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## Revised Abstract

**Background:** *E. coli* (Ec) remains a frequent cause of both community and hospital infections. Increasingly these isolates are multi-drug resistant and pose therapeutic challenges especially in paediatric populations where fluoroquinolones are generally contraindicated. The Tigecycline Evaluation and Surveillance Trial (TEST) has monitored trends in susceptibility of tigecycline and comparators globally since 2004. This report evaluates the *in vitro* activity of tigecycline and comparators to *E. coli* isolated from paediatric patients in North America (NA) and Europe (EU) utilizing continent-specific breakpoints (NA:FDA/CLSI, EU:EUCAST). **Methods:** In 2006-2009, 1,138 Ec (NA: 598, EU: 540) were collected in NA (Mexico, USA, Canada) and EU (26 countries). MICs were determined using supplied broth microdilution panels and interpreted according to CLSI (NA) or EUCAST (EU) breakpoints (BPs). **Results:** Summary data for tigecycline and comparators (% Susceptible) are shown by year and continent.

	Paediatric <i>E. coli</i> : % Susceptible							
	2006		2007		2008		2009	
	NA	EU	NA	EU	NA	EU	NA	EU
n=	212	99	220	129	110	210	56	102
Amikacin	99.0	85.0	99.6	96.9	100	92.1	100	93.6
Amox-clav	75.0	61.0	74.1	70.5	76.4	65.3	68.7	61.4
Cefepime	98.6	78.0	95.5	91.5	98.2	79.2	99.0	75.4
Ceftriaxone	95.0	78.0	92.7	90.0	95.5	77.8	97.0	71.9
Meropenem	97.6	100	99.1	100	84.6	99.5	100	99.7
Pip-tazo	97.7	94.0	97.3	93.0	96.4	84.7	96.0	85.4
Tigecycline	100	98.0	100	98.5	100	100	100	99.1

**Conclusions:** Decreased susceptibility of Ec to cefepime, ceftriaxone, minocycline and pip-tazo in EU vs NA in some study years may reflect lower susceptible BPs in EU vs NA. Detailed analysis of resistant isolates on both continents to confirm isolate distributions is needed.

## Introduction

*Escherichia coli* remains a frequent cause of both community and hospital infections and is a major cause of bloodstream and urinary tract infections worldwide. Increasingly these isolates are multi-drug resistant and pose therapeutic challenges especially in paediatric populations where fluoroquinolones are generally contraindicated. The Tigecycline Evaluation and Surveillance Trial (TEST) has monitored trends in susceptibility of tigecycline and comparators globally since 2004. This report evaluates the *in vitro* activity of tigecycline and comparators to *E. coli* isolated from paediatric patients in North America and Europe utilizing continent-specific breakpoints.

## Materials & Methods

- Isolates were identified to the species level and MICs determined at each participating laboratory. All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age, or gender. All sites identified each study isolate utilizing local laboratory criteria, with identification confirmed at International Health Management Associates (IHMA). All isolates were from the period 2006 - 2009 and originated in 26 countries in Europe (n=540) and three countries in North America (Mexico, USA, Canada, n=598).
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [1]. Tigecycline was supplied by Pfizer Inc. (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, Trek (TREK Diagnostic Systems, Cleveland, OH). The following antimicrobial agents were included on the panel: amikacin, amoxicillin-clavulanic acid (amox-clav), ampicillin, cefepime, ceftazidime, imipenem (2006 only), meropenem, minocycline, levofloxacin, tigecycline, piperacillin-tazobactam (pip-tazo), and ceftriaxone. MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [2] and the US Food and Drug Administration package insert for tigecycline [3] for North American isolates, and The European Committee on Antimicrobial Susceptibility Testing (EUCAST) [4] for European isolates.
- Quality controls (QC) were performed by each testing site on each day of testing using the appropriate ATCC control strains. Results were included in the analysis only when corresponding QC isolates tested were within the acceptable range according to CLSI guidelines [2].

## References

- Clinical Laboratory Standards Institute. 2009. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards -- Eighth Edition. CLSI document M07-A8. Wayne, PA.
- Clinical and Laboratory Standards Institute. 2011. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-First Informational Supplement. CLSI Document M100-S21. Wayne, PA.
- Tygacil®, 2010. Tigecycline FDA prescribing information. Pfizer, Inc., Collegeville, PA.
- The European Committee on Antimicrobial Susceptibility Testing – EUCAST Clinical Breakpoints 2010; [http://www.eucast.org/clinical\\_breakpoints/](http://www.eucast.org/clinical_breakpoints/)

## Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline Evaluation and Surveillance Trial program group. This study was sponsored by Pfizer Inc.

