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Oxazolidinone Susceptibility Patterns in 2004: Report from the Worldwide Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS) Program

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ABSTRACT

Background: As resistance (R) rates among Gram-positive pathogens increase, the oxazolidinone linezolid (LZD), remains a potent choice for community- and hospital-acquired infections. Worldwide ZAAPS program reports 3 years of LZD surveillance results.

Methods: A total of 4,098 Gram-positive strains in 2004 were collected from 42 laboratories located in North America (5 sites; Canada only), South America (10 sites), Europe (16 sites) and Asia-Pacific (11 sites). Each site submitted 200 isolates for reference CLSI broth microdilution MIC processing and identification confirmation. As many as 24 comparator agents were tested along with QC strains with interpretative criteria from the CLSI M100-S15 (2005) applied.

Results: No LZD resistance was detected in the 16 monitored countries for 2004, consistent with 2002-2003 results. Prior ZAAPS reports discovered LZD-R strains only in the USA. LZD remained highly active against *S. pneumoniae* (MIC_{90}, 1 µg/ml), viridans gr streptococci (MIC_{90}, 1 µg/ml) and ß-haemolytic streptococci (MIC_{90}, 1 µg/ml). Against *S. aureus* (MIC_{90}, 2 µg/ml), LZD showed 99.5% of results at 0.5 - 2 µg/ml with only 1 isolate at 4 µg/ml. MRSA rates varied between nations, ranging from 1.4% in Sweden to 29.5% in the UK for Europe and as high as 65.2% in Mexico. LZD MIC values were generally 1 log_2 dilution step lower for coagulase-negative staphylococci (CoNS) when compared to *S. aureus* and no LZD results at 4 µg/ml were observed. Compared to ZAAPS 2002 and 2003, enterococcus results, where 7 R strains were identified (USA), 2004 revealed no R and 98.1% of results were at 1 or 2 µg/ml. Vancomycin R enterococci rate was 5.3% overall, which varied markedly by country including a high of 47.2% in Korea.

Conclusions: LZD continues to be highly effective against Gram-positive pathogens from 5 continents. No resistant strains were identified in the year 2004 strains collected from 16 nations (20,158 strains for 2002-2004). LZD-R does not appear to be evolving rapidly.

INTRODUCTION

Linezolid was the first clinically applied oxazolidinone and has become a welcome addition to those agents used to treat infections caused by resistant Gram-positive cocci. Resistance to linezolid has been observed, particularly among *Staphylococcus aureus* and enterococci, but the occurrence rates have been classified as rare and usually associated with prolonged therapy and indwelling device infections. Some oxazolidinone-resistant strains have emerged in patients without prior drug exposure, each event attributed to clonal spread of strains from other patients in the hospital environment.

As linezolid use increases, both in the current prescription environment and geographically into new areas, the need for activity and resistance rate monitoring also becomes critical. In vitro studies of linezolid activity (ZAPS protocols) before release by the USA-FDA indicated that an excellent spectrum of activity could be expected against Gram-positive pathogens isolated in North America (23,261 strains), Latin America (2,640 strains), Europe (5,598 strains) and the Western Pacific (2,143 strains). The occurrence of linezolid-resistant isolates in the ZAPS international studies was extremely rare (one case in the Western Pacific) and when local laboratories detected resistance by MIC or disk diffusion methods, the local test method result was found to be erroneous by follow-up procedures performed in reference laboratories. The potential for continuing increases in oxazolidinone resistance in nations where the drug (linezolid) has been introduced requires well constructed and executed resistance surveillance protocols (ZAPS and ZAAPS) using reference MIC methods to assure accuracy of results.

This report summarizes the results of the 2004 Zyvox® Annual Appraisal of Potency and Spectrum (ZAAPS) Program for 16 nations (Table 1). These results will be compared to the ZAAPS Program results for 2002 - 2003, when the USA was part of the study. All tests were performed in a GLP reference laboratory using CLSI (formerly NCCLS) broth microdilution methods and published interpretive criteria.

MATERIALS AND METHODS

The central monitoring site (JMI Laboratories, North Liberty, IA, USA) collected a total of 4,089 isolates for the 2004 ZAAPS Program from sites in Latin America (four nations/10 sites), Europe (six nations/16 sites), the Western Pacific (five nations/11 sites) and North America (Canada only/five sites; see Table 1). Each participating site or country forwarded a target total of 200 consecutive, non-duplicate patient specimens originating from patients having infections of the bloodstream, respiratory tract, urinary tract or wounds/skin and soft tissue.

