

## Revised Abstract

**Background:** *Staphylococcus aureus* continues to be a therapeutic challenge for physicians despite the introduction of new antimicrobials to treat it. Linezolid has shown excellent activity against *Staphylococcus* spp., including methicillin-resistant *S. aureus*. This study evaluated the *in vitro* activity of linezolid as compared to 4 comparators: levofloxacin; minocycline; vancomycin; and tigecycline; against isolates of methicillin-resistant *Staphylococcus aureus* (MRSA). **Methods:** The isolates originated from 567 cumulative U.S. centers in the TEST program. A total of 3,090 clinical isolates from wound and respiratory sources were identified to the species level at each of participating sites and confirmed by the central laboratory. MICs were determined by each participating laboratory using broth microdilution panels. All testing was performed and interpreted according to CLSI and FDA (tigecycline) guidelines and manufacturer's instructions. **Results:** MRSA results are summarized in the following table:

Antibiotic	Respiratory			Wounds		
	N	MIC <sub>90</sub>	%S	N	MIC <sub>90</sub>	%S
Linezolid	907	4	100	2183	2	100
Levofloxacin	907	> 32	11.5	2183	> 32	39.3
Tigecycline	907	0.25	100	2183	0.25	100
Minocycline	907	0.5	99.2	2183	0.5	98.7
Vancomycin	907	1	100	2183	1	99.9

**Conclusions:** The *in vitro* activity of tigecycline, linezolid, minocycline and vancomycin were all comparable against MRSA with %S above 98%. MIC<sub>90</sub> values and %S were similar regardless of body infection.

## Introduction

Linezolid is a synthetic antibiotic used for the treatment of serious infections caused by gram-positive bacteria that are resistant to other antibiotics. A member of the oxazolidinone class of drugs, linezolid is active against most gram-positive bacteria that cause disease, including streptococci, vancomycin-resistant enterococci (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA). The main indications of linezolid are infections of the skin and soft tissues and pneumonia, particularly hospital-acquired pneumonia.

The current study investigated the activity of linezolid and 4 comparators: levofloxacin; minocycline; vancomycin and tigecycline during 2004 through 2010 against methicillin-resistant *S. aureus* as part of the Tigecycline Evaluation and Surveillance Trial (TEST).

## Materials & Methods

- Clinical isolates:** Isolates were identified to the species level utilizing local laboratory criteria and MICs determined at each participating laboratory. All organisms were deemed clinically significant by local participant criteria. All sites identified each study isolate utilizing local laboratory criteria. All isolates were from the period 2004 - 2010 and originated from site in the United States.
- Susceptibility testing:** Minimum inhibitory concentrations (MICs) were determined using custom panels manufactured by MicroScan (Siemens Medical Solutions Diagnostics, West Sacramento, CA, USA) or TREK (TREK Diagnostic Systems, Cleveland, OH, USA), following manufacturer and Clinical and Laboratory Standards Institute (CLSI) instructions for broth microdilution testing [1]. Susceptibility was determined using clinical breakpoints published by the CLSI (linezolid and comparators) [2] and the U.S. Food and Drug Administration package insert (tigecycline), where applicable [3].
- Quality controls:** Quality controls (QC) were performed by each testing site on each day of testing using appropriate ATCC control strains. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2011) guidelines [2].

## References

- CLSI, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Eighth Edition, in Document M7-A8 2009: Clinical and Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
- Clinical and Laboratory Standards Institute. 2011. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-First Informational Supplement. CLSI Document M100-S21. Wayne, PA.
- Tygacil<sup>®</sup>. 2010. Tigecycline FDA prescribing information. Pfizer, Inc., Collegeville, PA.

## 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 a grant from Pfizer Inc.

## Results

Figure 1. Percent of MRSA isolates from respiratory source in the United States from 2004-2010.

