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

JE ROSS, RN JONES, PA HOGAN, DJ SHEEHAN

JMI Laboratories, North Liberty, IA, USA; Pfizer Inc, New York, NY, USA

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

ABSTRACT

Background: The 2006 ZAAPS Program (year 5) has monitored various global areas for emerging resistance (R) to antimicrobial agents, especially linezolid (LZD), a first in class oxazolidinone. LZD use continues to increase, both in volume and geographically into other nations, resulting in the need for continued monitoring for sustained potency and the emergence of R.

Methods: 4,216 Gram-positive (GP) strains were collected at 50 medical centers in 16 countries. 200 isolates/nation were submitted (except for Canada where each site [5] submitted 200) for CLSI broth microdilution susceptibility (S) testing. Major organism groups tested were: *S. aureus* (SA; 2276), coag-neg staphylococci (CoNS; 615), enterococci (ENT; 423), *S. pneumoniae* (SPN; 398), viridans group (VGS; 209) and ß-haemolytic streptococci (BHS; 295). 13 to 15 comparator agents were included and current CLSI interpretative criteria applied.

Results: Table: Only 5 isolates (0.12%) were found to be LZD-R.

Species	Country/City	LZD MIC (µg/ml)	23S mutation
S. epidermidis	Italy/Rome	8	ND[a]
S. epidermidis	Brazil/Sao Paulo	>8	G2576T
S. epidermidis	Brazil/Sao Paulo	>8	G2576T
E. faecalis	China/Shenzhen	8	ND
E. faecium	Germany/Frankfurt	8	G2576T

a. ND = none detected

MRSA rates varied between nations but remained consistent with 2002-2005 ZAAPS reports: Latin America, 43.9%; Europe, 25.2%; and Asia-Pacific, 47.7%. The MIC_{90} for LZD was 2 µg/ml for SA and ENT and 1 µg/ml for all other organism groups; MIC creep was not detected. In ENT, LZD-R rate was 0.47% and the overall VRE rate was 8.3% (increasing), but not uniform across regions. No LZD-R was detected among SPN, VGS or BHS. Non-S for glycopeptides (GISA, 0.03%), streptogramins (0.17%) and daptomycin (0.17%) was also noted.

Conclusions: Within all monitored countries, LZD remained highly active (>99% S) in all GP organism groups. Rare R (0.47-0.49%) to LZD occurred in ENT and bacteremic CoNS (clonal by PFGE) organisms in 4 different nations.

INTRODUCTION

This represents the fifth year of global oxazolidinone post-approval surveillance that has monitored various geographic areas for emerging resistances to linezolid. The program followed a worldwide pre-launch sampling study called the Zyvox® Antimicrobial Potency Study (ZAPS) that published United States (USA) results using broth microdilution and Etest (AB BIODISK) MIC methods and the disk diffusion method. In Latin America, the disk diffusion and the Etest methods were applied. Also, for Europe and the Asia Pacific (APAC) nations, results were generated by the broth microdilution and Etest MIC methods in addition to the disk diffusion test. The ZAPS series of studies reported near complete coverage of pathogenic Gram-positive species by linezolid when either FDA or CLSI interpretative criteria were applied.

For 2002 and beyond, the linezolid resistance risk assessment trial was renamed as the Zyvox® Annual Appraisal of Potency and Spectrum (ZAAPS) program and initially included sampling of the USA and the rest-of-world (ROW). In 2004, the USA sample was expanded to approximately 50 sites (two-fold increase) and renamed the Linezolid Experience and Accurate Determination of Resistance (LEADER) program, but the ROW sampling remained in the ZAAPS Program initiative.

Linezolid, the first oxazolidinone class agent to be FDA approved for clinical use, has become a welcome therapeutic addition for infections caused by commonly occurring antimicrobial-resistant Gram-positive pathogens. Resistance to linezolid initially was very infrequent, however, documented occurrences have been noted, usually among enterococci and more recently coagulase-negative staphylococci (CoNS). The occurrence of linezolid resistance must be classified as very rare among *S. aureus* and streptococci, and is usually associated with prolonged therapeutic exposure or infected indwelling devices. Some oxazolidinone-resistant strains have emerged in patients without prior drug exposure, each event attributed to clonal, epidemic spread from other patients in the hospital environment.

This report presents summaries of the results from 50 laboratories providing isolates for the central laboratory-based surveillance study (16 nations; Table 1) in 2006. A total of 4,216 strains were tested and reported; the USA data will be reported separately as the LEADER (2006) program summary.