The collection included *S. aureus* (1,422 isolates), *Streptococcus pneumoniae* (796 isolates), coagulase-negative staphylococci (CoNS; 652 isolates), enterococci (719 isolates), ß-haemolytic streptococci (313 isolates) and viridans group streptococci (196 isolates). This represented a compliance rate of > 100% (target number was 4,000 strains; Table 1). All isolates were identified by the submitting laboratory and confirmed by the central monitor using standard biochemical algorithms and/or commercial methods (Vitek System; bioMerieux, Hazelwood, MO, USA). The results for the 2004 ZAAPS Program were similar to the numbers tested for the year 2002 - 2003 ZAAPS Program excluding USA, thus a total of 20,158 Gram-positive cocci were processed during the first three years of the ZAAPS oxazolidinone resistance surveillance program.

Antimicrobial susceptibility testing was performed on all isolates using the reference broth microdilution method as described in the Clinical and Laboratory Standards Institute (CLSI; formerly the National Committee for Clinical Laboratory Standards [NCCLS]) document. The validated, dry-form microdilution panels and cation-adjusted Mueller-Hinton broth (with 2 - 5% lysed horse blood added for testing of streptococci) were prepared by and/or purchased from TREK Diagnostics (Cleveland, OH, USA). Interpretations of quantitative minimum inhibitor concentration (MIC) results and quality control strains (*S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619) were in accordance with the CLSI tables.

All isolates were tested against antimicrobial agents active against Gram-positive organisms, including (not limited to) linezolid, amoxicillin/clavulanic acid, ampicillin, cefepime, ceftriaxone, chloramphenicol, ciprofloxacin, clindamycin, erythromycin, gentamicin, levofloxacin, oxacillin, penicillin, quinupristin/dalfopristin, rifampin, streptomycin, teicoplanin, tetracycline, trimethoprim/sulfamethoxazole and vancomycin.

All linezolid-resistant isolates (MIC, ≥ 8 µg/ml), if detected, were confirmed by Etest (AB BIODISK, Solna, Sweden) and/or disk diffusion methods. The determination of the domain V 23S ribosomal target mutation(s) was performed by polymerase chain reaction (PCR) amplification and sequence analysis as described previously.

RESULTS

- Activity of linezolid against *S. aureus*. A total of 1,422 *S. aureus* strains were tested by reference methods with sample sizes varying from 49 (France) to 257 (Canada) isolates per country (Tables 1 and 2). MRSA rates were quite different between nations and continents. Examples of differences within a continent or region were: for Europe MRSA ranged from 1.4 - 7.1% (Sweden and Germany) to 29.5 - 30.0% (UK and Italy); for Latin America MRSA rates were more uniformly high at 32.6 - 65.2% (highest in Mexico); for the Western Pacific the MRSA rate in Australia was lower (17.1%) compared to the other four monitored nations (40.0 - 75.0%); and finally Canada had a modest MRSA occurrence rate of only 14.0%.

- The linezolid results for *S. aureus* showed a narrow distribution of MIC values with 99.5% of results at 0.5 - 2 µg/ml (Table 3). The MIC_{50} and MIC_{90} of linezolid for all monitored isolates was 2 µg/ml. This was also true for every country except Italy where the MIC_{90} was 1 µg/ml. Only one isolate was observed to have a reproducible linezolid MIC at 4 µg/ml. These results are unchanged from ZAAPS Program reports in 2002 and 2003 for non-USA *S. aureus* strains. In fact, earlier reports (2002) documented one occurrence of a linezolid-resistant *S. aureus* and CoNS, both USA isolates. Also the modal linezolid MIC (2 µg/ml; 1,042 of 1,422 results) remains unchanged and the percentages of strains with a linezolid MIC at 4 µg/ml has remained stable or decreasing (0.53, 0.87 and 0.07%).

- Activity of linezolid against CoNS. Among the 652 isolates of CoNS tested, the variations in resistance rates to the listed drugs and from earlier reports were minimal. Examples include the oxacillin resistance rates that only ranged from 63.2% (Sweden) to 93.2% (Italy), but 14 of the 16 countries had rates between 71.1 - 85.0% (average, 77.5%). This compares favorably to the USA (prior years data) and Canada (76.9% in this report).

