

# Antibacterial Activity of Tigecycline Against Global Isolates of *H. influenzae* and *S. pneumoniae* (2004-08): T.E.S.T. Program 2008



PR023

J. Johnson<sup>1</sup>, R. Badal<sup>1</sup>, S. Hawser<sup>1</sup>, M. Hackel<sup>1</sup>, S. Bouchillon<sup>1</sup>, B. Johnson<sup>1</sup>, D. Hoban<sup>1</sup>, M. Renteria<sup>1</sup>, M. Dowzicky<sup>2</sup>

<sup>1</sup>International Health Management Associates, Inc., Schaumburg, IL, USA  
<sup>2</sup>Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.  
 2122 Palmer Dr.  
 Schaumburg, IL  
 60173  
 Tel: 847.303.5003  
 Fax: 847.303.5601

## Revised Abstract

**Objectives:** Tigecycline (TIG), a new glycylicycline, has been shown to have potent broad spectrum activity against most commonly encountered respiratory species. The T.E.S.T. program determined the in vitro activity of TIG and comparators against respective gram-positive/negative species. Isolates were collected from 1,016 hospital sites in 53 countries from 2004 to 2008. **Methods:** A total of 13,922 clinically significant respiratory isolates collected worldwide were analyzed in this survey. The isolates were identified to the species level at the participating sites and confirmed by the central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Activities of tigecycline and comparator antimicrobials are shown in the table below\*:

Drug	<i>H. influenzae</i> (n=6,976)			<i>S. pneumoniae</i> (n=6,946)		
	%Sus	MIC <sub>50</sub>	MIC <sub>90</sub>	%Sus	MIC <sub>50</sub>	MIC <sub>90</sub>
Tigecycline	na	0.25	0.5	na	0.03	0.12
AmoxClav	99.7	0.5	1	95.3	≤0.03	1
Ceftriaxone	99.9	≤0.06	≤0.06	97.7	≤0.03	1
Levofloxacin	100	0.015	0.03	99.8	0.5	1
Imipenem	100	0.5	1	75.1	≤0.12	0.5
Linezolid	--	--	--	100	≤0.5	1
Penicillin	--	--	--	62.4	≤0.06	2

\*na = breakpoints not defined.

Overall, 22% of *H. influenzae* were β-lactamase producers and 39% of *S. pneumoniae* presented some degree to non-susceptibility to penicillin. Tigecycline demonstrated potent inhibitory activity with MIC<sub>90</sub> values of ≤0.5 mcg/ml and ≤0.12 mcg/ml against β-lactamase positive *H. influenzae* and penicillin non-susceptible *S. pneumoniae*, respectively. **Conclusions:** Tigecycline showed excellent inhibitory activity against *H. influenzae* and *S. pneumoniae* regardless of the presence of β-lactamase or penicillin-resistance mechanisms. The results of this study suggest that Tigecycline may be a reliable therapeutic option for the treatment of respiratory infections due to these species.

## Introduction

Tigecycline is a broad-spectrum antimicrobial agent and first-in-class of the semisynthetic glycylicyclines to be approved for human use [1]. This synthetic analogue of the minocycline molecule exhibits significant antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity that is as much as fourfold better than vancomycin and daptomycin [2, 3]. The development of tigecycline is important in that tigecycline and other glycylicyclines are active against bacterial strains carrying either or both of the two major forms of tetracycline resistance: efflux and ribosomal protection. Certain substituents at the 9-position of the tetracycline molecule restored activity against bacteria harboring genes encoding either or both efflux and ribosomal protection. A single chemical modification of tigecycline overcomes the two molecularly distinct forms of resistance while maintaining activity against susceptible gram-positive, gram-negative, aerobic, and anaerobic bacteria [4].

