1673

Report of Linezolid Resistance from the Zyvox® Annual Appraisal of Potency and Spectrum Program for 2009 (Europe, Latin America, Asia Pacific)

JE ROSS[1], RN JONES[1], HS SADER[1], U UCHINO[2], F IKEDA[2], Y FUKUI[3], I KOBAYASHI[4]

[1]JMI Laboratories, North Liberty, USA; [2]Mitsubishi Chemical Medience Corporation, Japan; [3]Kochi Health Sciences Center, Japan; [4]Toho University Faculty of Medicine, Japan

ECCMID 2010

JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ph. 319.665.3370, fax 319.665.3371
ronald-jones@jmilabs.com

AMENDED ABSTRACT

Objectives: To monitor the in vitro activity and to detect resistance (R) to linezolid (LZD) in various geographic areas of the world, excluding the United States (USA), the Zyvox® Annual Appraisal of Potency and Spectrum Program (ZAAPS) surveillance program was established in 2002. LZD, the first oxazolidinone agent clinically applied, is an important therapeutic option for infections caused by antimicrobial-R Gram-positive (GP) pathogens. Although rare, LZD-R has been observed particularly in enterococci (ENT) and more recently among coagulase-negative staphylococci (CoNS). R rates remain extremely low for indicated *S. aureus* (SA) and streptococci.

Methods: 5,754 isolates were collected from 67 sites in 22 countries in 2009. Isolates were received from the following organism groups (n): SA (2,958), CoNS (827), ENT (744), *Streptococcus pneumoniae* (SPN; 636), viridans group streptococci (VGS; 214) and beta-haemolytic streptococci (BHS; 375). At least 200 isolates from each country (except China [n=800] and the United Kingdom [n=400]) were requested to be sent to a reference monitoring laboratory. CLSI broth microdilution susceptibility testing was performed using TREK Diagnostic (Cleveland, OH, USA) panels. LZD-R isolates were confirmed with Etest (bioMérieux, Solna, Sweden) and disk diffusion methods. PCR and sequencing were performed to detect mutations in 23S rRNA, L3, L4, and L22 proteins, and acquired gene (*cfr*).

Results: Overall LZD-susceptibility (S) in the ZAAPS study was >99.9% with only 4 LZD-R CoNS and 4 LZD-R ENT isolates identified (see Table). MRSA rates varied from 0.0% (Sweden) to 82.0% (Korea) with an overall rate of 37.9%. Vancomycin-R ENT rates ranged from 0.0% (Japan, Belgium, Mexico, Spain, Sweden) to 41.5% (Taiwan). Four ENT isolates were LZD-R (0.54%). SPN had overall penicillin and erythromycin R rates (MIC,≥2 mg/L) of 30.7% and 49.1%, respectively. All streptococci had LZD MIC values of ≤2 mg/L.

Table: Linezolid-R isolates found in the 2009 ZAAPS Program.

Species	City/Country	LZD MIC (mg/L)	R- mechanism (23S mutation)
S. epidermidis	Guadalajara/Mexico	>8	*cfr*
S. epidermidis	Guadalajara/Mexico	>8	*cfr*
S. epidermidis	Rome/Italy	8	*cfr*
S. cohnii	Guadalajara/Mexico	>8	*cfr*
E. faecium	Frankfurt/Germany	>8	G2576T
E. faecium	Frankfurt/Germany	8	G2576T
E. faecium	Seoul/Korea	>8	G2576T
E. faecalis	Shenzhen/China	8	L4 (F101L)

Conclusions: LZD-R was considered very low among contemporary pathogens from indicated organism groups in this worldwide ongoing surveillance study. As LZD use continues to evolve, the need for close monitoring of the in vitro activity of LZD versus Gram-positive pathogens and for the emergence of R mechanisms is apparent.

INTRODUCTION

The Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS) Program has completed its eighth year (2009) of resistance surveillance for linezolid, the first oxazolidinone class agent to be internationally developed and licensed for use in clinical practice. Since FDA approval in 2000, linezolid has been used primarily to treat multidrug-resistant (MDR) Gram-positive pathogens causing complicated skin and skin structure infections (cSSSI) and nosocomial pneumonia.