  Linezolid MIC values were generally one log_2 dilution step lower for CoNS when compared to the *S. aureus* results (Tables 2 and 3). The modal, MIC_{50} and MIC_{90} linezolid MIC for CoNS was 1 µg/ml with a range of only 0.25 - 2 µg/ml. These overall results were characteristic for all countries except Sweden, UK and Korea where the MIC_{90} was higher at 2 µg/ml. Like vancomycin, linezolid was active against all staphylococci at ≤ 4 µg/ml.

- Activity of linezolid against enterococci. A total of 719 enterococci were tested against linezolid and numerous other antimicrobials (Table 2). Among these isolates, *E. faecalis* (486 strains) and *E. faecium* (164 strains) predominated at 90.4% of strains tested. Vancomycin resistance (VRE) overall was 5.3% (includes intermediate category), but the rates by nation were not uniform. Chile, Mexico, Germany, Spain, Sweden, Australia, Hong Kong and Taiwan did not have any VRE isolates during the monitored interval. In contrast, moderate rates of VRE occurrence were detected in Canada (3.0%), Argentina (5.0%), Brazil (3.6%), France (6.7%; all intermediate), Italy (14.3%), UK (9.5%) and Japan (4.4%). The VRE rate was 47.2% in Korea, the highest ever recorded for a national sample in the ZAPS or ZAAPS programs.

  Although VRE appears to be endemic in several nations and compromises treatment, linezolid resistance was not observed. Linezolid modal, MIC_{50} and MIC_{90} results were 2 µg/ml (Table 2). The range of linezolid MIC values reported was only 0.5 - 2 µg/ml with 98.1% of MIC results at either 1 or 2 µg/ml. Five national samples of enterococci had a MIC_{90} result that varied from the all-nation average by being lower at 1 µg/ml (Mexico, Italy, Spain, Australia and Korea). All prior linezolid-resistant enterococci (seven strains) documented by the ZAAPS Program were detected in the USA (2002 - 2003). No change in the linezolid MIC distribution was found when comparing these 2004 results to previously reported survey years.

Table 1. Distribution of organism identifications for the ZAAPS Program (2004) sample indexed by nation of origin (4,098 strains).

	No. of strains						
Nation (no. medical centers)	SA	CoNS	ENT	SPN	VGS	ß-S	Total
Canada (5)	257	182	263	146	69	88	1,005
Argentina (2)	95	41	20	41	4	8	209
Brazil (4)	100	60	55	50	1	3	269
Chile (2)	165	13	1	14	0	4	197
Mexico (2)	85	74	58	6	0	0	223
France (5)	49	41	30	40	19	20	199
Germany (2)	70	45	50	7	11	17	200
Italy (3)	60	44	28	61	2	4	199
Spain (2)	79	20	28	33	1	39	200
Sweden (2)	73	19	30	50	14	14	200
United Kingdom (2)	88	17	21	46	5	23	200
Australia (4)	70	38	31	60	33	30	262
Hong Kong (1)	54	0	12	44	3	9	122
Japan (3)	68	40	45	83	16	7	259
Korea (2)	50	18	36	70	7	20	201
Taiwan (1)	59	0	11	45	11	27	153
TOTAL (42)	1,422	652	719	796	196	313	4,098

SA =*S. aureus*, ENT=Enterococci, SPN = *S. pneumoniae*, VGS = viridans group streptococci, ß-S = ß-streptococci

Table 2. Comparative activity of linezolid tested against 4,098 Gram-positive cocci from 16 nations in the ZAAPS Program (2004).