## Results

Figure 1. Isolate counts by source of specimen, European paediatric *E. coli* (n=540).

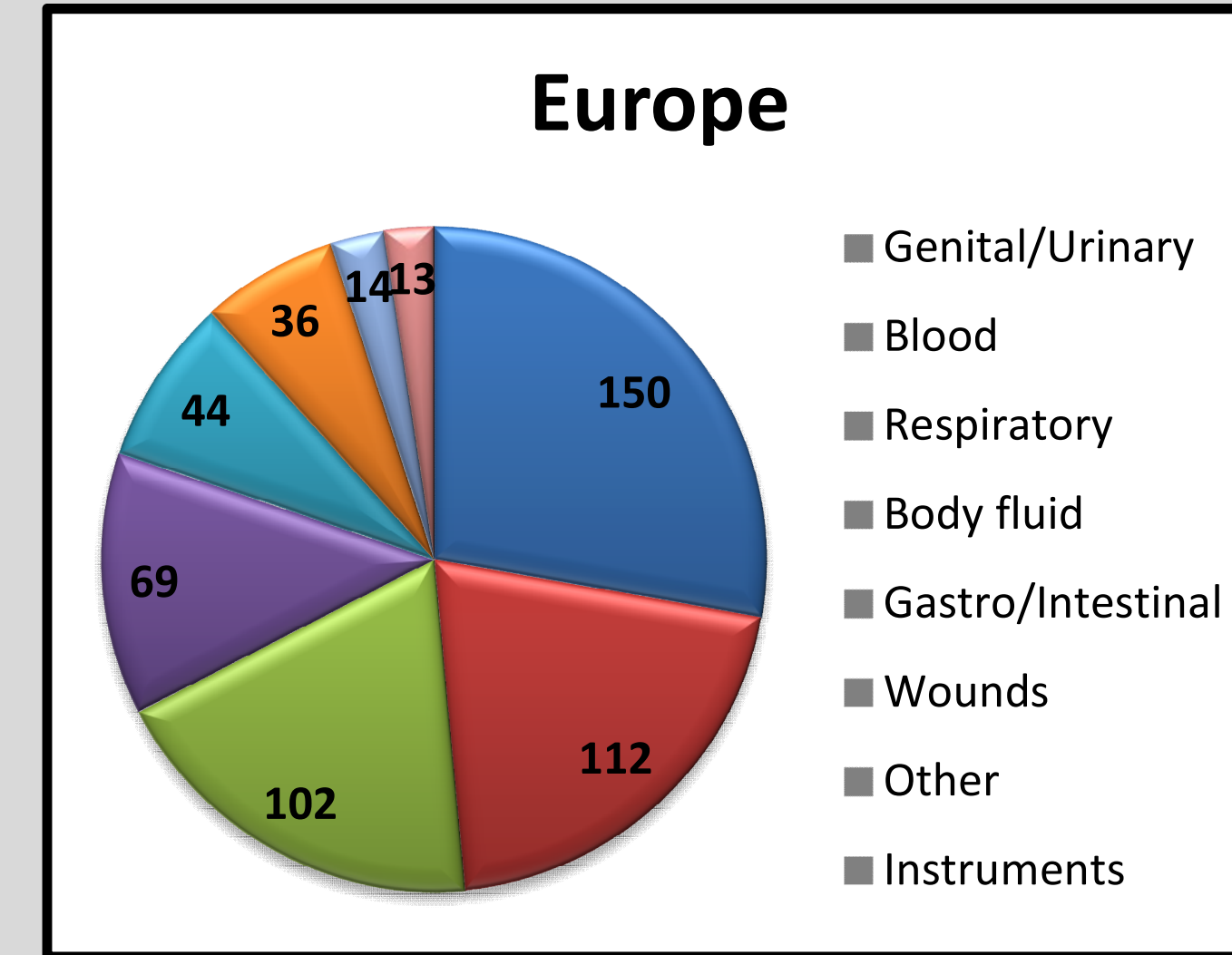


Table 2. Activity of tigecycline and comparators against paediatric *E. coli* from North America, 2006-2009.