Previous studies have demonstrated excellent in vitro activity for tigecycline against clinical and laboratory strains of gram-positive and gram-negative bacteria with minimum inhibitory concentrations for the 90<sup>th</sup> percentile inhibited at or below 2 mcg/ml, including difficult to treat methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE) and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [5-9]. This study was undertaken to document the in vitro activity of tigecycline against significant numbers of *H. influenzae* and *S. pneumoniae* collected from a diverse global population. This study is part of the ongoing Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

## Materials & Methods

- All isolates were derived from blood, respiratory tract, urine, skin, wound, body fluids and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested between January 2004 and December 2008 from 1,016 study centers globally. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, as well as, development and management of a centralized database was coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- 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 site criteria.
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [10]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., Sacramento, CA, USA). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.06-16); cefepime (0.5-32); ceftriaxone (0.06-64); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8); piperacillin/tazobactam (0.06/4-128/4), and vancomycin (0.12-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [11] and recent US Food and Drug Administration packaging insert for tigecycline [1], where applicable.
- Quality controls (QC) were performed by each testing site on each day of testing using ATCC control strains *S. aureus* ATCC 29213; *E. faecalis* ATCC 29212; *H. influenzae* ATCC 49247 and ATCC 49766. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2008) guidelines [11].

## References

- FDA. Tigecycline, NDA No. N021821. <http://www.fda.gov/oc/ohrt/ndasigs/tyg.htm> June 15, 2005. United States Federal Drug Administration (FDA), 5600 Fishers Lane, Rockville, MD, USA.
- Hoellman, D.B., et al. Antipneumococcal activities of GAR-936 (a new glycylicycline) compared to those of nine other agents against penicillin-susceptible and -resistant pneumococci. *Antimicrob Agents Chemother.* 2000; 44(4): p. 1085-8.
- Labthavikul, P., P.J. Petersen, and P.A. Bradford. In vitro activity of tigecycline against *Staphylococcus epidermidis* growing in an adherent-cell biofilm model. *Antimicrob Agents Chemother.* 2003; 47(12): p. 3967-9.
- Prager, S.J. Preclinical pharmacology of GAR-936, a novel glycylicycline antibacterial agent. *Pharmacotherapy.* 2000; 20(9 Pt 2): p. 219S-223S; discussion 224S-228S.
- Gales, A.C. and R.N. Jones. Antimicrobial activity and spectrum of the new glycylicycline, GAR-936 tested against 1,203 recent clinical bacterial isolates. *Diagn Microbiol Infect Dis.* 2000; 36(1): p. 19-36.
- Patel, R., et al. In vitro activity of GAR-936 against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*. *Diagn Microbiol Infect Dis.* 2000; 38(3): p. 177-9.
- Rupp, M.E. and P.D. Fey. Extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*: considerations for diagnosis, prevention and drug treatment. *Drugs.* 2003; 63(4): p. 353-65.
- Bouchillon, S.K., et al. In Vitro Activity of Tigecycline Against 3,989 Gram-Negative and Gram-Positive Clinical Isolates from the United States Tigecycline Evaluation and Surveillance Trial (TEST Program, 2004). *Diagn Microbiol Infect Dis.* 2005; 52(3): p. 173-179.
- Hoban, D.J., et al. In Vitro Activity of Tigecycline Against 6,792 Gram-Negative and Gram-Positive Clinical Isolates from the Global Tigecycline Evaluation and Surveillance Trial (TEST Program, 2004). *Diagn Microbiol Infect Dis.* 2005; 52(3): p. 215-227.
- CLSI. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. Approved Standard—Seventh Edition, in Document M7-A7. 2007. Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- CLSI. Performance Standards for Antimicrobial Susceptibility Testing, in Document M100-S18. 2008. Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.

## Acknowledgements

We gratefully acknowledge the contributions of the investigators, laboratory personnel and all members of the Tigecycline Evaluation Study Trials program group. This study was sponsored by a grant from Wyeth Pharmaceuticals.

## Results

Table 1. In vitro activity of tigecycline and comparative agents against 6,976 *Haemophilus influenzae* categorized by beta-lactamase production.

Organisms	Drug*	%Sus	%Int	%Res	MIC (mcg/ml)		
					MIC <sub>50</sub>	MIC <sub>90</sub>	Range
<i>H. influenzae</i> (n=6,976)	Tigecycline	na	na	na	0.25	0.5	≤0.008-2
	AmoxClav	99.7	0	0.3	0.5	1	≤0.12->32
	Ampicillin	76.9	2.1	21.1	≤0.5	32	≤0.5->32
	Cefepime	99.4	0	0.6	≤0.5	≤0.5	≤0.5->32
	Ceftriaxone	99.9	0	0.1	≤0.06	≤0.06	≤0.06-32
	Imipenem	100	0	0	0.5	1	≤0.06-4
	Levofloxacin	100	0	0	0.015	0.03	≤0.008-2
	PipTazo	99.8	0	0.2	≤0.06	≤0.06	≤0.06-16
β-Lactamase Positive <i>H. influenzae</i> (n=1,515)	Tigecycline	na	na	na	0.25	0.5	≤0.008-2
	AmoxClav	98.7	0	1.3	1	2	≤0.12->32
	Ampicillin	0	4.6	95.4	32	>32	2->32
	Cefepime	98.7	0	1.3	≤0.5	≤0.5	≤0.5->32
	Ceftriaxone	99.7	0	0.3	≤0.06	≤0.06	≤0.06-32
	Imipenem	100	0	0	0.5	1	≤0.06-4
	Levofloxacin	100	0	0	0.015	0.03	≤0.008-2
	PipTazo	99.5	0	0.5	≤0.06	≤0.06	≤0.06-16