	MIC (µg/ml)			% by category[a]
Antimicrobial agent	50%	90%	Range	%susceptible/resistant
S. aureus (1,422)				
Linezolid	2	2	0.12-4	100.0/-
Chloramphenicol	8	16	≤2->16	88.3/7.9
Ciprofloxacin	0.5	>4	≤0.03->4	63.8/35.3
Clindamycin	0.12	>8	≤0.06->8	71.5/28.3
Erythromycin	0.25	>8	≤0.06->8	59.1/39.9
Gentamicin	≤2	>8	≤2->8	77.1/22.3
Levofloxacin	0.25	>4	≤0.03->4	64.8/34.2
Oxacillin	0.5	>2	0.25->2	65.8/34.2
Quinupristin/dalfopristin	0.5	0.5	≤0.25->2	99.9/0.1
Rifampin	≤0.5	≤0.5	≤0.5->2	94.8/2.1
Teicoplanin	≤2	≤2	≤2-4	100.0/0.0
Tetracycline	0.5	>8	≤0.25->8	85.0/14.6
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	92.1/7.9
Vancomycin	1	1	0.25-4	100.0/0.0
CoNS (652)[b]				
Linezolid	1	1	0.25-2	100.0/-
Chloramphenicol	4	>16	≤2->16	88.5/11.0
Ciprofloxacin	0.5	>4	0.06->4	51.8/43.7
Clindamycin	0.12	>8	≤0.06->8	64.3/35.3
Erythromycin	>8	>8	≤0.06->8	37.3/61.7
Gentamicin	≤2	>8	≤2->8	60.0/26.7
Levofloxacin	0.5	>4	0.06->4	52.5/39.9
Oxacillin	>2	>2	≤0.25->2	22.5/77.5
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25-2	99.5/0.0
Rifampin	≤0.5	1	≤0.5->2	91.1/7.4
Teicoplanin	2	8	≤0.12->16	96.0/0.5
Tetracycline	≤2	>8	≤2->8	85.1/14.0
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	58.1/41.9
Vancomycin	1	2	0.25-4	100.0/0.0
Enterococcus spp. (719)[c]				
Linezolid	2	2	0.5-2	100.0/0.0
Ampicillin	2	>16	≤1->16	76.8/23.2
Chloramphenicol	8	>16	≤2->16	78.6/19.6
Ciprofloxacin	2	>4	0.06->4	46.2/47.8
Erythromycin	>8	>8	≤0.06->8	10.6/60.4
Gentamicin (HL)	≤500	>1000	≤500->1000	64.9/35.1
Levofloxacin	2	>4	0.25->4	52.6/45.2
Penicillin	4	>32	≤0.016->32	73.2/26.8
Quinupristin/dalfopristin	>2	>2	≤0.25->2	21.7/69.4
Rifampin	2	>2	≤0.25->2	25.3/49.4
Streptomycin (HL)	≤1000	>2000	≤1000->2000	68.8/31.2
Teicoplanin	≤2	≤2	≤2->16	95.8/3.6
Tetracycline	>8	>8	≤0.25->8	38.7/60.9
Vancomycin	1	2	0.25->16	94.7/4.5
S. pneumoniae (796)				
Linezolid	1	1	≤0.12-2	100.0/-
Amoxicillin/clavulanic acid	0.5	2	≤0.06-16	93.2/4.0
Cefepime	≤0.12	1	≤0.12-4	90.5/0.3
Ceftriaxone	≤0.25	1	≤0.25-4	94.6/0.3
Clindamycin	≤0.25	>2	≤0.25->2	71.9/27.2
Erythromycin	≤0.25	>32	≤0.25->32	58.2/41.0
Gatifloxacin	0.25	0.5	0.06->4	98.4/1.6
Levofloxacin	1	1	0.12->4	98.4/1.6
Penicillin	≤0.03	4	≤0.03-8	63.4/22.6
Quinupristin/dalfopristin	≤0.5	≤0.5	≤0.5-2	99.9/0.0
Rifampin	≤0.5	≤0.5	≤0.5->2	99.9/0.1
Tetracycline	≤2	>16	≤2->16	61.7/36.7
Trimethoprim/sulfamethoxazole	≤0.5	4	≤0.5->4	64.3/25.4
Vancomycin	0.25	0.5	≤0.06-1	100.0/-
viridans group streptococci (196)[d]				
Linezolid	1	1	≤0.12-2	100.0/-
Cefepime	≤0.12	1	≤0.12->16	92.9/3.1
Ceftriaxone	≤0.25	1	≤0.25->32	94.4/4.1
Chloramphenicol	≤2	4	≤2-16	98.5/0.5
Clindamycin	≤0.06	1	≤0.06->8	89.3/10.2
Erythromycin	≤0.06	>8	≤0.06->8	58.2/40.8
Levofloxacin	1	2	≤0.03->4	96.4/3.1
Penicillin	0.06	1	≤0.016->32	68.9/5.1
Quinupristin/dalfopristin	0.5	1	≤0.25-2	98.5/0.0
Tetracycline	≤2	>8	≤2->8	64.3/33.2
Vancomycin	0.5	1	≤0.12-1	100.0/-
ß-haemolytic streptococci (313)[e]				
Linezolid	1	1	0.25-2	100.0/-
Cefepime	≤0.12	≤0.12	≤0.12-0.25	100.0/-
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0/-
Chloramphenicol	≤2	4	≤2->16	97.1/2.9
Clindamycin	≤0.06	≤0.06	≤0.06->8	92.7/7.0
Erythromycin	≤0.06	8	≤0.06->8	77.0/22.7
Levofloxacin	0.5	1	0.25->4	99.4/0.3
Penicillin	≤0.016	0.06	≤0.016-0.06	100.0/-
Quinupristin/dalfopristin	≤0.25	0.5	≤0.25-1	100.0/0.0
Tetracycline	≤2	>8	≤2->8	52.1/47.3
Vancomycin	0.25	0.5	0.25-1	100.0/-

