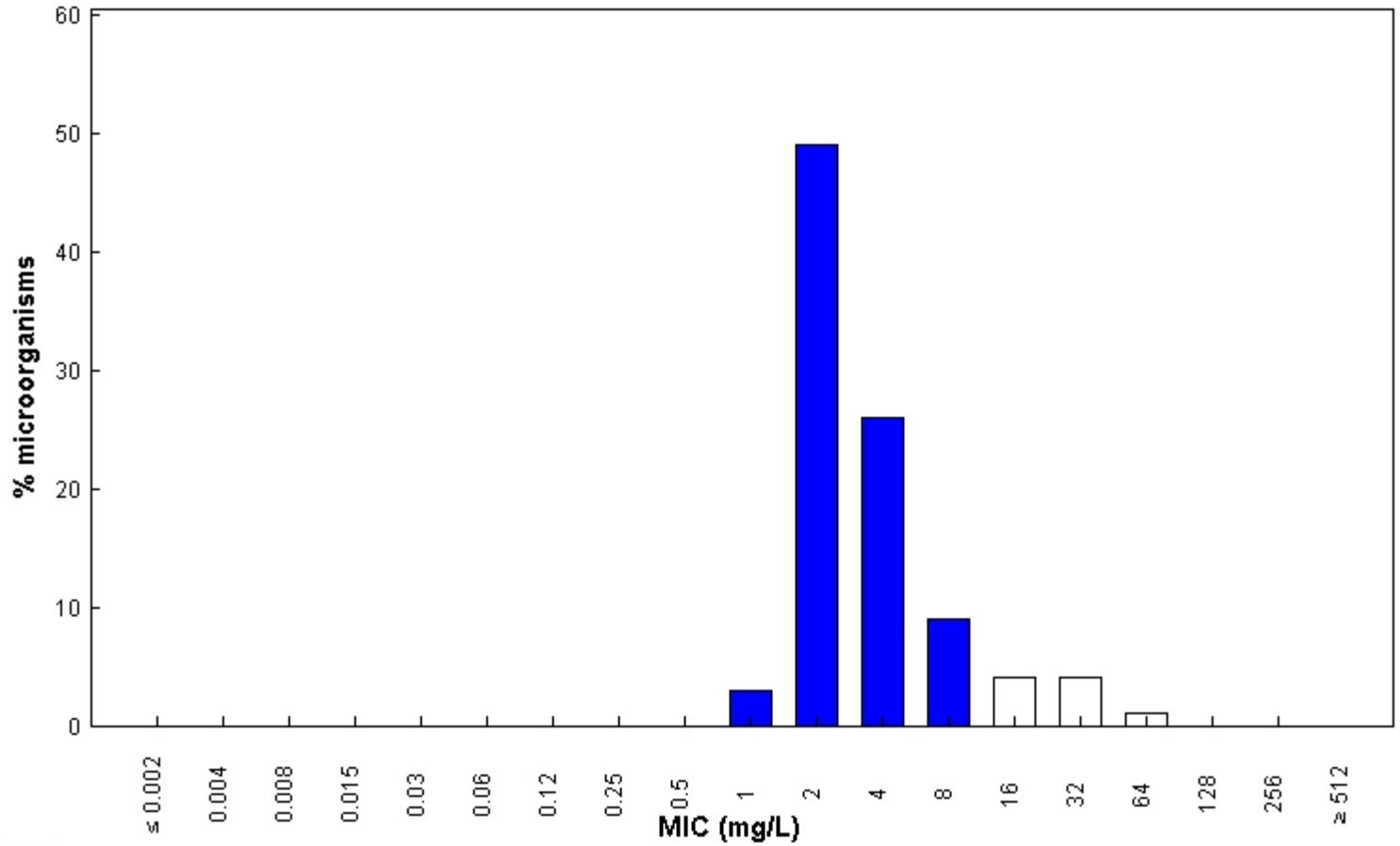
MIC
Epidemiological cut-off (ECOFF): 4 mg/L
Wildtype (WT) organisms: ≤ 4 mg/L

481 observations (2 data sources)

Doxycycline / Salmonella spp

International MIC Distribution - Reference Database 2019-06-13

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): 8 mg/L

Wildtype (WT) organisms: ≤ 8 mg/L

6839 observations (5 data sources)

January 2019 Action Items

Item #8

“Review other veterinary-specific breakpoints set by the GWG to determine whether other GWG breakpoints for E. coli *should be changed to Enterobacteriaceae, or left as E. coli.”*

Should these be converted to Enterobacteriaceae?

Thank you.

Any Questions?

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