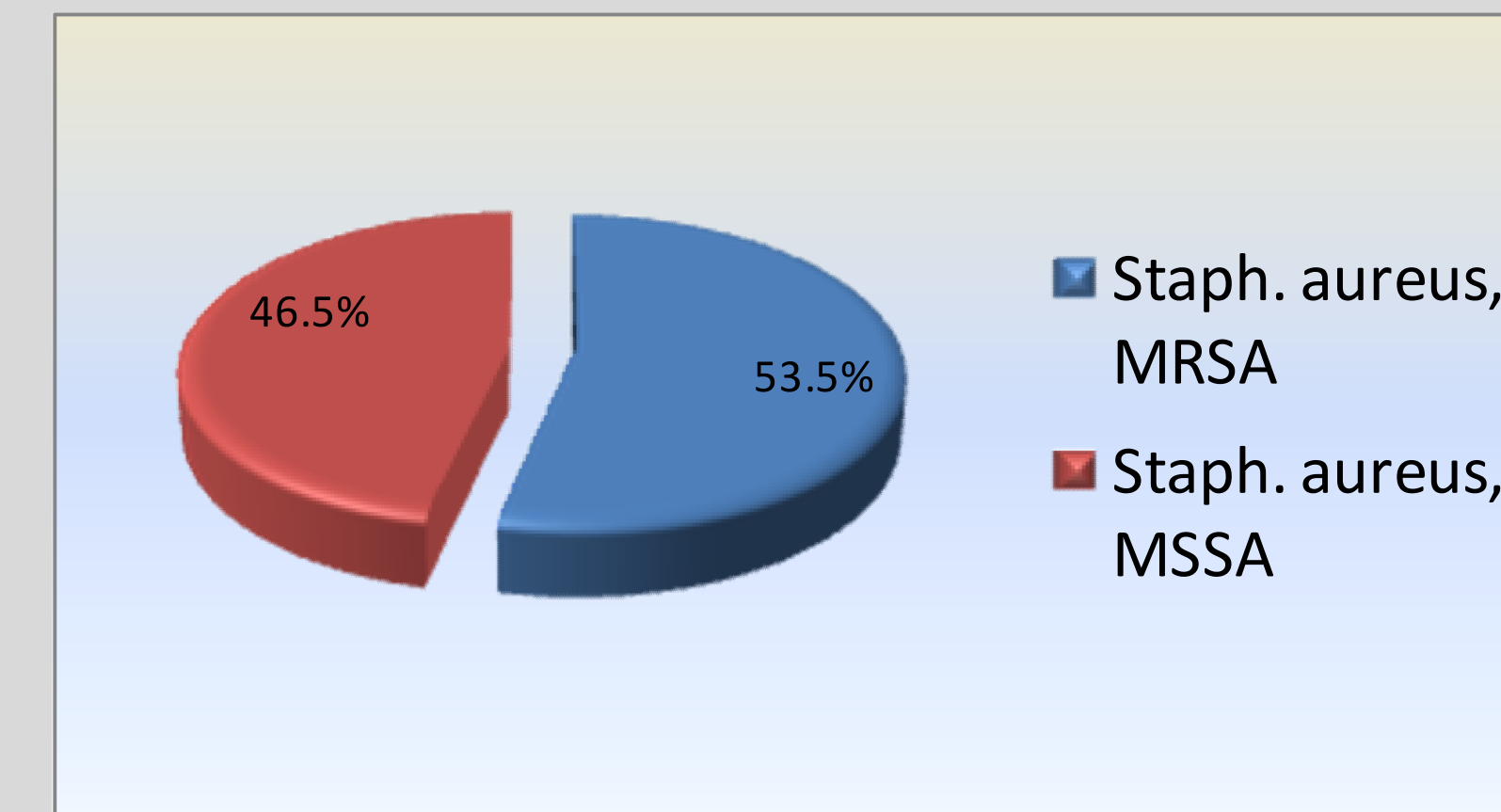


Table 1. *In vitro* activity of linezolid and comparators for 907 respiratory isolates of MRSA in the United States from 2004-2010.