Linezolid inhibits bacterial protein synthesis through a mechanism of action different from that of other antibacterial agents; therefore, cross resistance between linezolid and other classes of antibiotics is unlikely but may occur. Cases of linezolid resistance have been reported in staphylococci, enterococci, and streptococci with the G2576U or G2447T target site mutations as the dominant resistance mechanism. Recently, in rare cases, the *cfr* gene has been detected in coagulase-negative staphylococci (CoNS) and *S. aureus*.

Linezolid has emerged as a viable alternative for infections caused by Gram-positive organisms that are resistant to conventional drugs, such as methicillin-resistant *Staphylococcus aureus* (MRSA), drug-resistant *Streptococcus pneumoniae* (DRSP) and vancomycin-resistant enterococci (VRE). Therefore, it is important to continuously monitor the potency and potential for emerging resistance mechanisms to linezolid as the use of this agent increases, in volume and in geographic distribution.

MATERIALS AND METHODS

Organism collection. The number of processed strains (5,754; 106.6% compliance to protocol) were all from Gram-positive species collected from 67 medical centers in 22 countries (Table 1). Each participating country with the exception of the United Kingdom, Japan and China which submitted more isolates, forwarded a target total of 200 consecutively sampled, non-duplicate patient isolates from infections of the bloodstream, respiratory tract, urinary tract, or wound/SSSI.

All isolates were identified by the submitting laboratory and confirmed by the central facility using standardized and commercial methods (VITEK 2 system; bioMerieux, Hazelwood, Missouri, USA). Isolates were grouped for analysis as follows: *S. aureus* (2,958 strains), CoNS (827 strains), β-haemolytic streptococci (375 strains), viridans group streptococci (214 strains), *Streptococcus pneumoniae* (636 strains), and enterococci (744 strains).

Susceptibility testing. Antimicrobial susceptibility testing (linezolid and comparators) was performed using validated microdilution panels with cation-adjusted Mueller-Hinton broth (2-5% lysed horse blood supplement for testing fastidious streptococci) produced by TREK Diagnostics (Cleveland, Ohio, USA). The categorical interpretations of MIC results were those published by the Clinical and Laboratory Standards Institute (CLSI, formerly the NCCLS) in M100-S20 [2010] and EUCAST [2010]. Quality control (QC) organism (*S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619) results were within the acceptable published ranges.

Isolates having linezolid MIC values in the non-susceptible or resistant range were repeated by the CLSI M07-A8 method and further subjected to alternative tests using disk diffusion and Etest (AB bioMérieux, Solna, Sweden) methods.

Molecular testing was performed to identify the 23S rRNA target site mutation and possible epidemic clonality using pulsed-field gel electrophoresis (PFGE), automated ribotyping and various PCR tests as previously described. Furthermore, molecular tests to identify the *cfr* gene encoding resistances to oxazolidinones in staphylococci were performed as described by Mendes et al, [2008]. Other potential target site modifications associated with increased linezolid MIC results were also examined.

RESULTS

- The MRSA rates from a total of 2,958 *S. aureus* isolates tested included: for Latin America (average at 47.8%; range 27.3% [Brazil] to 55.8% [Chile]); for Europe (average 25.0%; range 0.0% [Sweden] to 46.8% [Ireland]); and the APAC region (average 46.3%; range 28.5% [Japan] to 82.0% [Taiwan]).
- The MIC results for linezolid versus *S. aureus* showed 98.7% of values at 1 or 2 mg/L. This did not change with oxacillin-resistant *S. aureus,* as the $MIC_{50/90}$ remained at 2 mg/L. None of the *S. aureus* isolates had a linezolid MIC greater than 2 mg/L (Tables 2 and 3).
- Among 827 CoNS isolates, oxacillin resistance increased to 80.2% (75.8% in 2008) with rates ranging from 5.6% (Malaysia) to 100.0% (Australia).
- Linezolid MIC values were generally lower by two-fold for CoNS when compared to *S. aureus*. The modal and MIC_{90} results for CoNS continue to be at 1 mg/L (same as 2008; Table 2).
- Three *S. epidermidis* (Mexico and Italy) and one *S. cohnii* (Mexico) were detected with linezolid MIC results at ≥8 mg/L, all of which contained the *cfr* gene.
- The overall VRE rate was 11.7% (Table 2) with the majority of these containing the VanA resistance type (77.8%). Four enterococci had linezolid MIC values of ≥8 mg/L (Germany [2], Korea, China) all containing the G2576T mutation.
- The overall penicillin and erythromycin non-susceptible rate for 636 *S. pneumoniae* isolates was 30.7 and 49.1%, respectively. No linezolid MIC was greater than 2 mg/L (Table 2).
- Beta-haemolytic streptococci and viridans group streptococci both had similar linezolid $MIC_{50/90}$ results of 1 mg/L with no MIC above 2 mg/L (Table 2).