MATERIALS AND METHODS

A total of 4,216 isolates were received by the central monitoring sites. Each participating site or country forwarded a target total of 200 consecutive, non-duplicate patient isolates from infections of the bloodstream, respiratory tract, urinary tract, or wounds/skin and soft tissue. The 16 countries and sites that participated were distributed as follows: Latin America (4 countries; 10 sites), Europe (6 countries; 14 sites), the APAC region (5 countries; 21 sites), and North America (Canada only; 5 sites).

All isolates were identified by the submitting laboratory and confirmed by the central facility using standardized and commercial methods. Isolates were grouped for analysis as follows: *S. aureus* (2,276 strains), CoNS (615 strains), ß-haemolytic streptococci (295 strains), viridans group streptococci (209 strains), *Streptococcus pneumoniae* (398 strains) and enterococci (423 strains). These isolates included regional sampling of Canada (991 strains), Latin America (902 strains), Europe (1,263 strains) and the APAC region (1,060 strains), see Table 1. With the addition of these 4,216 isolates, the total number of Gram-positive strains tested in the five years of the ZAAPS Program has reached 28,579.

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, OH, USA). Categorical interpretations of MIC results are found in the Clinical and Laboratory Standards Institute (CLSI) document M100-S17, and quality control organism results were within the acceptable published ranges.

Isolates that were resistant to linezolid upon initial testing were confirmed by repeat reference broth microdilution, Etest and disk diffusion 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.

RESULTS

- A total of 2,276 *S. aureus* isolates were tested (1,416 tested in 2005) from 16 nations and MRSA rate examples include: for Latin America (average at 43.9%, range 31.0% [Brazil] to 55.7% [Argentina]), for Europe (average at 25.2%, range 3.8% [Sweden] to 44.0% [UK]) and the APAC region (average at 47.7%; range 30.0% [Australia] to 76.3% [Korea]); see Tables 2 and 3.

- The *S. aureus* linezolid MIC_{50} and MIC_{90} was 2 µg/ml and the MIC distribution (Figure 1) illustrates a prominent mode at 2 µg/ml with a skewing of MIC results toward the lower MICs of 0.25 -1 µg/ml. When the MRSA and MSSA populations are compared, a clear difference was noted for greater susceptibility of MRSA to linezolid inhibition (modal MIC, 1 µg/ml). No evidence of MIC creep was detected, or escalation in the number of linezolid-resistant isolates (MIC, ≥8 µg/ml).

- The variations in CoNS resistance rates to the listed drugs and from earlier reports were minimal. Examples include oxacillin resistance rates that ranged from 52.2% (UK) to 89.3% (Argentina), but 7 of the 16 countries had rates greater than 80% (all in Latin America and APAC areas; Table 3).

  Linezolid MIC values were generally lower by one doubling dilution for CoNS when compared to the *S. aureus* results (Table 2). Three (3) CoNS strains were detected with linezolid MIC results at >8 µg/ml (non-susceptible).

- Among enterococci, vancomycin resistance (VRE) overall was 8.3% (3.0% increase over 2004), but the rates by nation were not uniform (0.0-30.0%; see Table 3). Increasing rates of VRE occurrence in 2006 were detected in Canada (4.3%), Argentina (10.0%), Brazil (15.0%), Chile (5.0%), Germany (9.5%), Italy (5.0%), UK (25.0%), Australia (4.8%), China (2.4%), Korea (30.0%) and Taiwan (20.0%).

  The range of linezolid MIC values reported was 0.25 - 8 µg/ml with 96.5% of MIC results at either 1 or 2 µg/ml (Table 2 and 3). Only two linezolid MIC values were found at 4 µg/ml (intermediate), and in contrast to the 2005 ZAAPS reports, two linezolid-resistant strains were detected.

Table 1. Distribution of organism identifications for the 2006 ZAAPS sample tested by nation of origin (4,216 strains).