Staph. aureus, MRSA						
Drug	N	MIC <sub>50</sub>	MIC <sub>90</sub>	%S	%I	%R
Linezolid	907	2	4	100	0	0
Levofloxacin	907	16	>32	11.5	1.3	87.2
Tigecycline	907	0.12	0.25	100	0	0
Minocycline	907	≤0.25	0.5	99.2	0.3	0.4
Vancomycin	907	1	1	100	0	0

Table 2. Frequency distribution of linezolid and comparators for 907 respiratory isolates of MRSA in the United States from 2004-2010.

Drug	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Linezolid							34	132	619	122				
							3.7	18.3	86.5	100				
Levofloxacin				13	50	31	9	1	12	129	87	136	199	240
				1.4	6.9	10.4	11.4	11.5	12.8	27.0	36.6	51.6	73.5	100
Tigecycline	1	1	4	130	586	145	40							
	0.1	0.2	0.7	15.0	79.6	95.6	100							
Minocycline						809	48	13	16	14	3	4		
						89.2	94.5	95.9	97.7	99.2	99.6	100		
Vancomycin				1	25	305	545	31						
				0.1	2.9	36.5	96.6	100						

MIC where ≥90% of the isolates were inhibited are highlighted in red.

Figure 2. Percent of MRSA isolates from wound source in the United States from 2004-2010.