Table 1. Distribution of organism identifications for the 2009 ZAAPS sample indexed by nation of origin (5,754 strains).

Nation (no. medical centers)	No. of strains						
	S. aureus	CoNS	ENT	SPN	VGS	β-S	Total
Canada (2)	99	40	20	19	8	12	198
Argentina (2)	110	61	20	31	13	10	245
Brazil (4)	110	60	20	23	15	11	239
Chile (2)	120	27	20	30	3	14	214
Mexico (2)	120	26	20	17	8	10	201
Belgium (1)	70	46	33	12	6	37	204
France (5)	100	93	20	40	18	13	284
Germany (3)	100	102	22	30	22	13	289
Ireland (1)	109	4	41	40	16	29	239
Italy (3)	99	80	35	1	1	3	219
Poland (1)	100	3	25	7	13	23	171
Spain (3)	100	37	20	30	8	12	207
Sweden (2)	142	29	20	30	17	13	251
Turkey (2)	105	35	20	26	6	2	194
United Kingdom (2)	259	16	28	37	8	35	383
Australia (6)	180	11	50	19	16	69	345
China (17)	563	16	160	200	1	0	940
Hong Kong (1)	48	0	3	0	3	14	68
Japan (2)	200	79	40	37	21	18	395
Korea (2)	111	37	48	0	1	8	205
Malaysia (1)	28	19	38	0	0	7	92
Taiwan (3)	85	6	41	7	10	22	171
TOTAL (67)	2958	827	744	636	214	375	5,754

ENT = Enterococci; SPN = *S. pneumoniae*; VGS = vir. group streptococci; β-S = β-streptococci

Figure 1. Linezolid MIC distribution for all isolates in the 2009 ZAAPS Program in 22 nations (non-USA; 5,754 strains).

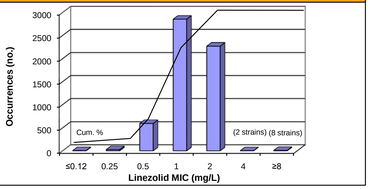

Table 3. Cumulative % inhibited results at each linezolid MIC when testing six different groups of Gram-positive cocci isolated on four continents (ZAAPS, 2009)[a].

Organism group (no. tested)	Cum. % inhibited at linezolid MIC (mg/L)						
	≤0.12	0.25	0.5	1	2	4	≥8
β-haemolytic streptococci (375)	0.0	0.0	7.2	98.4	100.0	-	-
Viridans group streptococci (214)	0.0	1.9	30.4	96.3	100.0	-	-
S. pneumoniae (636)	1.1	2.5	38.8	98.7	100.0	-	-
S. aureus (2,958)	0.0	0.1	1.3	37.5	100.0	-	-
Enterococci (744)	0.0	0.0	4.3	51.5	99.5	99.5	100.0
CoNS (827)	0.0	0.9	25.9	94.1	99.3	99.5	100.0

a. Organism groups were ranked in decreasing order of susceptibility to the oxazolidinone.

Table 2. Comparative activity of linezolid tested against 5,754 Gram-positive cocci from 22 nations in the ZAAPS Program (2009).

