

## Revised Abstract

**Background:** Levofloxacin resistance in pneumococci emerged several years after its introduction in clinical use. However, there are few studies that track the temporal trends in resistance to levofloxacin in pneumococci. In order to more precisely describe such trends, large scale surveillance studies are useful. This report documents the rates of resistance to levofloxacin in pneumococci collected worldwide from 2004 - 2009, as part of the Tigecycline Evaluation Surveillance Trial (T.E.S.T.) study. **Methods:** A total of 9,692 pneumococcal clinical isolates of were collected in this study: 1411, 1539, 1923, 2306, 1881 and 632 isolates from 2004, 2005, 2006, 2007, 2008 and respectively. MICs were performed and interpreted according to CLSI and FDA guidelines where appropriate. **Results:** The table below illustrates the incidence of levofloxacin resistant pneumococci with time.

Year	Total <sup>a</sup>	LVX <sup>R</sup>	%LVX <sup>R</sup>	LVX <sup>NS</sup>	%LVX <sup>NS</sup>
2004	1411	6	0.4	9	0.6
2005	1539	9	0.6	10	0.6
2006	1923	15	0.8	25	1.3
2007	2306	11	0.5	18	0.8
2008	1881	3	0.2	13	0.7
2009	632	0	0	4	0.6

<sup>a</sup>, total pneumococcal isolates per each year; LVX<sup>R</sup>, isolates exhibiting full resistance to levofloxacin (MIC breakpoint > 4 µg/ml); LVX<sup>NS</sup>, isolates exhibiting intermediate or full resistance to levofloxacin (MIC breakpoint > 2 µg/ml).

**Conclusions:** Taken together, this substantial body of data shows that levofloxacin resistance in pneumococci remains persistently low. Only a very minor and transient increase appears to have occurred during 2006. This “peak” has since returned to resistance rates of < 1 % during the last two years.

## Introduction

Levofloxacin resistance in pneumococci emerged several years after its introduction in clinical use. However, there are few studies that track the temporal trends in resistance to levofloxacin in pneumococci. Levofloxacin is clinically used for the treatment of multiple types of infection, including those due to *Streptococcus pneumoniae*. Considering its wide use in all worldwide geographical regions, continued surveillance that determines numbers and rates of levofloxacin-resistance and levofloxacin non-susceptibility are warranted. The present study investigates the numbers and rates of such resistance patterns in isolates derived from the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.).

## Materials & Methods

- Clinical isolates:** Isolates were identified to the species level and tested 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. All isolates were from the period 2004 - 2009 and originated from Africa, Asia, Europe, Latin America, Middle East, North America and the South Pacific.
- Susceptibility testing:** Minimum inhibitory concentrations (MICs) were determined using plates manufactured by Trek Diagnostics, 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 (2).

## References

- Clinical Laboratory Standards Institute, *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.

## Acknowledgements

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## Results

Table 1. Isolate counts by phenotype, numbers of levofloxacin-resistant and levofloxacin- non-susceptible isolates from 2004 – 2009

Organism	Demographics	2004	2005	2006	2007	2008	2009	Total
<i>Streptococcus pneumoniae</i>	ALL	1411	1539	1923	2306	1881	633	9693
	Levo- <sup>NS</sup>	9	10	25	18	13	4	79
	Levo- <sup>R</sup>	6	9	15	11	3	0	44
<i>Streptococcus pneumoniae</i> (PISP)	ALL	359	427	502	564	420	132	2404
	Levo- <sup>NS</sup>	5	4	6	3	4	1	23
	Levo- <sup>R</sup>	3	4	2	1	2	0	12
<i>Streptococcus pneumoniae</i> (PRSP)	ALL	165	205	258	365	348	94	1435
	Levo- <sup>NS</sup>	2	5	10	8	4	2	31
	Levo- <sup>R</sup>	2	4	8	6	1	0	21
<i>Streptococcus pneumoniae</i> (PSSP)	ALL	887	907	1163	1377	1113	406	5853
	Levo- <sup>NS</sup>	2	1	9	7	5	1	25
	Levo- <sup>R</sup>	1	1	5	4	0	0	11

Table 2. Susceptibility of isolates to levofloxacin: analysis by phenotype, MIC<sub>50</sub>, MIC<sub>80</sub> and MIC<sub>90</sub>