a. Criteria as published by the CLSI (2005). ß-lactam susceptibility should be directed by the oxacillin test results.
b. Includes: Unspecated coagulase-negative staphylococci (311 strains), *Staphylococcus auricularis* (three strains), *S. capitis* (11 strains), *S. cohnii* (one strain), *S. epidermidis* (231 strains), *S. haemolyticus* (38 strains), *S. hominis* (23 strains), *S. intermedius* (one strain), *S. lugdunensis* (four strains), *S. saprophyticus* (10 strains), *S. schleiferi* (one strain), *S. sciuri* (one strain), *S. simulans* (three strains), *S. warneri* (nine strains) and *S. xylosis* (five strains).
c. Includes: Unspecated *Enterococcus* (33 strains), *E. avium* (11 strains), *E. casseliflavus* (two strains), *E. durans* (two strains), *E. faecalis* (486 strains), *E. faecium* (164 strains), *E. gallinarum* (15 strains), *E. hirae* (three strains) and *E. raffinosus* (three strains).
d. Includes: Unspecated viridans group streptococci (65 strains), *S. anginosus* (17 strains), *S. bovis* (19 strains), *S. constellatus* (10 strains), *S. gordonii* (one strain), *S. intermedius* (two strains), *S. milleri* (four strains), *S. mitis* (36 strains), *S. mutans* (one strain), *S. oralis* (20 strains), *S. parasanguis* (two strains), *S. salivarius* (eight strains) and *S. sanguis* (11 strains).
e. Includes: Unspecated ß-haemolytic streptococci (one strain), group A streptococci (170 strains), group B streptococci (102 strains), group C streptococci (four strains), group G streptococci (35 strains) and *Streptococcus dysgalactiae* (one strain).

- Activity of linezolid against *S. pneumoniae*. This population of pneumococci (796 strains) had overall penicillin and erythromycin resistance rates of 22.6 and 41.0%, respectively (Table 1). These rates, however, varied greatly between nations. The highest penicillin resistance (≥ 2 µg/ml) rates were observed in the Western Pacific (Hong Kong at 52.3%; Japan at 34.9%; Korea at 62.9%; and Taiwan at 64.4%) and in France at 30.0%. The lowest penicillin-resistant rates were found in Canada (5.5%), Argentina (7.3%), Italy (4.9%), Sweden (4.0%) and the UK (4.3%). Similarly, macrolide resistance has markedly escalated for some nations in the ZAAPS sample (overall resistance rate at 41.0% for erythromycin). The countries with the highest erythromycin resistance rates were: Taiwan (91.1%) > Japan (77.1%) > Korea (75.7%) > Hong Kong (72.7%) > France (55.0%) > Spain (51.5%) > Italy (51.5%). The fluoroquinolones (0.6 - 1.6% resistant), ceftriaxone (0.3% resistant), cefepime (0.3% resistant), quinupristin/dalfopristin (0.0% resistant), rifampin (0.1% resistant) and vancomycin (0.0% resistant) remained very active against this international collection of *S. pneumoniae*.

  Linezolid activity versus pneumococci was excellent (Table 2). The clear modal MIC was 1 µg/ml and this value was also the MIC_{50} and MIC_{90}. For this distribution of linezolid MIC values, 98.5% of results were at 0.5 or 1 µg/ml. No significant variations in linezolid potency were noted between countries, and these results were unchanged from the 2002 and 2003 ZAAPS reports.

- Activity of linezolid against viridans group streptococci. A smaller sample of viridans group streptococci (196 strains) were tested and the results for linezolid and comparison drugs are found in Table 2. These α-haemolytic species had an overall penicillin-resistant (MIC, ≥ 4 µg/ml) rate of 5.1% and a non-susceptibility rate of 31.1%. Many countries had smaller samples because of fewer cases of bloodstream infections with these species, however, among those nations with ≥ 10 isolates collected, the penicillin resistance rate varied from 0.0% (Germany, Sweden and Japan) to 15.8 - 18.2% (France and Taiwan).

