

Revised Abstract

Objectives: Tigecycline has demonstrated significant broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative microorganisms. The Tigecycline European Surveillance Trial (TEST) monitors susceptibility of European anaerobic bacteria to tigecycline, cefoxitin, clindamycin, meropenem, piperacillin-tazobactam (pip-tazo), and metronidazole. In this study we evaluated tigecycline and the five comparator compounds against European gram-negative anaerobic isolates from 2007-2010. **Methods:** 2,778 gram-negative anaerobic pathogens were collected and identified from 44 cumulative sites in 6 countries in Europe. MICs of tigecycline and five comparators were determined per EUCAST guidelines using agar dilution at a central laboratory. Percents susceptible (%S) are based on EUCAST breakpoints where available (clindamycin, meropenem, metronidazole, pip-tazo), CLSI (cefoxitin) and the FDA (tigecycline). **Results:** Results are shown below, with MIC values in mg/L:

	<i>B. fragilis</i> group (n=1765)		Other <i>Bacteroides</i> spp. (n=220)		<i>Prevotella</i> spp. (n=793)	
	MIC _{50/90}	%S	MIC _{50/90}	%S	MIC _{50/90}	%S
Tigecycline	0.5/2	98.6	0.25/2	97.3	0.25/1	99.1
Cefoxitin	8/32	80.1	4/32	84.1	≤2/8	97.2
Clindamycin	1/>8	75.9	0.5/>8	75.6	≤0.25/>8	81.1
Meropenem	0.12/0.5	95.0	0.12/1	95.8	≤0.06/0.25	99.5
Metronidazole	0.5/1	100	0.5/2	99.9	0.5/2	99.4
Pip-tazo	0.5/8	90.8	0.5/4	92.5	≤0.06/2	98.4

Conclusions: Tigecycline showed excellent *in vitro* activity against gram-negative anaerobic microorganisms isolated from European hospitals. MIC₅₀ values for tigecycline against all isolates tested were 0.5 mg/L, while MIC₉₀ values were 2 mg/L. Metronidazole also performed well, with MIC_{50/90} values of 0.5/2 or less and %S at >99% for the three pathogen groups tested.

Introduction

Susceptibility patterns of anaerobes have become less predictable owing to increasing antibacterial resistance. To counteract these trends, regular surveillance of the antibiotic susceptibilities of anaerobes is important. At present, metronidazole, penems, and beta-lactam/beta-lactamase inhibitor combinations exhibit the most consistent activity though reports of increasing resistance to these agents are emerging [1]. Recent data from the Tigecycline European Surveillance Trial (TEST) has shown that in addition to the above agents, tigecycline also exhibits promising activity against a wide range of anaerobes including drug-resistant and multi-drug resistant isolates with reports of high percents susceptible [2, 3]. The current study describes data from TEST from 2007 to 2010, based on the activity of tigecycline and comparators against 2,778 gram-negative anaerobic isolates from various European countries.

Materials & Methods

- All isolates were derived from blood, wounds, fluids, lower respiratory, intra-abdominal and various other sources. Isolates were identified to genus and species by the local laboratory. Only one isolate per patient was accepted.
- For this study 2,778 clinical isolates were collected from 2007 to 2010 from 44 cumulative hospitals in six European countries (Belgium, Czech Republic, France, Germany, Hungary and the United Kingdom). The collection and transportation of organisms, confirmation of identification, and construction and management of a centralized database were conducted and coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA).
- Minimum inhibitory concentrations (MICs) were determined following CLSI guidelines for agar dilution [4] at the central laboratory (LIMS). Tigecycline was supplied by Pfizer, Inc. (Collegetown, PA, USA). The following antimicrobial agents were tested with their dilution ranges (expressed in mg/L): tigecycline (0.06-32); clindamycin (0.25-8); metronidazole (0.12-16); piperacillin-tazobactam (pip-tazo, 0.06/4-64/4); meropenem (0.06-8); and cefoxitin (0.25-32).
- MIC interpretive criteria followed published breakpoints established by EUCAST [5] where available, CLSI [6] for cefoxitin and the FDA [7] for tigecycline.
- Quality control followed CLSI guidelines using the following ATCC strains: *Bacteroides fragilis* ATCC 25285, and *Bacteroides thetaiotaomicron* ATCC 29741.
- Gram-negative anaerobes consisted of 1762 *Bacteroides fragilis* group (*B. fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*), 220 other *Bacteroides* spp. and 793 *Prevotella* spp.