Drug	N	MIC <sub>50</sub>	MIC <sub>90</sub>	%S <sup>a</sup>	%I	%R
Tigecycline	598	0.12	0.5	100	0	0
Amikacin	598	2	8	99.5	0.2	0.3
Imipenem <sup>b</sup>	136	0.25	0.5	99.3	0	0.7
Meropenem	462	≤ 0.06	≤ 0.06	98.9	0.4	0.7
Pip-tazo	598	1	4	97.5	1.0	1.5
Cefepime	598	≤ 0.5	≤ 0.5	97.3	0.7	2.0
Ceftriaxone	598	≤ 0.06	0.25	94.5	0.3	5.2
Levofloxacin	598	0.03	8	86.8	1.0	12.2
Amox-clav	598	8	32	74.1	14.4	11.5
Ampicillin	598	> 32	> 32	43.0	1.2	55.9

<sup>a</sup> Interpretive criteria are defined by CLSI where available; Tigecycline breakpoints are defined by the FDA.  
<sup>b</sup> Meropenem replaced imipenem on TEST panel in 2006.

Figure 5. Comparison of percent susceptible of European (EU) and North American (NA) paediatric *E. coli* isolates using EUCAST breakpoints for EU isolates and CLSI breakpoints for NA isolates (FDA breakpoint for tigecycline).

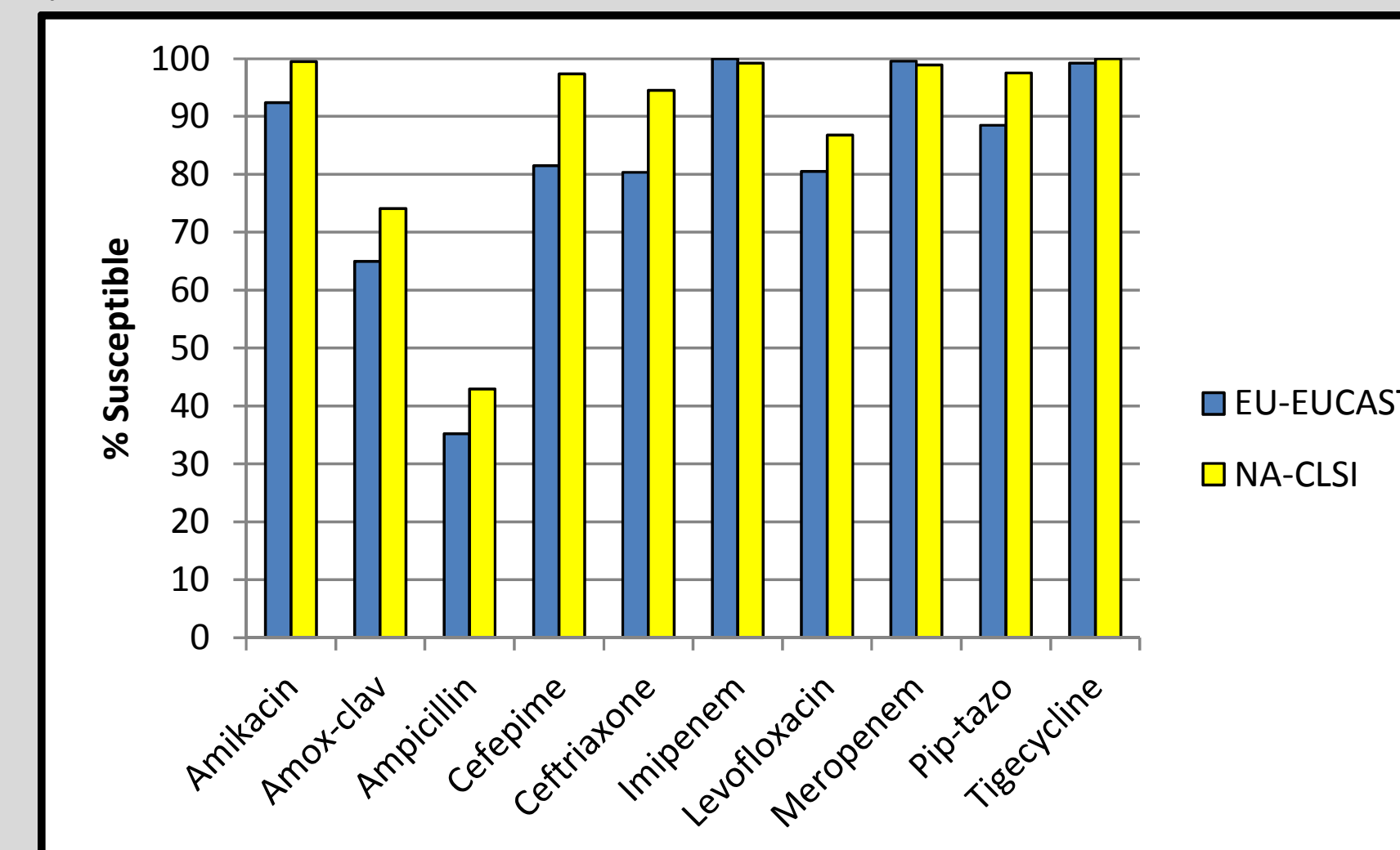


Figure 2. Isolate counts by source of specimen, North American paediatric *E. coli* (n=598).

