Recent Trends in Resistance Among *S. pneumoniae* Isolates Worldwide Including an In Vitro Evaluation of BMS284756: Report from the SENTRY Antimicrobial Surveillance Program, 1999-2000

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AMENDED ABSTRACT

Background: The therapeutic use of quinolones (Q) for community-acquired respiratory infections (CARTI) has increased dramatically worldwide. BMS284756 (BMSQ), a new candidate desfluoroquinolone that exhibits a broad spectrum, and enhanced activity against Gram-positive (G+) organisms, was evaluated against *S. pneumoniae* (SPN) from centers participating in the SENTRY Program (1999-2000) in North America (NA), Latin America (LA), Europe (EU) and the Asia-Pacific (APAC) regions. **Methods**: A total of 4,168 SPN isolates were tested against BMSQ and other Q's by NCCLS microdilution in lysed horse blood MH broth. The potency and somewhat stable spectrum demographics by region were determined for each year as follows: PEN-susceptibility (S) in 1999-NA 67.2%, LA 72.4%, EU 58.7%, APAC 56.6%; and in 2000-NA 66.0%, LA 66.9%, EU 66.0%, APAC 47.9%. Erythromycin (ER)-resistance (R) ranged from APAC 47.1% in 1999 to 12.1% in LA, also in 1999; M-phenotypes predominate in NA and LA (62.6 - 67.8%) compared to EU (25.2%). **Results**: BMSQ was the most active Q tested against SPN in all monitored regions regardless of PEN- or ER-S. The BMSQ MIC_{90} for both years was essentially the same (0.06 μg/ml) for all regions. Overall BMSQ MICs ranged from ≤0.03 to 4 μg/ml (100% S using proposed breakpoint). In the PEN-R subset (765 strains), ciprofloxacin (CIPRO)-R rates at MICs ≥ 4 μg/ml (Chen et al., 1999) increased from 2.5 to 5.5% in 1 year. Overall, regional Q-R (CIPRO/LEVO %) differences were: APAC (4.4/1.5%), LA (1.8/0.2%), EU (1.5/0.1%) and NA (2.6/0.9%), but stable overall between monitored years. **Conclusions**: SPN-R strains continue to be documented worldwide, usually involving multi-R clones and Q-R strains (> in NA and APAC). PEN-R strains emphasized here, remain very S to BMSQ (MIC_{90}, 0.06 μg/ml; 16-fold more potent than LEVO), and BMSQ was consistently more active than all currently available quinolones.

INTRODUCTION

Pathogens isolated from patients diagnosed with community-acquired pneumonia continue to present therapeutic problems due to the variability of resistance profiles among common isolates including *S. pneumoniae*. Pneumococcal isolates not susceptible to currently used oral agents such as penicillin and tetracycline are now common in all geographic areas of the world. The extent of the resistance rates should be closely and longitudinally monitored using surveillance studies and reference methods, which can establish trends and document resistance mechanisms. As a result of the increasing resistance to commonly prescribed antimicrobials such as ß-lactams and macrolides in the treatment of community-acquired pneumonia, other therapeutic modalities have been utilized over the past decade. The application of quinolones has become more prevalent in the treatment of respiratory infections of all types. The broad-spectrum of the newer generation quinolones has prompted their use in the treatment of community-acquired pneumonia as the spectrum of quinolones covers all key pathogens including *H. influenzae*, *S. pneumoniae* and atypical pathogens.

BMS284756 is a novel des-fluoro(6) quinolone which has excellent antibacterial activity and pharmacokinetic properties. This compound has proven particularly potent against Gram-positive pathogens including resistant phenotypes such as oxacillin-resistant staphylococci and ciprofloxacin-resistant *S. pneumoniae*. The activity of BMS284756 has also been documented against *H. influenzae*, *M. catarrhalis* and atypical pneumonia-causing pathogens making it a favorable therapeutic option in the treatment of community-acquired respiratory tract infections. This study documents the activity of BMS284756 and other quinolones, ß-lactams, macrolide-lincosamide-streptogramin compounds and other commonly prescribed orally administered agents against recent (1999-2000) *S. pneumoniae* isolates. This study also compares the resistance rates in pneumococcus to those commonly prescribed antimicrobials found in Latin America, North America, Europe and the Asia-Pacific medical centers participating in the SENTRY Antimicrobial Surveillance Program.