References

- Boyanova L, Kolarov R, Mitov I. 2007. *Antimicrobial resistance and the management of anaerobic infections*. Exp Rev Anti Infect Ther. 5: 685-701.
- Nagy E, Dowzicky MJ. 2010. *In vitro activity of tigecycline and comparators against a European compilation of anaerobes collected as part of the Tigecycline Evaluation and Surveillance Trial (TEST)*. Scand. J. Infect. Dis. 2010. 42: 33-38.
- Hawser SP. 2010. *Activity of tigecycline against multidrug-resistant clinical isolates of Clostridium spp. from Europe*. Int. J. Antimicrob. Agents. 35: 310-311.
- 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.
- The European Committee on Antimicrobial Susceptibility Testing – EUCAST. *Clinical Breakpoints*; http://www.eucast.org/clinical_breakpoints/
- 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., Collegetown, PA.

Acknowledgements

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

Results

Figure 1. 2,778 gram-negative anaerobes by specimen type, 2007-2010.

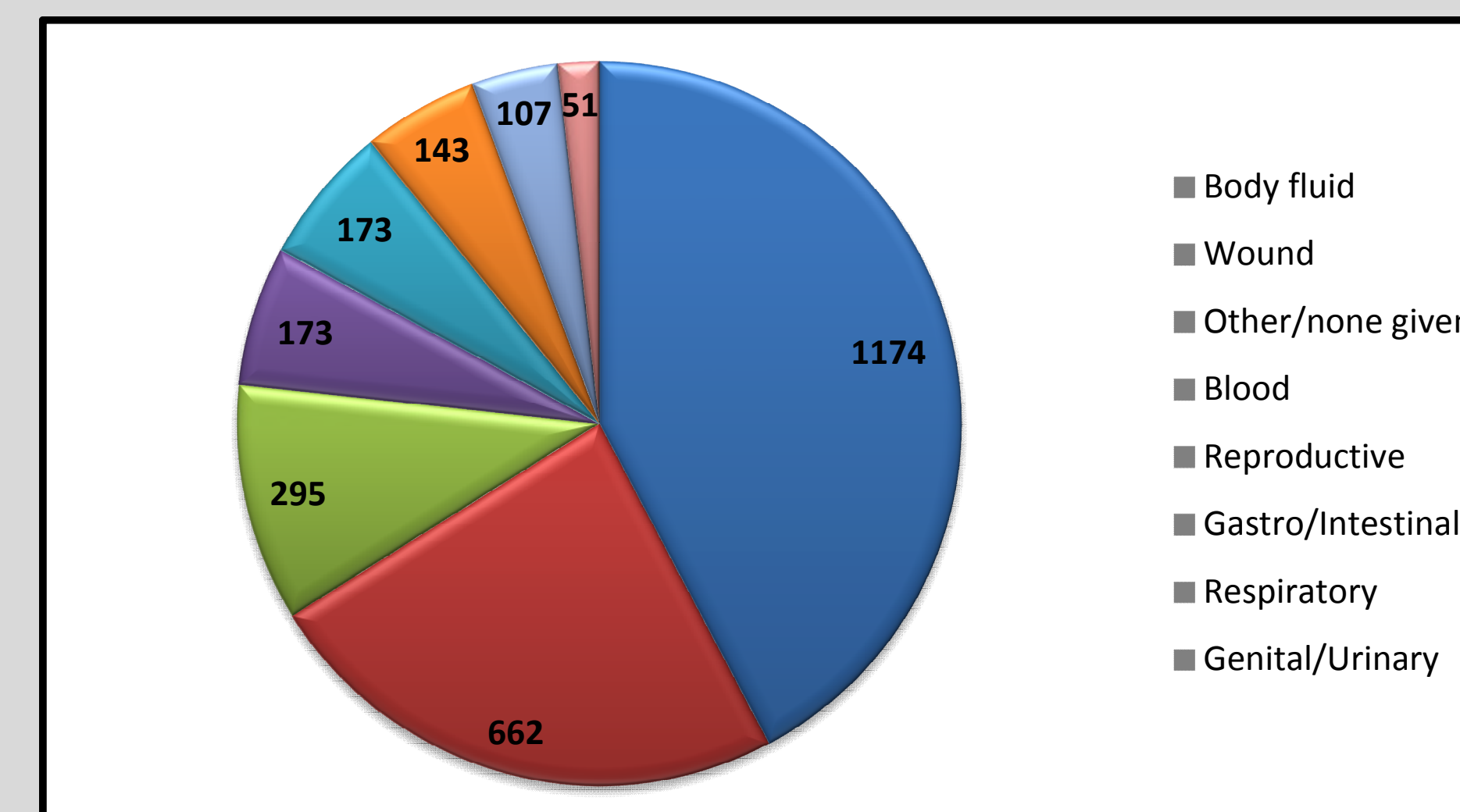


Figure 3. Susceptibility of 220 other *Bacteroides* spp. isolates from 2007-2010.

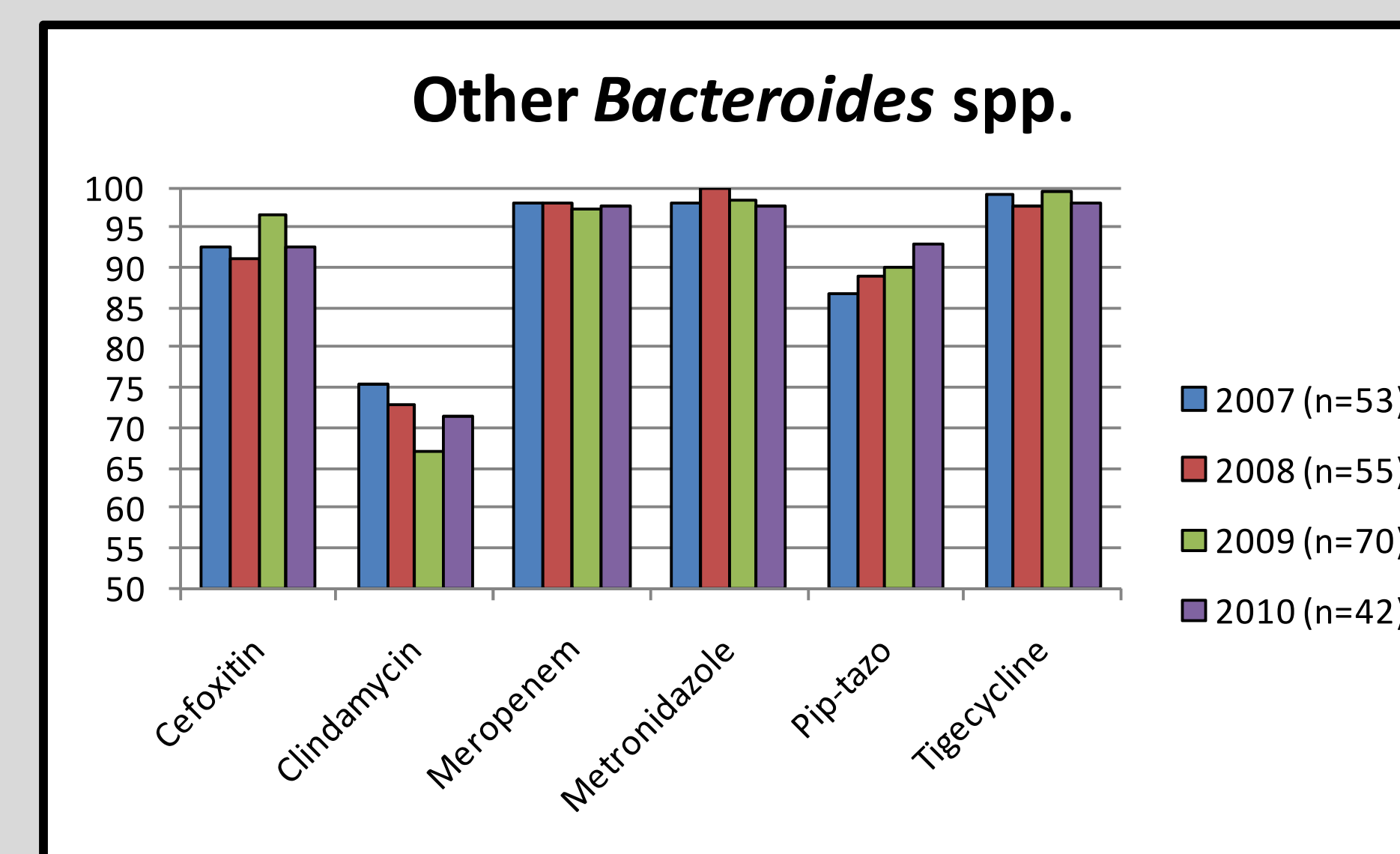


Table 1. Activity of tigecycline and comparators against 2,778 gram-negative anaerobes, 2007-2010.