\* Interpretive criteria as defined by CLSI, document M100-S18 (2008), where applicable [11]; na=breakpoints not defined.

Table 2. In vitro activity of tigecycline and comparative agents against 6,946 *Streptococcus pneumoniae* categorized by penicillin susceptibility.

Organisms	Drug*	%Sus	%Int	%Res	MIC (mcg/ml)		
					MIC <sub>50</sub>	MIC <sub>90</sub>	Range
<i>S. pneumoniae</i> (n=6,946)	Tigecycline	na	na	na	0.03	0.12	≤0.008-0.5
	AmoxClav	95.3	2.8	1.9	≤0.03	1	≤0.03->8
	Ceftriaxone	97.7	1.3	1	≤0.03	1	≤0.03->64
	Imipenem	75.1	21.5	3.4	≤0.12	0.5	≤0.12->16
	Levofloxacin	99.8	0.2	0	0.5	1	≤0.06-4
	Linezolid	100	0	0	≤0.5	1	≤0.5-2
	Penicillin	62.4	26.7	10.9	≤0.06	2	≤0.06->8
	Vancomycin	99.9	0	0.1	0.25	0.5	≤0.12-2
Penicillin-Susceptible <i>S. pneumoniae</i> (n=4,244)	Tigecycline	na	na	na	0.03	0.12	≤0.008-0.5
	AmoxClav	100	0	0	≤0.03	≤0.03	≤0.03-0.5
	Ceftriaxone	100	0	0	≤0.03	≤0.03	≤0.03-1
	Imipenem	99.9	0.1	0	≤0.12	≤0.12	≤0.12-1
	Levofloxacin	99.9	0.1	0	0.5	1	≤0.06-4
	Linezolid	100	0	0	≤0.5	1	≤0.5-2
	Penicillin	100	0	0	≤0.06	≤0.06	≤0.06-≤0.06
	Vancomycin	100	0	0	0.25	0.5	≤0.12-1
Penicillin-Intermediate <i>S. pneumoniae</i> (PISP) (n=1,751)	Tigecycline	na	na	na	0.03	0.12	≤0.008-0.5
	AmoxClav	99.2	0.7	0.1	0.12	1	≤0.03-8
	Ceftriaxone	98.6	1.1	0.4	0.12	0.5	≤0.03-4
	Imipenem	45.8	51.4	2.8	0.25	0.5	≤0.12->16
	Levofloxacin	99.7	0.3	0	0.5	1	≤0.06-4
	Linezolid	100	0	0	≤0.5	1	≤0.5-2
	Penicillin	0	100	0	0.25	1	0.12-1
	Vancomycin	100	0	0	0.25	0.5	≤0.12-1
Penicillin-Resistant <i>S. pneumoniae</i> (n=951)	Tigecycline	na	na	na	0.03	0.06	≤0.008-0.5
	AmoxClav	58.5	23.8	17.7	2	8	≤0.03->8
	Ceftriaxone	82.5	9.2	8.3	1	2	0.25->64
	Imipenem	1.2	73.9	24.9	0.5	1	≤0.12->16
	Levofloxacin	99.3	0.7	0	1	1	0.25-4
	Linezolid	100	0	0	≤0.5	1	≤0.5-2
	Penicillin	0	0	100	2	4	2->8
	Vancomycin	99.5	0	0.5	0.25	0.5	≤0.12-2

\* Interpretive criteria as defined by CLSI, document M100-S18 (2008), where applicable [11]; na=breakpoints not defined.

Figure 1. Cumulative percents inhibited (%) of tigecycline and comparative agents against 6,976 *Haemophilus influenzae* at each MIC (mcg/ml).