Table 1. Regional variation of antimicrobial susceptibility among 4,168 strains of *S. pneumoniae* isolated in 1999-2000 from North and Latin America, Europe and the Asia-Pacific region.

	MIC (μg/ml) distributions by geographic region (no. tested)									
	Asia-Pacific (614)		Europe (749)		Latin America (502)		North America (2,303)		All regions (4,168)	
Antimicrobial agent	$MIC_{50/90}$	% susc.[a]	$MIC_{50/90}$	% susc.	$MIC_{50/90}$	% susc.	$MIC_{50/90}$	% susc.	$MIC_{50/90}$	% susc
BMS284756	0.06/0.12	100.0	0.06/0.06	100.0	0.06/0.12	100.0	0.06/0.06	100.0	0.06/0.06	100.0
Ciprofloxacin	1/2	-	1/2	-	1/2	-	1/2	-	1/2	-
Gatifloxacin	0.25/0.5	98.4	0.25/0.5	99.9	0.25/0.5	99.8	0.25/0.5	99.0	0.25/0.5	99.2
Levofloxacin	1/1	98.0	1/1	99.9	1/1	99.8	1/1	99.0	1/1	99.1
Moxifloxacin	0.12/0.25	97.8	0.12/0.25	100.0	0.12/0.12	100.0	0.12/0.25	99.0	0.12/0.25	99.2
Trovafloxacin	0.12/0.12	100.0	0.12/0.25	100.0	0.12/0.25	99.6	0.12/0.25	99.1	0.12/0.25	99.4
Penicillin	0.06/4	51.3	≤0.03/2	64.0	≤0.03/2	69.7	≤0.03/2	66.6	≤0.03/2	64.3
Cefpodoxime	0.25/4	60.6	≤0.03/2	74.4	≤0.03/2	84.3	≤0.03/2	74.8	≤0.03/2	73.8
Cefuroxime	0.5/8	59.8	≤0.06/8	74.6	≤0.06/4	84.3	≤0.06/8	73.7	≤0.06/8	73.1
Ceftriaxone	0.25/2	89.7	0.03/1	95.1	0.03/1	96.7	0.03/1	94.6	0.03/1	94.2
Cefepime	0.25/2	85.8	≤0.06/1	97.2	≤0.06/1	97.6	≤0.06/1	97.4	≤0.06/1	95.7
Erythromycin	2/>32	48.4	≤0.25/>32	73.0	≤0.25/2	86.1	≤0.25/8	74.2	≤0.25/>32	71.6
Clindamycin	≤0.25/>2	72.3	≤0.25/>2	79.8	≤0.25/≤0.25	94.8	≤0.25/≤0.25	91.7	≤0.25/>2	87.1
Quinupristin/Dalfopristin	0.5/1	100.0	0.5/0.5	99.7	0.5/0.5	100.0	≤0.25/0.5	100.0	0.5/0.5	99.8
Vancomycin	0.5/0.5	99.8	0.25/0.5	100.0	0.25/0.5	100.0	0.25/0.5	100.0	0.25/0.5	99.9
Tetracycline	16/>16	47.6	≤2/>16	70.9	≤2/>16	79.5	≤2/>16	82.0	≤2/>16	74.6
Trimethoprim/Sulfamethoxazole	≤0.5/>4	54.7	≤0.5/4	59.1	≤0.5/>4	59.0	≤0.5/>4	66.0	≤0.5/>4	62.2
Chloramphenicol	4/16	83.9	≤2/16	88.0	≤2/4	95.4	≤2/4	91.2	≤2/4	90.1
Rifampin	≤1/≤1	99.2	≤1/≤1	98.7	≤1/≤1	98.2	≤1/≤1	99.7	≤1/≤1	99.2

a. The susceptiblity rates were determined using NCCLS breakpoint criteria. The susceptibility percentage for BMS284756 was determined using suggested breakpoint criteria (≤ 4 μg/ml) by Fung-Tomc et al. [2000]