Organism (no.tested)/ antimicrobial agent	MIC (mg/L)			% by category[a] Susceptible/Resistant	
	50%	90%	Range	CLSI [2010]	EUCAST [2010]
S. aureus					
All strains (2,958)					
Linezolid	2	2	0.25-2	100.0 / 0.0	100.0 / 0.0
Ceftriaxone[a]	4	>32	≤0.25->32	62.1 / 37.9	62.1 / 37.9
Clindamycin	≤0.25	>2	≤0.25->2	72.4 / 27.3	72.0 / 27.6
Erythromycin	0.5	>2	≤0.25->2	55.6 / 43.4	56.4 / 43.4
Gentamicin	≤2	>8	≤2->8	75.7 / 23.1	75.3 / 24.7
Levofloxacin	≤0.5	>4	≤0.5->4	64.8 / 34.8	64.8 / 34.8
Oxacillin[a]	1	>2	≤0.25->2	62.1 / 37.9	62.1 / 37.9
Quinupristin/dalfopristin	0.5	1	≤0.25->2	99.8 / 0.1	99.8 / 0.1
Tetracycline	≤2	>8	≤2->8	77.9 / 21.6	77.3 / 22.7
TMP/SMX[b]	≤0.5	≤0.5	≤0.5->2	94.8 / 5.2	94.8 / 5.2
Teicoplanin	≤2	≤2	≤2-8	100.0 / 0.0	97.6 / 2.4
Vancomycin	1	1	0.25-2	100.0 / 0.0	100.0 / 0.0
MRSA (1,121)					
Linezolid	2	2	0.25-2	100.0 / 0.0	100.0 / 0.0
MSSA (1,837)					
Linezolid	2	2	0.5-2	100.0 / 0.0	100.0 / 0.0
Coagulase-negative staphylococci (827)[c]					
Linezolid	1	1	0.25->8	99.5 / 0.5	99.5 / 0.5
Ceftriaxone[a]	16	>32	≤0.25->32	19.8 / 80.2	19.8 / 80.2
Clindamycin	≤0.25	>2	≤0.25->2	65.1 / 33.9	63.4 / 34.9
Erythromycin	>2	>2	≤0.25->2	36.4 / 63.1	36.4 / 63.1
Gentamicin	4	>8	≤2->8	51.0 / 41.6	46.4 / 53.6
Levofloxacin	4	>4	≤0.5->4	44.0 / 53.9	44.0 / 53.9
Oxacillin[a]	>2	>2	≤0.25->2	19.8 / 80.2	19.8 / 80.2
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25->2	98.1 / 1.2	98.1 / 1.2
Tetracycline	≤2	>8	≤2->8	86.8 / 12.2	81.5 / 18.5
TMP/SMX[b]	≤0.5	>2	≤0.5->2	62.8 / 37.2	62.8 / 37.2
Teicoplanin	≤2	8	≤2->16	97.3 / 0.2	88.1 / 11.9
Vancomycin	2	2	≤0.12-4	100.0 / 0.0	98.5 / 1.5
Enterococci					
All strains (744)[d]					
Linezolid	1	2	0.5->8	99.5 / 0.5	99.5 / 0.5
Ampicillin[a]	2	>16	≤1->16	64.7 / 35.3	62.8 / 35.3
Erythromycin	>2	>2	≤0.25->2	6.7 / 73.5	- / -
Levofloxacin	>4	>4	≤0.5->4	44.8 / 52.3	- / -
Piperacillin/tazobactam	8	>64	1->64	62.8 / -	62.8 / -
Quinupristin/dalfopristin	>2	>2	≤0.25->2	26.5 / 64.1	26.5 / 64.1
Tetracycline	>8	>8	≤2->8	39.1 / 60.5	- / -
Teicoplanin	≤2	8	≤2->16	90.3 / 9.1	89.5 / 10.5
Vancomycin	1	>16	0.5->16	87.4 / 11.7	64.2 / 12.6
VRE (94)					
Linezolid	1	2	1-8	98.9 / 1.1	98.9 / 1.1
VSE (650)					
Linezolid	1	2	0.5->8	99.5 / 0.5	99.6 / 0.5