Nation (no. medical centers)	No of strains: *S. aureus*	CoNS[a]	Enterococci	*S. pneumoniae*	Viridans gr. streptococci	ß-haemolytic streptococci	Total
Canada (5)	517	191	94	91	46	52	991
Argentina (2)	122	28	20	20	6	15	211
Brazil (4)	100	98	20	20	5	15	258
Chile (2)	138	12	20	20	34	10	234
Mexico (2)	93	23	46	27	4	6	199
France (4)	100	40	20	20	10	19	209
Germany (2)	100	40	21	20	19	10	210
Italy (3)	100	40	20	20	1	26	207
Spain (2)	110	30	20	20	4	27	211
Sweden (2)	132	17	19	20	15	15	218
United Kingdom (1)	125	23	20	20	10	10	208
Australia (5)	160	23	21	25	20	20	269
Hong Kong (1)	72	0	11	1	5	12	101
China (10)	220	16	41	50	16	0	343
Korea (3)	135	28	20	18	9	10	220
Taiwan (2)	52	6	10	6	5	48	127
TOTAL (50)	2,276	615	423	398	209	295	4,216

a. CoNS = coagulase-negative staphylococci.

- This population of pneumococci (398; Table 2) had overall penicillin and erythromycin non-susceptibility rates of 28.1% (increased 5.5% from 2004) and 32.4% (decreased since 2005), respectively. The highest penicillin resistance rates were observed in the APAC region (Hong Kong at 57.1% [2005]; Korea at 61.1%; and Taiwan at 69.7% [2005]) and in France at 25.0%. The fluoroquinolones (stable at 1.3% resistant), ceftriaxone (2.3% resistant; 1.6% increase), quinupristin/dalfopristin (0.0% resistant) and vancomycin (0.0% resistant) remained the most active agents tested against *S. pneumoniae*.

- Linezolid activity versus pneumococci was excellent (modal MIC was 1 µg/ml). No significant variations in linezolid potency were observed between countries, and these results were unchanged from the 2002 ZAAPS report.

Table 2. Comparative activity of linezolid tested against 4,216 Gram-positive cocci from 16 nations in the ZAAPS Program (2006).

Organism (no. tested)/antimicrobial agent	MIC (µg/ml) 50%	90%	Range	% by category[a] Susceptible/Resistant
S. aureus (2,276)				
Linezolid	2	2	0.25-4	100.0 / -
Ciprofloxacin	0.5	>4	0.06->4	59.1 / 39.5
Clindamycin	≤0.25	>2	≤0.25->2	68.8 / 31.1
Erythromycin	0.5	>2	≤0.25->2	53.3 / 46.2
Gentamicin	≤2	>8	≤2->8	77.9 / 21.8
Oxacillin[a]	0.5	>2	≤0.25->2	60.2 / 39.8
Quinupristin/dalfopristin	0.5	0.5	≤0.25->2	99.8 / 0.1
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	92.8 / 7.2
Vancomycin	1	1	≤0.12-4	99.9 / 0.0
Coagulase-negative staphylococci (615)				
Linezolid	1	1	≤0.06->8	99.5 / -
Ciprofloxacin	4	>4	≤0.03->4	46.5 / 51.5
Clindamycin	≤0.25	>2	≤0.25->2	60.7 / 38.7
Erythromycin	>2	>2	≤0.25->2	33.8 / 65.3
Gentamicin	≤2	>8	≤2->8	57.7 / 29.9
Oxacillin[a]	>2	>2	≤0.25->2	25.7 / 74.3
Quinupristin-dalfopristin	≤0.25	0.5	≤0.25->2	99.0 / 0.5
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	59.3 / 40.7
Vancomycin	1	2	≤0.12-2	100.0 / 0.0
Enterococci (423)				
Linezolid	1	2	0.5-8	99.1 / 0.5
Ampicillin[b]	≤1	>16	≤1->16	76.4 / 23.6
Ciprofloxacin	4	>4	0.12->4	45.6 / 50.1
Gentamicin (HL)	≤500	>1000	≤500->1000	61.7 / 38.3
Quinupristin/dalfopristin	>2	>2	≤0.25->2	19.6 / 74.0
Streptomycin (HL)	≤1000	>2000	≤1000->2000	65.6 / 34.4
Teicoplanin	≤2	≤2	≤2->16	94.8 / 5.2
Vancomycin	1	4	0.25->16	91.7 / 6.6
S. pneumoniae (398)				
Linezolid	1	1	0.25-2	100.0 / -
Amoxicillin/clavulanic acid	≤1	2	≤1->16	91.4 / 5.8
Ceftriaxone	≤0.25	1	≤0.25-16	94.0 / 2.3
Ciprofloxacin	1	2	0.12->4	(4.8)[b]
Clindamycin	≤0.25	>2	≤0.25->2	77.6 / 21.9
Erythromycin	≤0.25	>2	≤0.25->2	67.6 / 32.4
Levofloxacin	1	1	≤0.5->4	98.7 / 1.0
Penicillin	≤0.03	2	≤0.03-16	71.9 / 13.8
Quinupristin/dalfopristin	0.5	1	≤0.25-2	98.0 / 0.0
Vancomycin	≤1	≤1	≤1	100.0 / -
Viridans group streptococci (209)				
Linezolid	1	1	≤0.06-2	100.0 / -
Ceftriaxone	≤0.25	0.5	≤0.25-8	97.6 / 1.4
Ciprofloxacin	1	4	0.06->4	(14.4)[b]
Clindamycin	≤0.25	≤0.25	≤0.25->2	90.4 / 9.6
Erythromycin	≤0.25	>2	≤0.25->2	64.1 / 34.4
Levofloxacin	1	2	≤0.5->4	96.7 / 3.3
Penicillin[a]	0.06	0.5	≤0.015-4	78.5 / 0.5
Quinupristin/dalfopristin	0.5	1	≤0.25->2	98.6 / 0.5
Vancomycin	0.5	1	≤0.12-1	100.0 / -
ß-haemolytic streptococci (295)				
Linezolid	1	1	0.5-2	100.0 / -
Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0 / -
Ciprofloxacin	0.5	1	0.25->4	(1.0)[b]
Clindamycin	≤0.25	>2	≤0.25->2	84.7 / 15.3
Erythromycin	≤0.25	>2	≤0.25->2	75.3 / 23.7
Levofloxacin	≤0.5	1	≤0.5->4	99.3 / 0.7
Penicillin[a]	≤0.015	0.06	≤0.015-0.12	100.0 / -
Quinupristin-dalfopristin	≤0.25	0.5	≤0.25-2	99.7 / 0.0
Vancomycin	0.5	0.5	0.25-1	100.0 / -