MATERIALS AND METHODS

Bacterial isolates. As part of the SENTRY Antimicrobial Surveillance Program, a large collection of *S. pneumoniae* isolates were forwarded to regional monitors in the United States (North Liberty, IA) and Australia (North Adelaide) during 1999 and 2000. Upon receipt, the isolates identification was confirmed using sodium de-oxycholate and all bile-soluble reactive strains were further evaluated against numerous antimicrobial agents including newer quinolones. The total number of isolates tested from all regions combined equaled 4,168 and were separated for analysis purposes into four geographic regions including the Asia-Pacific (n=614), Europe (n=749), Latin America (n=502) and North America (n=2,303).

The strains were consecutively isolated from patients (one per patient) diagnosed with community-acquired respiratory tract infections. Over 50 medical centers were enrolled to forward isolates to the regional monitors during the appropriate respiratory disease season. Quality control strains were tested concurrently and included *S. pneumoniae* ATCC 49619, *S. aureus* ATCC 29213, and *E. faecalis* ATCC 29212. Colony counts from the positive control well provided additional quality assurance with regards to cellular concentration.

Antimicrobial susceptibility testing. Once species confirmation was determined to be accurate, the strains were tested against commonly prescribed antimicrobial agents including quinolones, penicillin, oral cephalosporins, macrolide-lincosamide-streptogramin agents, vancomycin, tetracycline, trimethoprim/sulfamethoxazole, chloramphenicol, and rifampin. Susceptibility testing conformed to NCCLS criteria using broth microdilution methods [NCCLS, 2000]. After purification and overnight incubation, the strains were suspended into cation-adjusted Mueller-Hinton broth equivalent to a 0.5 McFarland standard. A dilution of 100 μl of this inoculum into 10 ml of Mueller-Hinton supplemented with 3% lysed horse blood was utilized as the final bacterial test concentration. This suspension was then inoculated (100 μl) into validated, dry-form antimicrobial panel wells containing serial two-fold concentrations of antimicrobial agents using an autoinoculating device (TREK Diagnostics, Westlake, OH). Panels were incubated in ambient air at 35°C for 24 hours. Minimum inhibitory concentrations (MICs) were determined visually as the lowest concentration to completely inhibit the growth of the test organism.

Table 2. The distribution of quinolone MIC values among penicillin-susceptible, -intermediate, and -resistant *S. pneumoniae* strains isolated world-wide between 1999-2000.

	Penicillin susceptibility (no. tested)								
	Susceptible (2,678)			Intermediate (725)			Resistant (765)		
Antimicrobial agent	MIC_{50}	MIC_{90}	% susceptible	MIC_{50}	MIC_{90}	% susceptible	MIC_{50}	MIC_{90}	% susceptible
BMSQ	0.06	0.06	100.0	0.06	0.06	100.0	0.06	0.12	100.0
Ciprofloxacin	1	2	-	1	2	-	1	2	-
Gatifloxacin	0.25	0.5	99.8	0.25	0.5	99.3	0.25	0.5	97.6
Levofloxacin	1	1	99.8	1	1	99.3	1	1	97.5
Moxifloxacin	0.12	0.25	99.7	0.12	0.12	100.0	0.12	0.25	97.7
Trovafloxacin	0.12	0.25	99.8	0.12	0.25	98.7	0.12	4	98.6

Table 3. The distribution of quinolone MIC values among erythromycin-susceptible and non-susceptible strains of *S. pneumoniae* (4,168) isolated in 1999-2000 world-wide.