Organism (no. tested)/ antimicrobial agent	MIC (mg/L)			% by category[a] Susceptible/Resistant	
	50%	90%	Range	CLSI [2010]	EUCAST [2010]
S. pneumoniae					
All strains (636)					
Linezolid	1	1	≤0.12-2	100.0 / -	100.0 / 0.0
Amoxacillin/clavulanic acid	≤1	8	≤1-16	81.1 / 13.8	- / -
Ceftriaxone	≤0.25	2	≤0.25-8	80.5 / 6.9	56.8 / 17.6
Ciprofloxacin	1	2	≤0.5->4	(4.1)[e]	0.0 / 4.1
Clindamycin	≤0.25	>2	≤0.25->2	60.4 / 38.7	61.3 / 38.7
Erythromycin	≤0.25	>2	≤0.25->2	50.8 / 49.1	50.8 / 49.1
Levofloxacin	1	2	≤0.5->4	98.3 / 1.3	98.3 / 1.7
Penicillin	≤0.03	4	≤0.03->4	56.8 (82.4)/ 30.7 (2.0)[f]	56.8 / 17.6
Quinupristin/dalfopristin	0.5	1	≤0.25-1	100.0 / 0.0	- / -
Tetracycline	≤2	>8	≤2->8	53.0 / 45.8	53.0 / 47.0
TMP/SMX[b]	≤0.5	>2	≤0.5->2	56.2 / 35.7	62.4 / 35.7
Vancomycin	1	1	≤1	100.0 / -	100.0 / 0.0
MDR-3[g] (148)					
Linezolid	0.5	1	0.25-2	100.0 / -	100.0 / -
MDR-4[h] (140)					
Linezolid	0.5	1	0.25-2	100.0 / -	100.0 / -
MDR-5[i] (115)					
Linezolid	0.5	1	0.25-1	100.0 / -	100.0 / -
Viridans group streptococci (214)[j]					
Linezolid	1	1	0.25-2	100.0 / -	- / -
Amoxacillin/clavulanic acid	≤1	2	≤1->16	- / -	- / -
Ceftriaxone	≤0.25	2	≤0.25->32	88.8 / 5.6	82.7 / 17.3
Clindamycin	≤0.25	≤0.25	≤0.25->2	90.2 / 8.4	91.6 / 8.4
Erythromycin	≤0.25	>2	≤0.25->2	60.3 / 38.3	- / -
Levofloxacin	1	2	≤0.5->4	95.8 / 3.3	- / -
Penicillin[a]	0.06	1	≤0.015-32	71.0 / 5.6	80.8 / 5.6
Quinupristin/dalfopristin	0.5	1	≤0.25->2	96.7 / 0.9	- / -
Tetracycline	≤2	>8	≤2->8	53.3 / 43.5	- / -
Vancomycin	0.5	1	≤0.12-1	100.0 / -	100.0 / 0.0
β-haemolytic streptococci (375)[k]					
Linezolid	1	1	0.5-2	100.0 / -	100.0 / 0.0
Amoxacillin/clavulanic acid[a]	≤1	≤1	≤1	100.0 / -	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0 / -	100.0 / 0.0
Clindamycin	≤0.25	0.5	≤0.25->2	89.8 / 9.6	90.4 / 9.6
Erythromycin	≤0.25	>2	≤0.25->2	81.1 / 18.1	81.1 / 18.1
Levofloxacin	1	1	≤0.5->4	98.1 / 1.9	90.9 / 1.9
Penicillin[a]	≤0.015	0.06	≤0.015-0.12	100.0 / -	100.0 / 0.0
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25-2	99.7 / 0.0	- / -
Tetracycline	4	>8	≤2->8	49.1 / 46.7	49.1 / 50.9
Vancomycin	0.5	0.5	0.25-1	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2010], beta-lactam susceptibility should be directed by the oxacillin test results for staphylococci and by ampicillin or penicillin for enterococci or streptococci.
b. TMP/SMX=trimethoprim/sulfamethoxazole.
c. Includes: 14 species (544 strains) and unidentified coagulase-negative staphylococci (283 strains).
d. Includes: *Enterococcus faecalis* (444 strains), *Enterococcus faecium* (277 strains), and 23 other enterococci.
e. Percentage of pneumococci or other streptococci with ciprofloxacin MICs at ≥4 mg/L, indicating possible QRDR mutations.
f. CLSI 2010 susceptibility breakpoints for high-dose parenteral penicillin (nonmeningitis).
g. MDR-3 = resistant to three agents eg. penicillin ≥2 mg/L, erythromycin ≥1 mg/L, and clindamycin ≥1 mg/L.
h. MDR-4 = resistant to four agents eg. penicillin ≥2 mg/L, erythromycin ≥1 mg/L, and tetracycline ≥8 mg/L.
i. MDR-5 = resistant to five agents eg. penicillin ≥2 mg/L, erythromycin ≥1 mg/L, clindamycin ≥1 mg/L, tetracycline ≥8 mg/L, and trimethoprim-sulfamethoxazole ≥4 mg/L.
j. Includes: 15 species (135 strains), *Streptococcus bovis* group (11 strains), unidentified viridans group streptococci (68 strains).
k. Includes: Group A (135 strains), Group B (174 strains), Group C (17 strains), Group F (1 strain), Group G (39 strains), and two other species (9 strains).