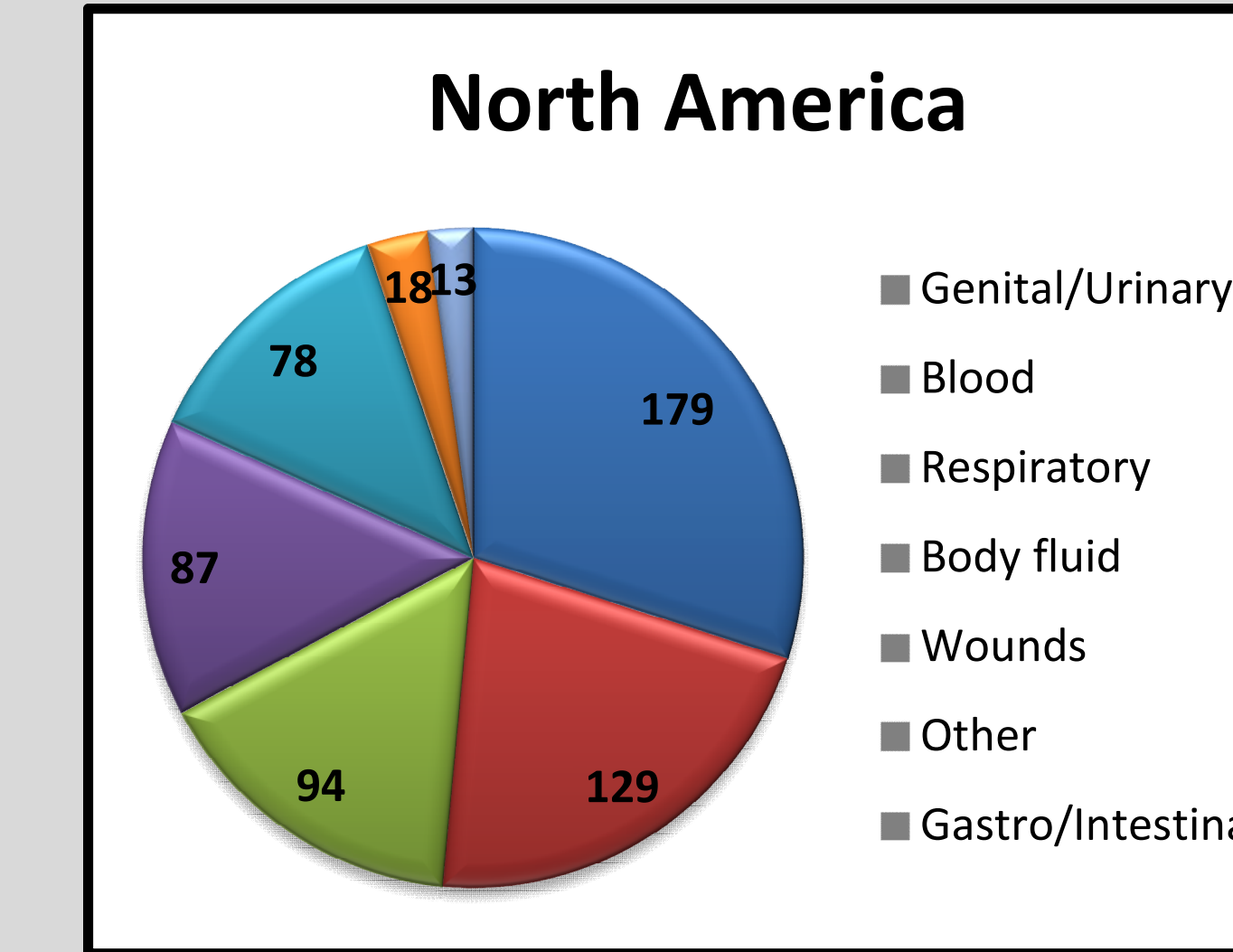


Figure 3. Percent susceptible of paediatric *E. coli* from Europe from 2006-2009.