  Linezolid was very active against viridans group streptococci with an overall MIC mode, MIC_{50} and MIC_{90} of 1 µg/ml. Again a narrow range of oxazolidinone MIC values was found (0.12 - 2 µg/ml), with 94.4% of MICs at 0.5 or 1 µg/ml. No variations from this pattern of linezolid activity was detected in any monitored nation. In 2002, a single linezolid-resistant *S. oralis* was isolated (USA) with a high MIC (> 8 µg/ml) and a documented G2576U 23S rRNA mutation. No other resistant isolates have been detected in the 2003 or 2004 ZAAPS samples.

- Activity of linezolid against ß-haemolytic streptococci. Table 2 lists the activity of linezolid and comparators tested against 313 isolates of ß-haemolytic *Streptococcus* species. The dominant serotypes were group A (*S. pyogenes*, 170 strains) and group B (*S. agalactiae*, 102 strains), or 86.9% of tested isolates. Penicillin remained active against all strains, but macrolide resistance was observed at 22.7% of the organisms. Where national samples were ≥ 10 strains, the resistance rates for erythromycin varied from 5.9% (Germany) to 41.0% (Spain). The countries with macrolide resistance at ≥ 20.0% were: Canada (22.7%), France (25.0%), Spain (41.0%), Korea (20.0%) and Taiwan (29.6%).

  Linezolid activity against ß-haemolytic streptococci was similar to that described earlier for *S. pneumoniae*, viridans group streptococci and CoNS (MIC_{50} and MIC_{90}, 1 µg/ml; Table 2). None of the national samples varied from the all linezolid activity results. The range of linezolid MIC values against ß-haemolytic streptococci was 0.25 - 2 µg/ml and 98.4% of MIC results were either 0.5 or 1 µg/ml (86.3% at 1 µg/ml). No variation in linezolid activity was observed for this 2004 sample compared to prior years (2002 or 2003) potency against this organism group.

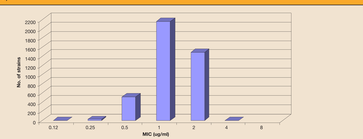
- Linezolid activity summary against all monitored Gram-positive species (Table 3). Across six groups of Gram-positive pathogens isolated in 16 nations (not USA), the linezolid activity remains stable and without significant occurrence of strains with MICs of ≥ 4 µg/ml. The limited range of linezolid MIC values (Figure 1) for each organism group was also unchanged from earlier reports from ZAPS and ZAAPS (2002 and 2003), thus indicating no significant "creep" in the MIC results for the wild-type Gram-positive organism population.

Table 3. Cumulative % inhibited results at each linezolid MIC when testing six different groups of Gram-positive cocci isolated on four continents (ZAAPS Program, 2004)[a].

	Cum. % inhibited at linezolid MIC (µg/ml)						
Organism group (no. tested)	≤0.12	0.25	0.5	1	2	4	8
viridans group streptococci (196)	1.0	4.1	30.1	99.5	100.0	-	-
S. pneumoniae (796)	0.1	1.4	19.7	98.0	100.0	-	-
ß-haemolytic streptococci (313)	0.0	0.3	12.5	98.7	100.0	-	-
CoNS (652)	0.0	0.2	24.1	94.3	100.0	-	-
Enterococci (719)	0.0	0.0	1.9	45.8	100.0	-	-
S. aureus (1,422)	0.1	0.3	1.4	26.6	99.9	100.0	-
All strains (4,098)	0.1	0.6	10.9	63.6	>99.9	100.0	-

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

Figure 1. Linezolid MIC distribution for all isolates in the 2004 ZAAPS Program in 16 nations (non-USA; 4,098 strains).



CONCLUSIONS

- Linezolid was observed to remain highly active against all tested Gram-positive cocci in the 16 monitored nations (4,098 strain sample).
- Linezolid MICs of 4 µg/ml were rare and should require retesting, if observed.
- No evidence of MIC "creep" of the linezolid wild-type strain distribution was observed (Figure 1), nor any isolates with linezolid resistance (MIC, ≥ 8 µg/ml).
- Continued surveillance appears prudent in nations where use has escalated due to emerging multidrug-resistant Gram-positive species.

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