CONCLUSIONS

- Overall, linezolid remained active against 5,746 of 5,754 (99.86% susceptible; Figure 1) strains that were processed in the 2009 ZAAPS Program. This resistance rate (0.14%) was less than that of any glycopeptide, lipopeptide or streptogramin combination due to escalating rates of VRE and other MDR strains.
- Linezolid resistant CoNS isolates were observed for the first time from a single hospital in Mexico and was possibly due to the spread of a *cfr*+ clone.
- Only 0.54% of tested enterococci were resistant to linezolid, a rate which has remained stable for several years.
- Linezolid continues to demonstrate potent in vitro activity against Gram positive pathogens. Linezolid refractory strains appear to be unusual and without escalating occurrence (<1%) overall.

ACKNOWLEDGEMENTS

The authors would like to thank all participating centers worldwide for contributing isolates to this surveillance protocol. This study was sponsored by an educational/research grant from Pfizer (New York, NY).

REFERENCES

1. Anderegg TR, Sader HS, Fritsche TR, Ross JE, Jones RN (2005). Trends in linezolid susceptibility patterns: Report from the 2002-2003 worldwide Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS) Program. *Int J Antimicrob Agents* 26: 13-21.
2. Clinical and Laboratory Standards Institute. (2008). *M07-A7, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - eighth edition*. Wayne, PA: CLSI.
3. Clinical and Laboratory Standards Institute. (2010). *M100-S20, Performance standards for antimicrobial susceptibility testing, 20th informational supplement*. Wayne, PA: CLSI.
4. Draghi DC, Sheehan DJ, Hogan P, Sahm DF (2005). In vitro activity of linezolid against key gram-positive organisms isolated in the United States: Results of the LEADER 2004 surveillance program. *Antimicrob Agents Chemother* 49: 5024-5032.
5. EUCAST (2010). Clinical MIC breakpoints. http://www.eucast.org/clinical_breakpoints/ March 12, 2010.
6. Farrell DJ, Mendes RE, Ross JE and Jones RN. Linezolid surveillance program results for 2008 (LEADER Program for 2008). *Diagn. Microbiol. Infect. Dis.* 65: 392-403, 2009.
7. Jones RN, Fritsche TR, Sader HS and Ross JE. Zyvox® Annual Appraisal of Potency and Spectrum Program results for 2006: An activity and spectrum analysis of linezolid using clinical isolates from 16 countries. *Diagn. Microbiol. Infect. Dis.* 59: 199-209, 2007.
8. Jones RN, Kohno S, Ono Y, Ross JE and Yanagihara K. ZAAPS International Surveillance Program (2007) for linezolid resistance: Results from 5591 Gram-positive clinical isolates in 23 countries. *Diagn. Microbiol. Infect. Dis.* 64: 191-201, 2009.
9. Jones RN, Ross JE, Bell JM, Utsuki U, Fumiaki I, Kobayashi I and Turnidge JD. Zyvox Annual Appraisal of Potency and Spectrum program: Linezolid surveillance program results for 2008. *Diagn. Microbiol. Infect. Dis.* 65: 404-413, 2009.
10. Jones RN, Ross JE, Fritsche TR and Sader HS. Oxazolidinone susceptibility patterns in 2004: Report from the Zyvox® Annual Appraisal of Potency and Spectrum (ZAAPS) Program assessing isolates from 16 nations. *J. Antimicrob. Chemother.* 57: 279-287, 2006.
11. Mutnick AH, Biedenbach DJ, Turnidge JD and Jones RN. Spectrum and potency evaluation of a new oxazolidinone, linezolid: Report from the SENTRY Antimicrobial Surveillance Program, 1998-2000. *Diagn. Microbiol. Infect. Dis.* 43: 65-73, 2002.
12. Pillar CM, Draghi DC, Sheehan DJ and Sahm DF. Prevalence of multidrug-resistant, methicillin-resistant *Staphylococcus aureus* in the United States: Findings of the stratified analysis of the 2004 to 2005 LEADER Surveillance Programs. *Diagn. Microbiol. Infect. Dis.* 60: 221-224, 2008.
13. Ross JE, Anderegg TR, Sader HS, Fritsche TR, Jones RN (2005). Trends in linezolid susceptibility patterns in 2002: Report from the worldwide Zyvox Annual Appraisal of Potency and Spectrum Program. *Diagn Microbiol Infect Dis* 52: 53-58.
14. Ross JE, Fritsche TR, Sader HS, Jones RN (2007). Oxazolidinone susceptibility patterns for 2005: International report from the Zyvox® Annual Appraisal of Potency and Spectrum Study. *Int J Antimicrob Agents* 29: 295-301.