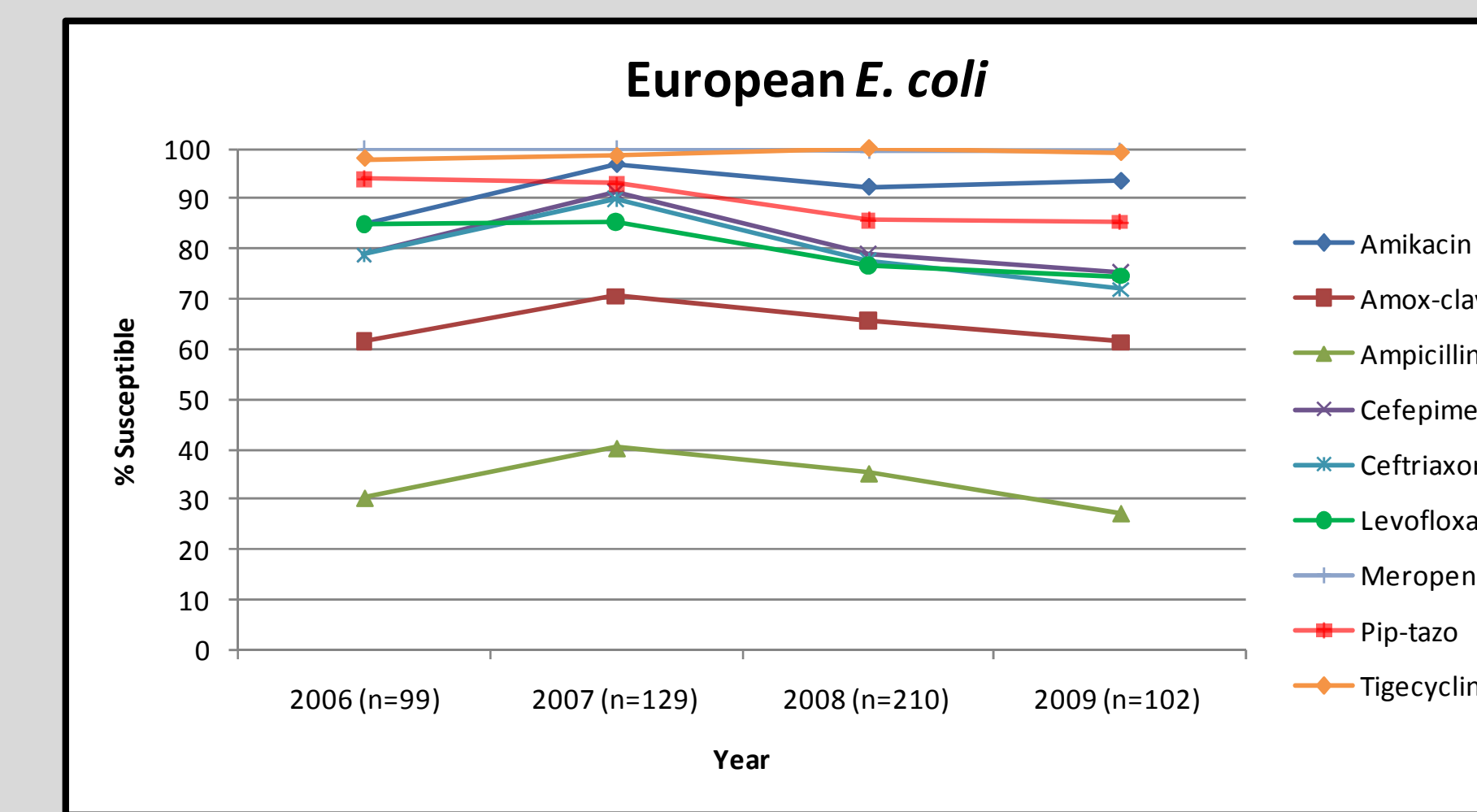
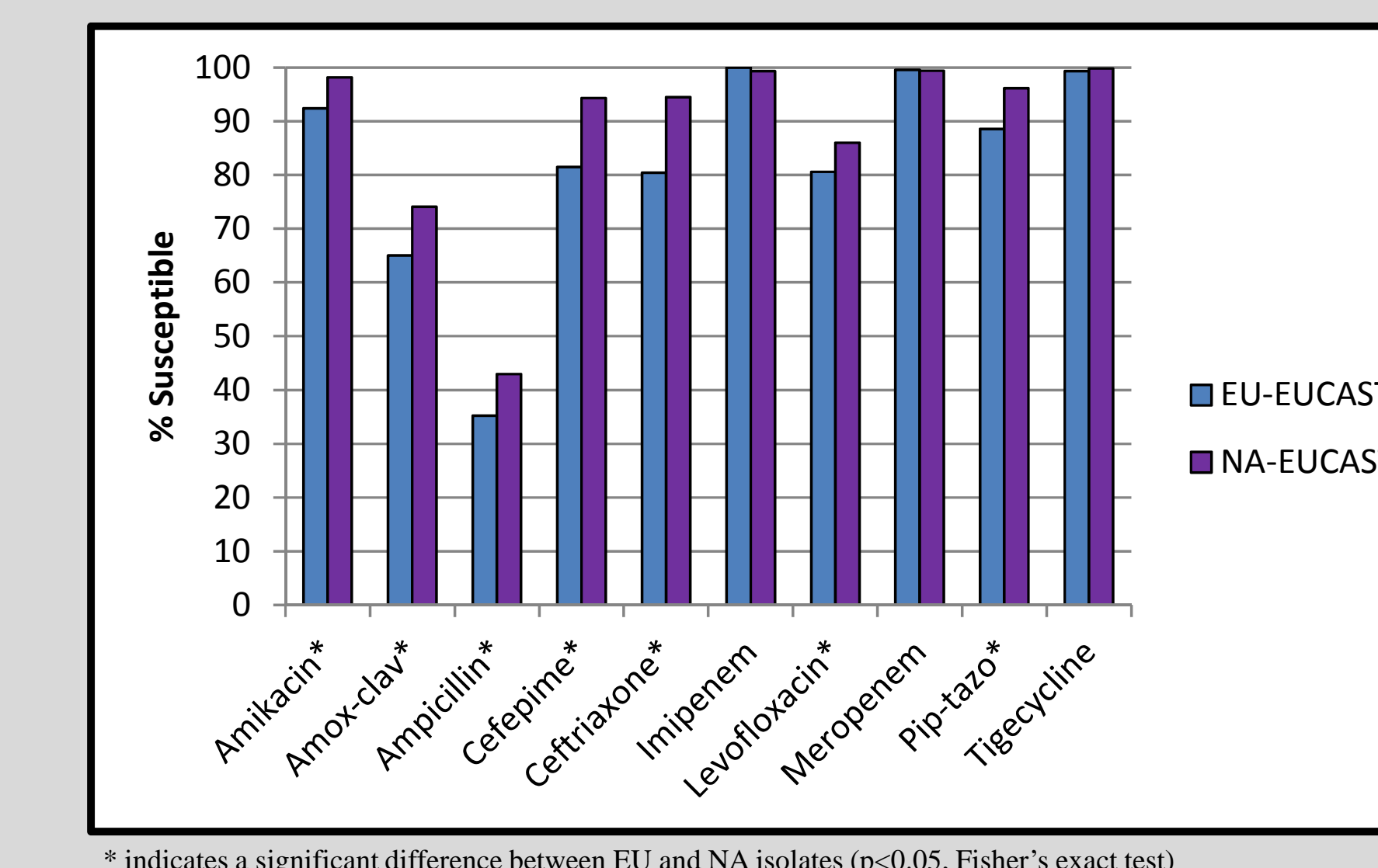