Organism	Drug	Year	N	MIC <sub>50</sub>	MIC <sub>80</sub>	MIC <sub>90</sub>	
<i>Streptococcus pneumoniae</i>	Levofloxacin	n	2004	1411	0.5	1	1
		2005	1539	0.5	1	1	
		2006	1923	1	1	1	
		2007	2306	0.5	1	1	
		2008	1881	1	1	1	
		2009	632	1	1	1	
		2009	632	1	1	1	
<i>Streptococcus pneumoniae</i> (PSSP)	Levofloxacin	n	2004	887	0.5	1	1
		2005	907	0.5	1	1	
		2006	1163	1	1	1	
		2007	1377	0.5	1	1	
		2008	1113	1	1	1	
		2009	406	1	1	1	
		2009	406	1	1	1	
<i>Streptococcus pneumoniae</i> (PISP)	Levofloxacin	n	2004	359	0.5	1	1
		2005	427	0.5	1	1	
		2006	502	0.5	1	1	
		2007	564	0.5	1	1	
		2008	420	1	1	1	
		2009	132	1	1	1	
		2009	132	1	1	1	
<i>Streptococcus pneumoniae</i> (PRSP)	Levofloxacin	n	2004	165	0.5	1	1
		2005	205	1	1	1	
		2006	258	1	1	1	
		2007	365	0.5	1	1	
		2008	348	1	1	1	
		2009	94	1	1	1	
		2009	94	1	1	1	

Table 3. Percent susceptibility of isolates to levofloxacin, percent isolates resistant and percent non-susceptible during 2004 - 2009

Organism	Drug	Year	N	%Sus	%Int	%Res	%NS
<i>Streptococcus pneumoniae</i>	Levofloxacin	2004	1411	99.4	0.2	0.4	0.6
		2005	1539	99.4	0.1	0.6	0.7
		2006	1923	98.7	0.5	0.8	1.3
		2007	2306	99.2	0.3	0.5	0.8
		2008	1881	99.3	0.5	0.2	0.7
		2009	632	99.4	0.6	0.0	0.6
<i>Streptococcus pneumoniae</i> (PSSP)	Levofloxacin	2004	887	99.8	0.1	0.1	0.2
		2005	907	99.9	0.0	0.1	0.1
		2006	1163	99.2	0.3	0.4	0.8
		2007	1377	99.5	0.2	0.3	0.5
		2008	1113	99.6	0.5	0.0	0.5
		2009	406	99.8	0.3	0.0	0.3
<i>Streptococcus pneumoniae</i> (PISP)	Levofloxacin	2004	359	98.6	0.6	0.8	1.4
		2005	427	99.1	0.0	0.9	0.9
		2006	502	98.8	0.8	0.4	1.2
		2007	564	99.5	0.4	0.2	0.5
		2008	420	99.1	0.5	0.5	1.0
		2009	132	99.2	0.8	0.0	0.8
<i>Streptococcus pneumoniae</i> (PRSP)	Levofloxacin	2004	165	98.8	0.0	1.2	1.2
		2005	205	97.6	0.5	2.0	2.4
		2006	258	96.1	0.8	3.1	3.9
		2007	365	97.8	0.6	1.6	2.2
		2008	348	98.9	0.9	0.3	1.2
		2009	94	97.9	2.1	0.0	2.1

Figure 1. Geographical distribution of levofloxacin-non-susceptible isolates during 2004 – 2009

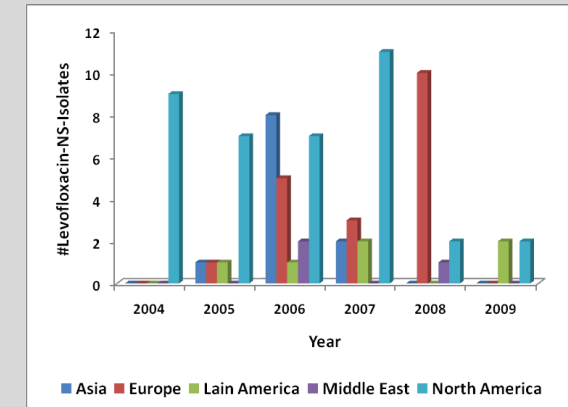
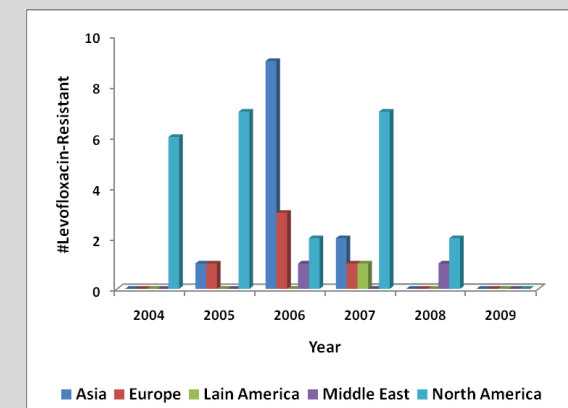


Figure 2. Geographical distribution of levofloxacin-resistant isolates during 2004 – 2009



## Conclusions

- Levofloxacin non-susceptibility and levofloxacin resistance in pneumococci remained very low throughout 2004 – 2009.
- Susceptibility patterns were similar for all pneumococci, PSSP, PISP and PRSP.
- Geographical distributions showed levofloxacin-resistance and levofloxacin non-susceptibility to be very low and sporadic.