	MIC ₅₀	MIC ₉₀	%S	%I	%R
Metronidazole	0.5	2	99.6	0	0.4
Tigecycline	0.5	2	97.8	1.4	0.8
Meropenem	0.12	0.5	97.0	2.3	0.7
Pip-tazo	0.25	8	94.0	3.6	2.4
Cefoxitin	4	32	87.5	7.1	5.4
Clindamycin	1	>8	76.9	0.0	23.1

*Interpretive criteria follow published breakpoints established by EUCAST where available, CLSI for cefoxitin and the FDA for tigecycline

Figure 4. Susceptibility of 793 *Prevotella* spp. isolates from 2007-2010.

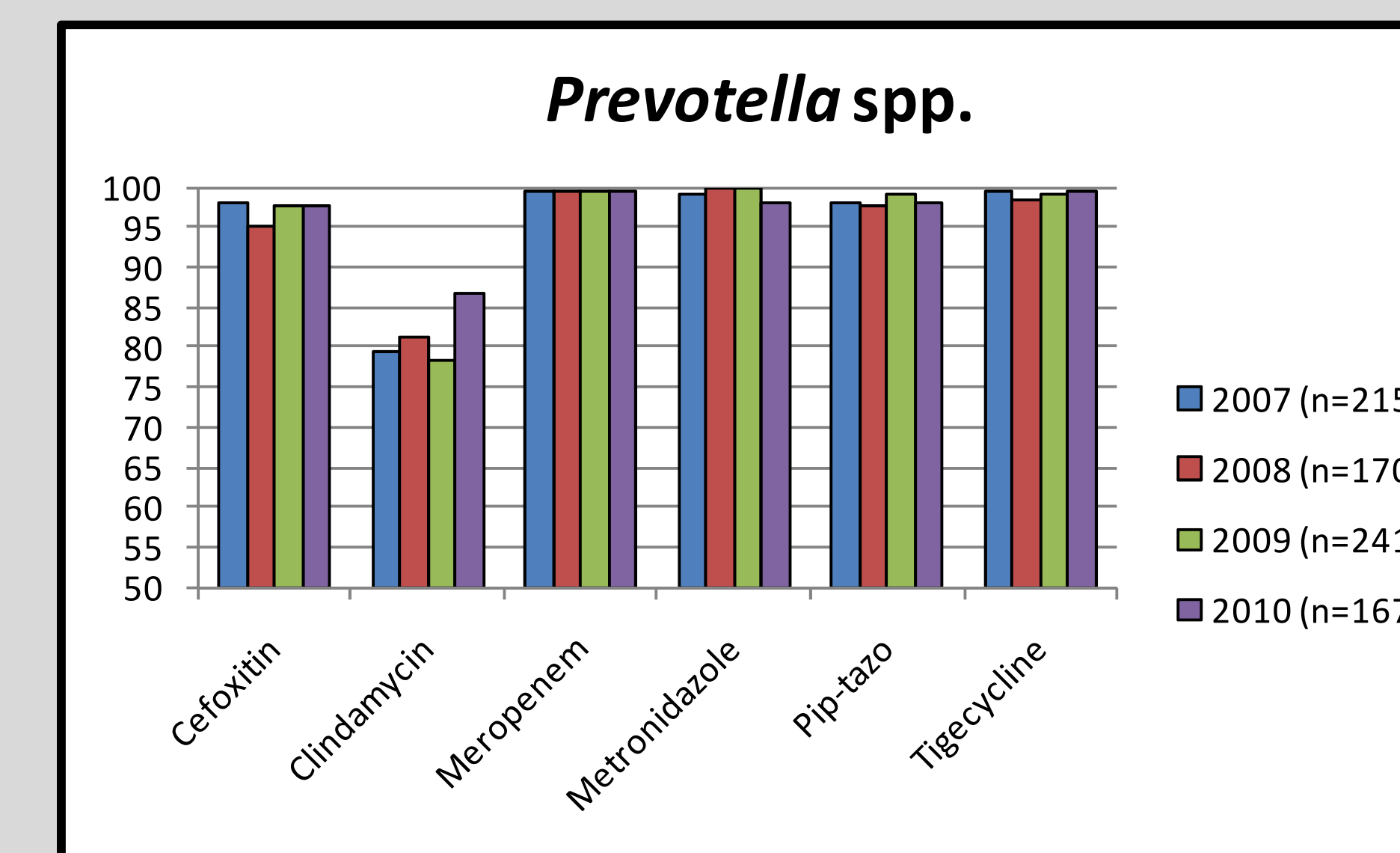