Figure 6. Comparison of percent susceptible of European (EU) and North American (NA) paediatric *E. coli* isolates using EUCAST breakpoints for all isolates.



\* indicates a significant difference between EU and NA isolates (p<0.05, Fisher's exact test)

Table 1. Activity of tigecycline and comparators against paediatric *E. coli* from Europe, 2006-2009.

Drug	N	MIC <sub>50</sub>	MIC <sub>90</sub>	%S <sup>a</sup>	%I	%R
Tigecycline	540	0.25	0.5	99.3	0.7	0
Amikacin	540	2	8	92.4	3.0	4.6
Imipenem <sup>b</sup>	79	≤ 0.06	0.25	100	0	0
Meropenem	461	≤ 0.06	≤ 0.06	99.6	0.4	0
Pip-tazo	540	2	16	88.5	2.2	9.3
Cefepime	540	≤ 0.5	16	81.5	6.3	12.2
Levofloxacin	540	0.03	> 8	80.6	0.4	19.1
Ceftriaxone	540	≤ 0.06	> 64	80.4	1.3	18.3
Amox-clav	540	8	32	65.0	- <sup>c</sup>	35.0
Ampicillin	540	> 32	> 32	35.2	-	64.8

<sup>a</sup> Interpretive criteria are defined by EUCAST.  
<sup>b</sup> Meropenem replaced imipenem on TEST panel in 2006.  
<sup>c</sup> No defined intermediate breakpoint.