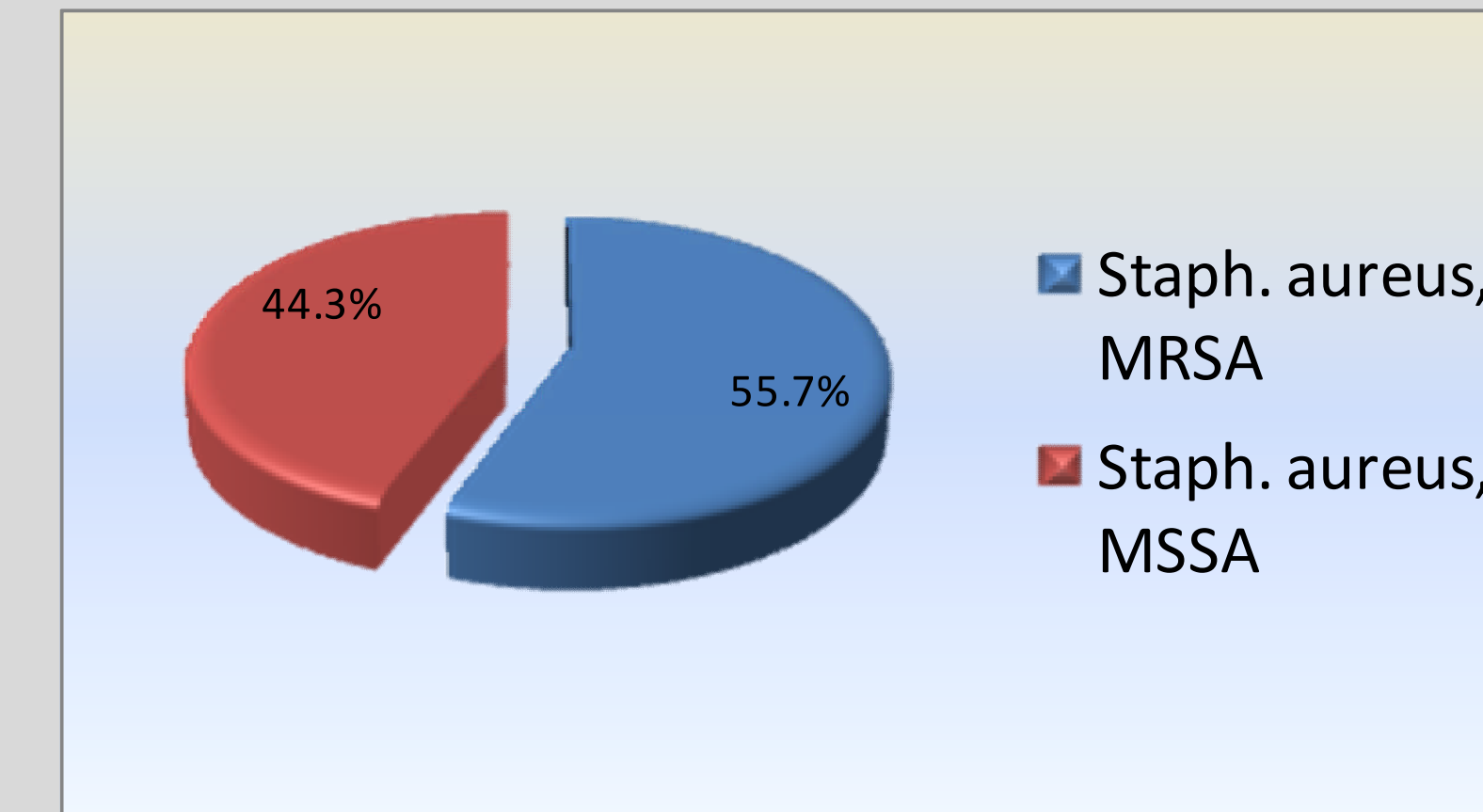


Table 3. *In vitro* activity of linezolid and comparators for 2,183 wound isolates of MRSA in the United States from 2004-2010.

Staph. aureus, MRSA						
Drug	N	MIC <sub>50</sub>	MIC <sub>90</sub>	%S	%I	%R
Linezolid	2183	2	2	100	0	0
Levofloxacin	2183	4	>32	39.3	3.5	57.2
Tigecycline	2183	0.12	0.25	100	0	0
Minocycline	2183	≤0.25	0.5	98.7	1.1	0.3
Vancomycin	2183	1	1	99.8	0.2	0

Table 4. Frequency distribution of linezolid and comparators for 2,183 wound isolates of MRSA in the United States from 2004-2010.

Drug	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
Linezolid							29	434	1552	168				
							1.3	21.2	92.3	100				
Levofloxacin				27	523	219	70	18	77	480	145	176	210	238
				1.2	25.2	35.2	38.4	39.3	42.8	64.8	71.4	79.5	89.1	100
Tigecycline	1	1	16	387	1471	223	84							
	0	0.1	0.8	18.6	85.9	96.2	100							
Minocycline						1948	116	35	28	27	23	6		
						89.2	94.5	96.2	97.4	98.7	99.7	100		
Vancomycin				33	1039	1059	48	4						
				1.5	49.1	97.6	99.8	100						

MIC where ≥90% of the isolates were inhibited are highlighted in red.

Table 5. *In vitro* activity of linezolid and comparators for 4 MRSA/VISA isolates from wound sites.

Drug	N <sup>a</sup>	Staph. aureus, MRSA and VISA				Minimum MIC	Maximum MIC
		%S	%I	%R			
Linezolid	4	100	0	0	1	2	
Levofloxacin	4	25.0	0	75.0	0.25	>32	
Tigecycline	4	100	0	0	0.06	0.5	
Minocycline	4	100	0	0	≤0.25	1	
Vancomycin	4	0	100	0	4	4	

<sup>a</sup>MIC<sub>50-90</sub>s not shown for n <10.

## Conclusions

- MRSA isolates comprised 53.5% and 55.7% of all the *S. aureus* isolates collected from respiratory and wound sources, respectively, in the United States during 2004-2010.
- Among the isolates from respiratory sources, linezolid, tigecycline, minocycline and vancomycin all exhibited percents susceptible ≥99%.
- Tigecycline's MIC<sub>90</sub> at 0.25 mcg/ml was the lowest among all comparators for both respiratory and wound MRSA isolates.
- Linezolid and tigecycline were the only two antimicrobials to exhibit 100% susceptibility against MRSA wound isolates.
- Four MRSA vancomycin-intermediate (VISA) isolates were discovered in this study, all from wound sources. No vancomycin-resistant (VRSA) isolates were encountered. All VISA strains were 100% susceptible to linezolid, tigecycline, and minocycline.