	Erythromycin susceptibility (no. tested)					
	Susceptible (2,984)			Intermediate/-resistant (1,184)		
Antimicrobial agent	MIC_{50}	MIC_{90}	% susceptible	MIC_{50}	MIC_{90}	% susceptible
BMSQ	0.06	0.06	100.0	0.06	0.12	100.0
Ciprofloxacin	1	2	-	1	2	-
Gatifloxacin	0.25	0.5	99.8	0.25	0.5	97.5
Levofloxacin	1	1	99.8	1	1	97.2
Moxifloxacin	0.12	0.25	99.7	0.12	0.25	97.8
Trovafloxacin	0.12	0.25	99.9	0.12	0.25	97.8

RESULTS

- BMS284756 was the most potent quinolone tested in all regions against over 4,109 *S. pneumoniae* isolates (MIC_{50} and MIC_{90}, 0.06 μg/ml).
- BMS284756 was the only antimicrobial agent which provided 100.0% susceptibility against *S. pneumoniae* isolated in all geographic regions (Table 1).
- The rank order of potency (MIC_{90} values) among the quinolones tested was: BMS284756 (0.06 μg/ml) > moxifloxacin = trovafloxacin (0.25 μg/ml) > gatifloxacin (0.5 μg/ml) > levofloxacin (1 μg/ml) > ciprofloxacin (2 μg/ml).
- All *S. pneumoniae* isolates were also highly susceptible (> 99.0%) to the newer quinolones, quinupristin/dalfopristin, vancomycin and rifampin.
- Penicillin susceptibility among *S. pneumoniae* isolates was lowest in Asia-Pacific (51.3%) compared to Europe (64.0%), North America (66.6%) and Latin America (69.7%).
- Susceptibility rates of macrolides mirrored that of penicillin with low rates in Asia-Pacific (48.4%) compared to Europe (73.0%), North America (74.2%) and Latin America (86.1%). Susceptibility to clindamycin was higher in North and Latin America (91.7 - 94.8%) compared to Europe and Asia-Pacific (72.3 - 79.8%).
- Although quinolone resistance among *S. pneumoniae* isolated between 1999 - 2000 remains low, a correlation between penicillin- or tetracycline-resistant *S. pneumoniae* and resistance to quinolones was determined with a trend towards increased (1.2 - 2.6%) resistance among the non-susceptible populations (Tables 2 and 3).
- Overall susceptibility among *S. pneumoniae* isolated globally to tetracycline, trimethoprim/sulfamethoxazole and chloramphenicol was 74.6%, 62.2%, and 90.1%, respectively. The resistance to these compounds was highest in Asia-Pacific and lowest in North America.

CONCLUSIONS

- The quinolones continue to provide excellent potency against pathogens causing community-acquired pneumonia including *S. pneumoniae*. More recently developed compounds such as BMS284756, gatifloxacin, trovafloxacin and moxifloxacin have better potency against pneumococcus compared to ciprofloxacin and levofloxacin. BMS284756 showed 32-fold higher potency compared to ciprofloxacin.
- The variability of quinolone resistance rates among pneumococcus from different geographic regions was limited, and the frequency of occurrence was low in all monitored institutions.
- The variability of commonly prescribed antimicrobials such as penicillin and macrolides was in contrast, quite variable in the different regions surveyed. The highest resistance to these compounds was found among strains isolated in Asia-Pacific. European medical centers and those in the United States had approximately the same amount of resistance rates to penicillin and erythromycin in pneumococcus while Latin American isolates had the lowest rates of resistance. The resistance rates to tetracycline, trimethoprim/sulfamethoxazole and chloramphenicol were much higher in Asia-Pacific compared to North America.
- This study documents the variabilityof drug-resistant pneumococcus world-wide and illustrates the excellent potency of BMS284756 and other newer generation quinolones against recent isolates of *S. pneumoniae* from patients with community-acquired respiratory tract infections.

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