a. Criteria as published by the CLSI [2007], beta-lactam susceptibility should be directed by the oxacillin test results for staphylococci and by ampicillin or penicillin for *Enterococcus* or streptococci when testing selected penicillins or carbapenems.
b. Percentage of pneumococci or other streptococci with ciprofloxacin MICs at ≥4 µg/ml , indicating possible QRDR mutations.

- The sample of α-haemolytic streptococcal species had an overall penicillin resistance (MIC, 4 µg/ml) rate of only 0.5%, but a non-susceptibility rate of 21.5%. Note the elevated levels of ciprofloxacin resistance at 14.4%. Linezolid ($MIC_{50/90}$, 1 µg/ml) was very active against viridans group streptococci.

- Table 2 lists the activity of linezolid tested against 295 isolates of ß-haemolytic *Streptococcus* spp. Penicillin remained very active against all strains, but macrolide resistance was observed in 23.7% (16.5% in 2005) of these organisms. Linezolid activity was most similar to that described earlier for *S. pneumoniae* and CoNS ($MIC_{50/90}$, 1 µg/ml; Tables 2 and 4).

- All linezolid non-susceptible strains were examined for mechanisms of resistance and by molecular methods for epidemic/endemic clonality. One of these strains was a *S. epidermidis* isolated in Italy (Table 5) and further examination of other *S. epidermidis* isolates from the same medical center discovered four other CoNS strains with elevated linezolid MIC values (4 or 8 µg/ml). All of these organisms were clonally related (PFGE/riboprint pattern, A/328.5; see Table 5). The remaining two linezolid-resistant strains were discovered in Brazil, and were a clonal population with local dissemination (PFGE/riboprint pattern, A/351.6).

  In 2006, linezolid resistant enterococcal strains were isolated in Germany (*E. faecium*) and China (*E. faecalis*). The strain from Germany had a G2576T ribosomal target mutation, but the Chinese isolates did not show a mutation at that target site (Table 5).

Table 3. Resistance rates for national samples obtained in the 2006 ZAAPS Program.