Figure 4. Percent susceptible of paediatric *E. coli* from North America from 2006-2009.

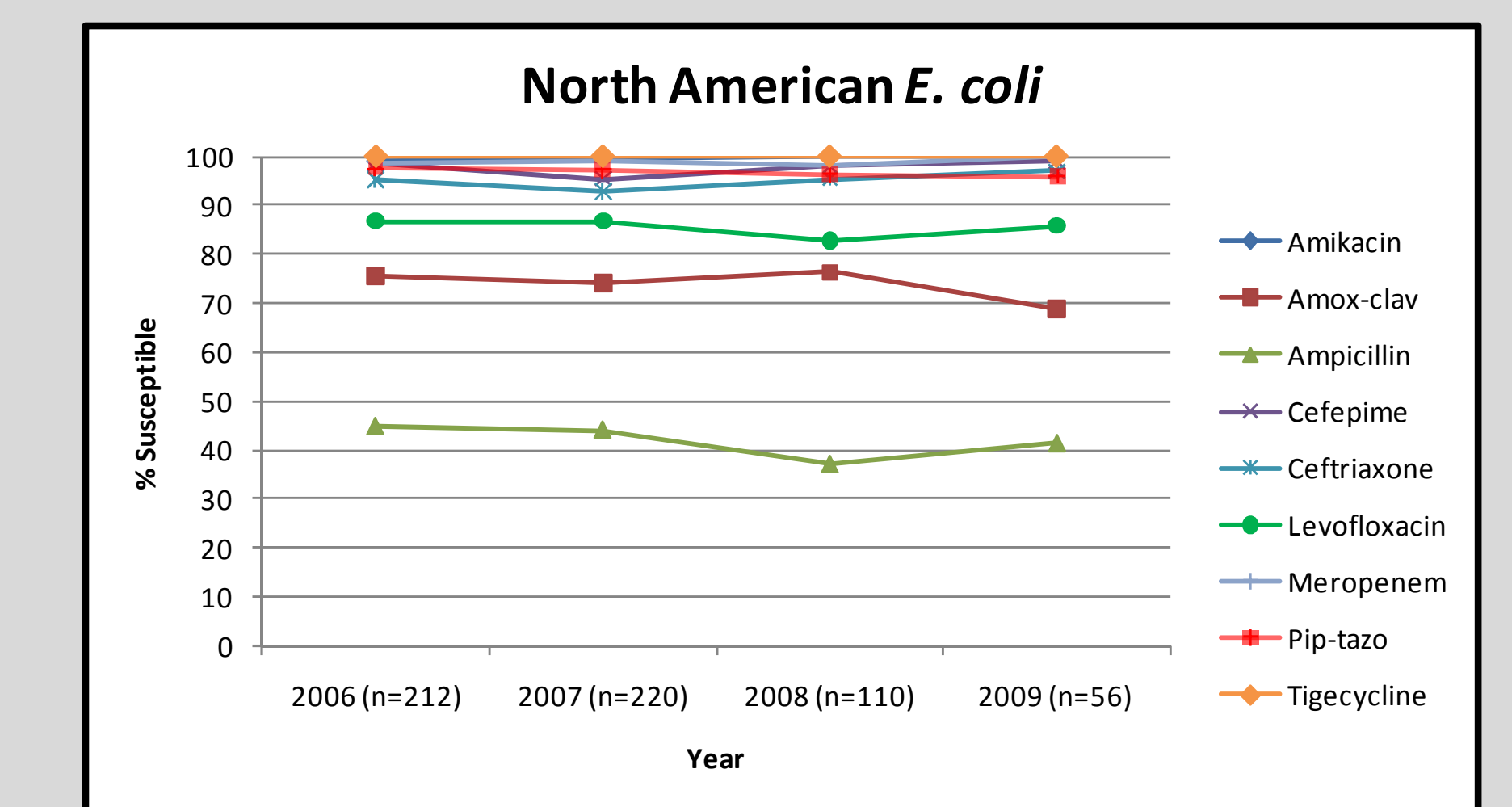
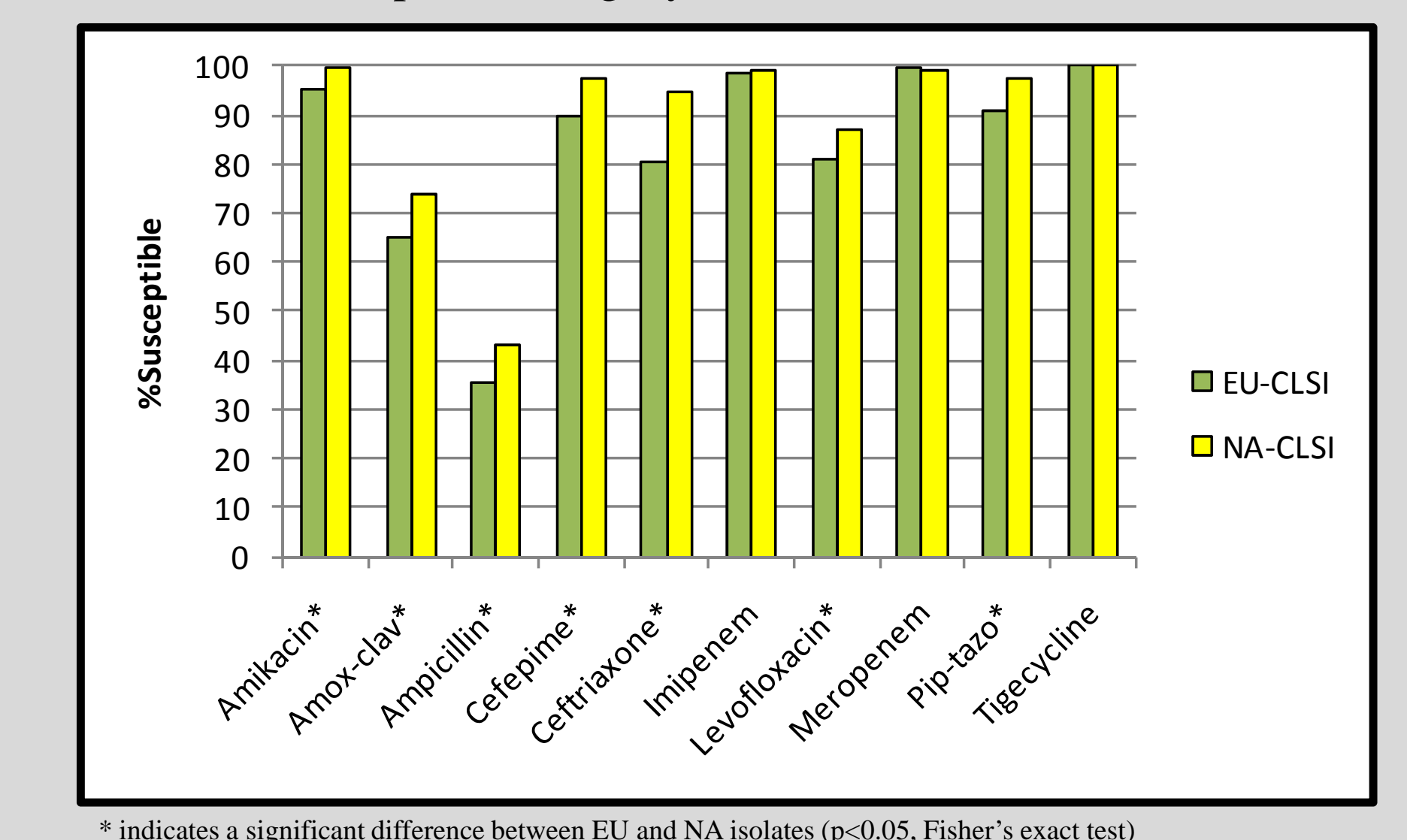


Figure 7. Comparison of percent susceptible of European (EU) and North American (NA) paediatric *E. coli* isolates using CLSI breakpoints for all isolates (FDA breakpoint for tigecycline).



\* indicates a significant difference between EU and NA isolates (p<0.05, Fisher's exact test)

## Conclusions

- No significant decrease in susceptibility was noted for any antimicrobial from 2006 to 2009 in European or North American *E. coli* isolates (p>0.05, Fisher's exact test).
- Significantly lower susceptibilities of *E. coli* isolates from Europe compared to isolates from North America were shown for all antimicrobials tested except imipenem, meropenem and tigecycline when standardizing breakpoints to either EUCAST or CLSI for both sets of isolates.
- Tigecycline, imipenem and meropenem were the most active agents in this *in vitro* study, with >99% all isolates susceptible. >92% of European isolates and >99% of North American isolates were susceptible to amikacin.