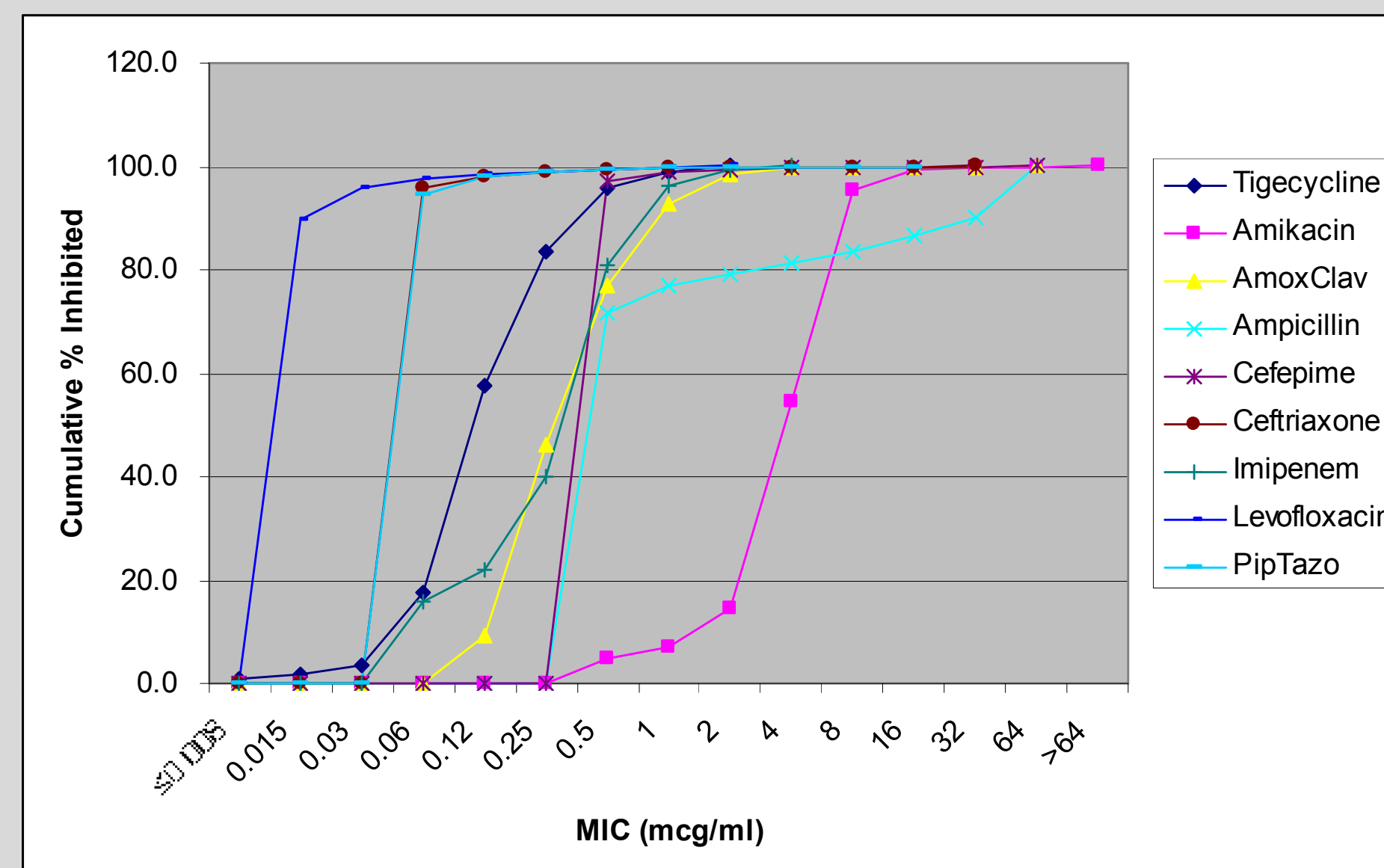
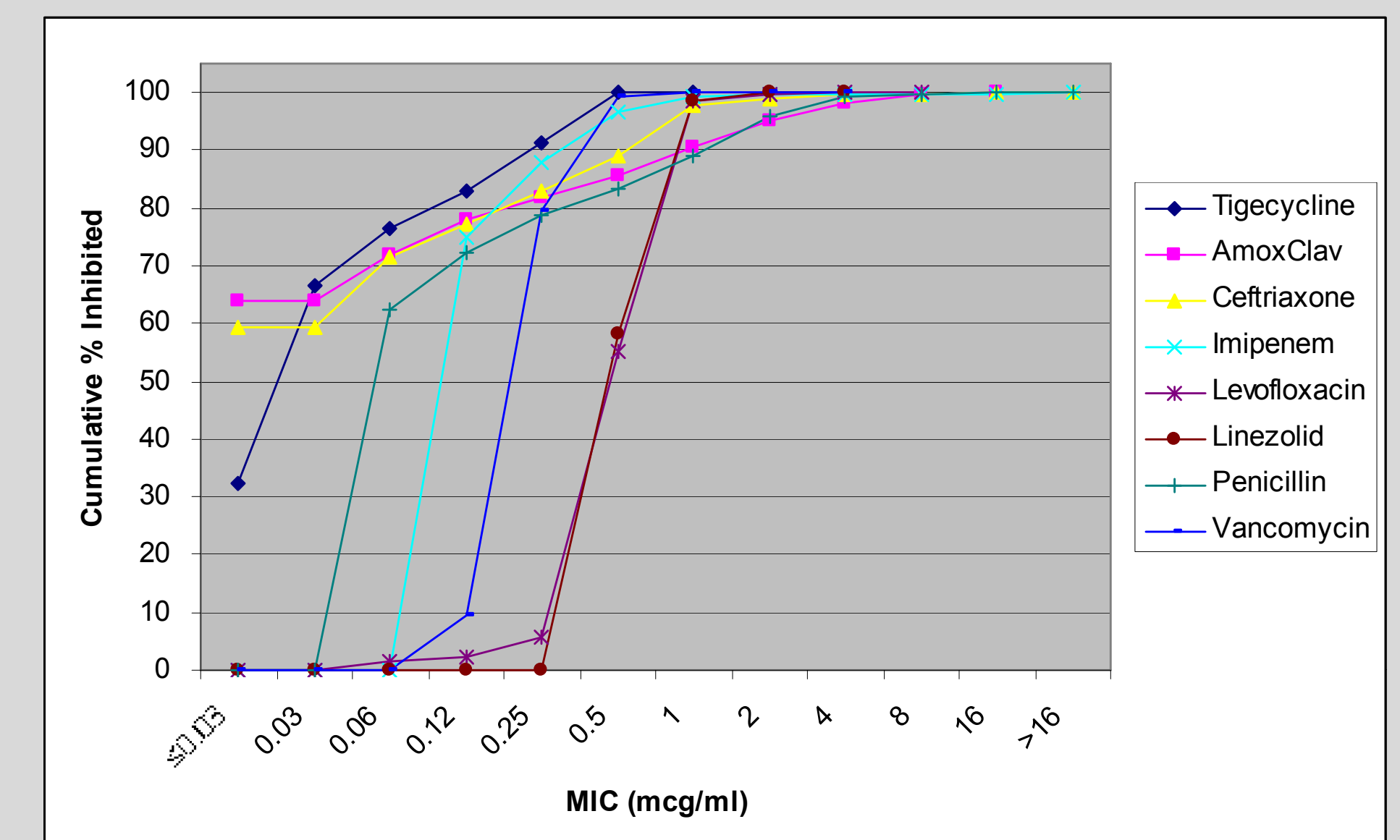


Figure 2. Cumulative percents inhibited (%) of tigecycline and comparative agents against 6,946 *Streptococcus pneumoniae* at each MIC (mcg/ml).



## Conclusions

- Tigecycline demonstrated potent in vitro activity against *H. influenzae* and *S. pneumoniae* in this surveillance study of clinical isolates from a large diverse global population.
- Tigecycline MIC<sub>50</sub> and MIC<sub>90</sub> values of 0.25 and 0.5 mcg/ml, respectively, against *H. influenzae* were not affected in the presence of β-lactamase.
- Tigecycline MIC<sub>50</sub> and MIC<sub>90</sub> values of 0.03 and 0.12 mcg/ml, respectively, against *S. pneumoniae* remained constant against all isolates and was unaffected by the penicillin-resistant phenotype.
- The in vitro activity of tigecycline in this study suggests that tigecycline is highly active against all study strains of *H. influenzae* and *S. pneumoniae* and may be an effective treatment option for these clinical pathogens.