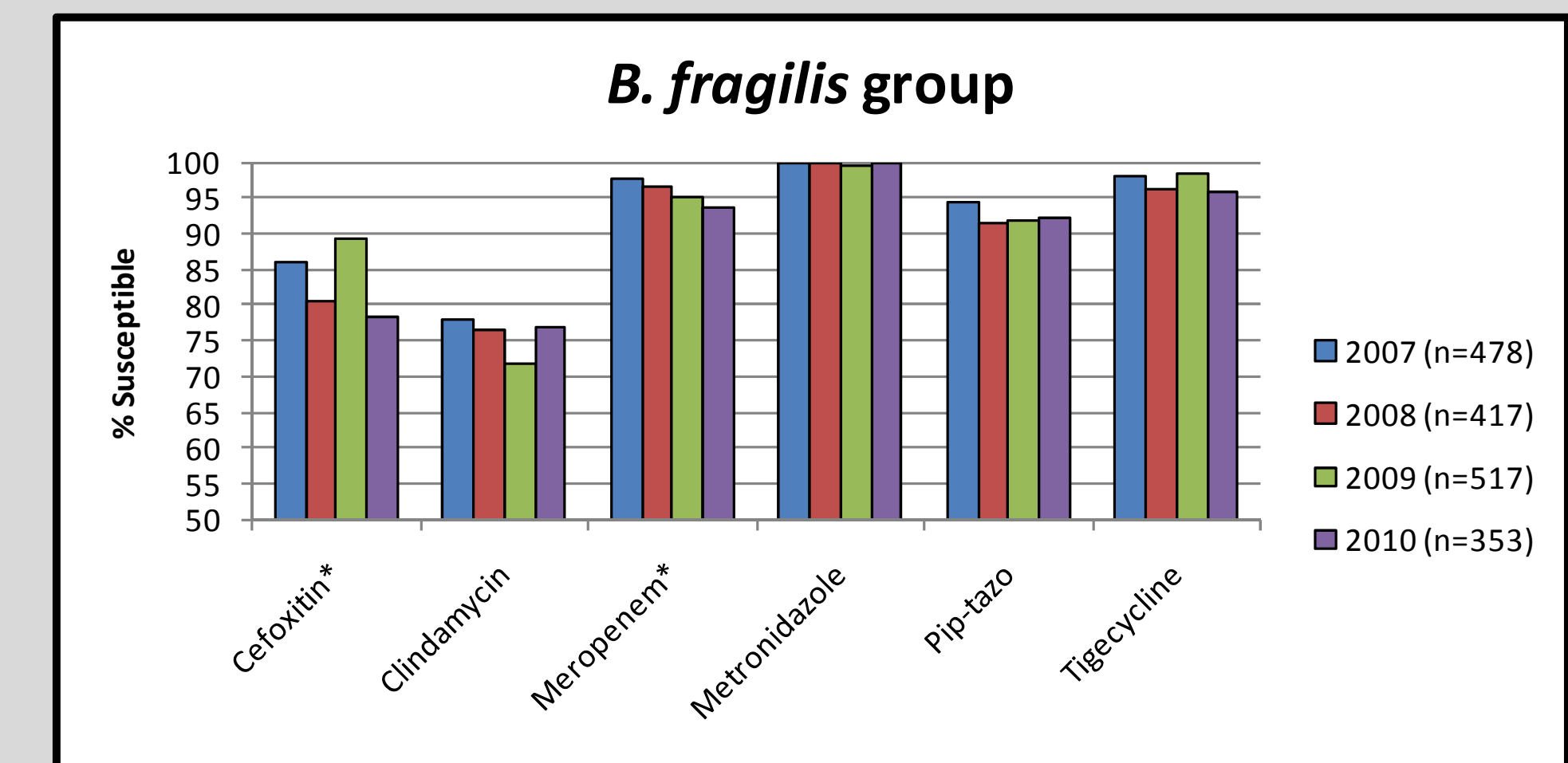
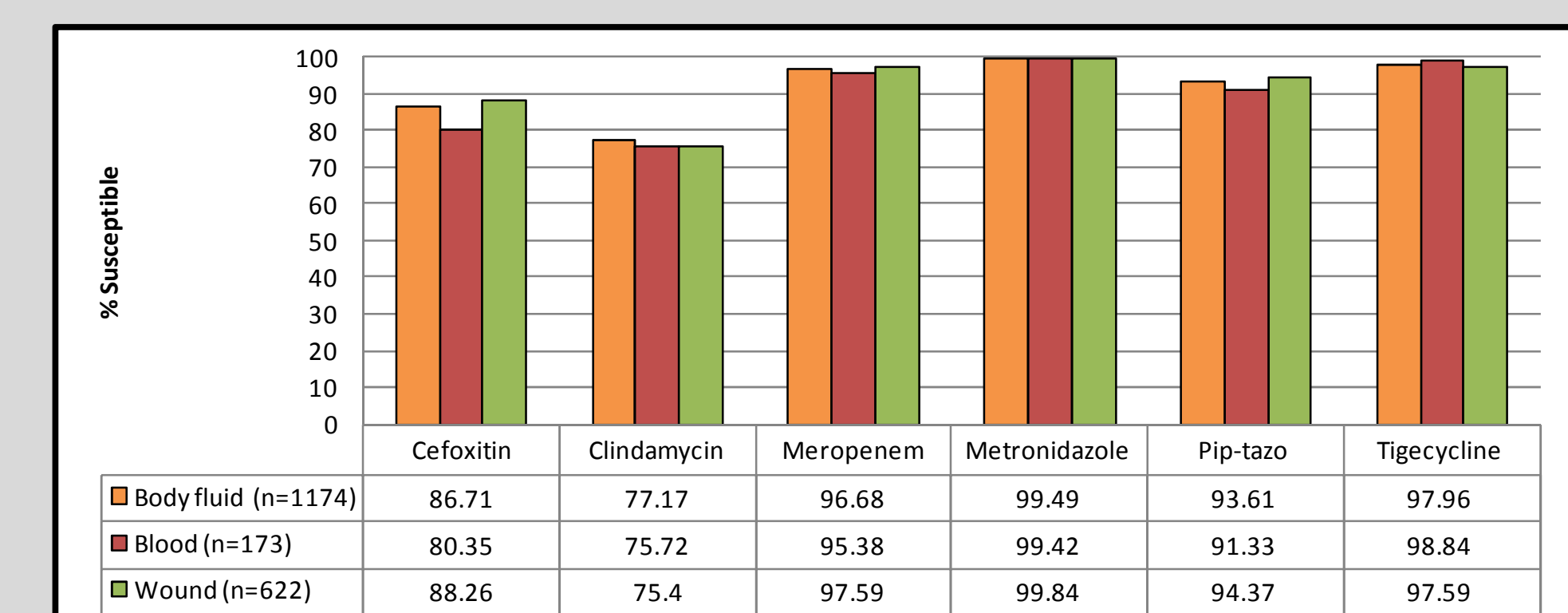


Figure 2. Susceptibility of 1,765 *B. fragilis* group (*B. fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*) isolates from 2007-2010.



*Indicates a significant decrease in percent susceptible between 2007 and 2010 (p<0.05, Fisher's exact test)

Figure 5. Susceptibility of gram-negative anaerobes by infection site.



Conclusions

- Over the four-year study period, metronidazole, tigecycline, meropenem and piperacillin-tazobactam all exhibited excellent *in vitro* activity against gram-negative anaerobes with %S of ≥94%.
- Significant decreases in susceptibilities of *B. fragilis* group isolates were noted for cefoxitin and meropenem between 2007 and 2010. No significant changes were found for other *Bacteroides* or *Prevotella* spp.
- With the common use of empirical therapy for anaerobic infections, monitoring of antimicrobial agents and treatment strategies is warranted.