Country	% Oxacillin-resistant *S. aureus*	CoNS	% *S. pneumoniae* resistance to: Penicillin	Erythromycin	Clindamycin	Levofloxacin	VRE[a]
Canada	48.2[b]	67.5	5.5	12.1	2.2	0.0	4.3
Argentina	55.7	89.3	5.0	15.0	15.0	0.0	10.0
Brazil	31.0	88.8	5.0	10.0	0.0	0.0	15.0
Chile	50.0	75.0	20.0	30.0	0.0	5.0	5.0
Mexico	38.7	87.0	3.7	22.2	0.0	0.0	0.0
France	33.0	60.0	25.0	60.0	45.0	0.0	0.0
Germany	14.0	70.0	0.0	20.0	5.0	5.0	9.5
Italy	30.0	75.0	0.0	40.0	20.0	0.0	5.0
Spain	26.4	63.3	0.0	30.0	25.0	0.0	0.0
Sweden	3.8	70.6	5.0	5.0	0.0	0.0	0.0
United Kingdom	44.0	52.2	0.0	5.0	5.0	0.0	25.0
Australia	30.0	82.6	24.0	24.0	16.0	0.0	4.8
Hong Kong	37.5	-	-	-	-	-	0.0
China	35.0	87.5	28.0	82.0	82.0	2.0	2.4
Korea	76.3	85.7	61.1	88.9	72.2	5.6	30.0
Taiwan	59.6	-	-	-	-	-	20.0
All	39.8	74.3	13.8	32.4	21.9	1.0	6.6

a. VRE = vancomycin-resistant enterococci; - = small sample size (see Table 1).
b. Canada was not sampled in a prevalence design, target was 50% MRSA.

Table 4. Cumulative percentage inhibited results at each linezolid MIC when testing six different groups of Gram-positive cocci isolated on four continents (ZAAPS, 2006)[a].

Organism group (no. tested)	Cumulative % inhibited at linezolid MIC (µg/ml): ≤0.12	0.25	0.5	1	2	4	8
Viridans group streptococci (209)	0.5	4.3	41.1	99.0	100.0	-	-
S. pneumoniae (398)	0.0	2.8	27.4	97.5	100.0	-	-
ß-haemolytic streptococci (295)	0.0	0.0	20.3	99.3	100.0	-	-
CoNS (615)	0.5	2.0	33.3	97.7	99.5	99.5	99.7[b]
Enterococci (423)	0.0	0.0	2.6	60.8	99.1	99.5[c]	100.0[d]
S. aureus (2,276)	0.0	0.2	1.7	43.0	>99.9	100.0[e]	-

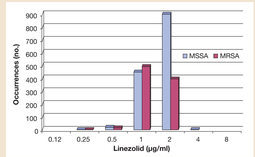
a. Organism groups are ranked in decreasing order of susceptibility to the oxazolidinone.
b. Three *S. epidermidis* strains from two medical centers (Italy and Brazil).
c. Two strains.
d. Two strains from medical centers in China and Germany.
e. Only one strain.

Table 5. Distribution of linezolid-non-susceptible pathogens and results of target mutation and epidemiologic analysis.

Isolate	Species	Country	Linezolid MIC (µg/ml)	Epidemiology pattern: PFGE/riboprint	23S rRNA mutation
I-1	*S. epidermidis*	Italy	8	A/328.5	ND[a]
B-1	*S. epidermidis*	Brazil	>8	A/351.6	G2576T
B-2	*S. epidermidis*	Brazil	>8	A/351.6	G2576T
C-1	*E. faecalis*	China	8	ND	ND
G-1	*E. faecium*	Germany	8	ND	G2576T

a. ND = not determinable.

Figure 1. Linezolid MIC distributions for *S. aureus* comparing by MRSA (905) and MSSA (1371) groups.



CONCLUSIONS

- In this report for non-USA samples, the CLSI reference method was applied and non-susceptible results confirmed by molecular tests for target mutational events and alternative susceptibility tests. Across all six groups of Gram-positive pathogens monitored in the 16 nations, linezolid activity remains stable and without significant occurrence of organisms with MIC values of ≥ 4 µg/ml (8 strains).

- No evidence of linezolid MIC creep was observed when comparing ZAAPS 2006 results to those reported for 2002-2005 or to the quantitative in vitro MIC values in the ZAPS reports (prior to 2000).

- It is noteworthy that clonality of the CoNS linezolid-resistant strains was proven by two epidemiologic methods (Table 5). This emphasizes the importance of infection control in limiting oxazolidinone resistance dissemination in the hospital environment.

- Other Gram-positive-active agents were also noted to be less active against contemporary *S. aureus* isolates such as: vancomycin (0.03% non-susceptible [intermediate]), teicoplanin (0.03% non-susceptible [intermediate]), quinupristin/dalfopristin (0.17% non-susceptible [intermediate and resistant]), and daptomycin (0.17% non-susceptible).

- Overall, linezolid remained active against 4,211 of 4,216 (99.88% susceptible) strains that were processed in the 2006 ZAAPS Program. This rate (0.12% non-susceptible) was superior to that of any glycopeptide, lipopeptide or streptogramin combination due to escalating rates of VRE and other multidrug-resistant strains.

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