Susceptibility Trends of *H. influenzae* (HI) and *M. catarrhalis* (MCAT) Including Screening of BMS284756 (BMS) Potency: Report from the SENTRY Antimicrobial Surveillance Program, 1999-2000

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ABSTRACT

Background: The vast majority of *H. influenzae* and *M. catarrhalis* infections occur in the community setting and are treated with orally administered agents such as fluoroquinolones (FQ), macrolides and various ß-lactams. BMS284756, a novel desfluoroquinolone, was compared to numerous oral agents.
Methods: 4,195 HI and 1,850 MCAT isolated from respiratory tract infection samples were collected by SENTRY Program participants in the Asia-Pacific, Latin America (LA), Europe (EU) and North America (NA) and tested at a central laboratory using NCCLS methods. ß-lactamase production was assessed by the chromogenic cephalosporin test. 37 compounds were tested including BMS284756, ciprofloxacin (CIP), penicillin, amoxicillin/clavulanate (A/C), cefuroxime, clarithromycin (CLARI), tetracycline and trimethoprim/sulfamethoxazole.
Results: Trends in susceptibility (S) for BMS284756 and comparison drugs follows:

	HI % susc.		MCAT % susc.	
Agent	1999	2000	1999	2000
Penicillins[a]	74	78	5	4
A/C	>99	>99	100	100
Cefuroxime	98	99	98	98
CLARI	91	86[b]	99	99
Tetracycline	99	98	99	98
BMS284756 (≤4)	100	100	100	100
CIP	100	>99	100	99

a. S per ß-lactamase test result. b. Significant decline.

ß-lactamase-mediated resistances were similar between years with greater HI Amp-R in NA (28-31%). All S patterns were stable between years and across regions except CLARI, where an overall decline was noted. The BMS284756 potency ($MIC_{50/90}$/% S at ≤4 µg/ml) was: *H. influenzae* (≤0.03/≤0.03/100) and MCAT (≤0.03/≤0.03/100). FQ-R in HI and MCAT increased in 2000 (one versus eight isolates).
Conclusions: Continued use of commonly prescribed oral agents for *H. influenzae* and *M. catarrhalis* respiratory disease appears justified based on the world-wide surveillance results that only showed a decline in *H. influenzae* spectrum for clarithromycin. BMS284756 appears to be potent against these species overall, especially versus less fluoroquinolone-susceptible (ciprofloxacin MIC, ≥ 0.12 µg/ml) isolates.

Table 1. Antimicrobial activity of BMS284756 and 16 other orally administered compounds tested against 4,195 *H. influenzae* strains isolated in the SENTRY Antimicrobial Surveillance Program 1999-2000 medical centers in Europe, North America, Latin America, and the Asia-Pacific.

	Ampicillin susceptibility (no. tested)					
	Susceptible (n=3,194)			Intermediate/resistant (n=1,001)		
Antimicrobial agent	MIC_{50}	MIC_{90}	% susc.[a]	MIC_{50}	MIC_{90}	% susc.[a]
BMS284756	≤0.03	≤0.03	100.0	≤0.03	≤0.03	100.0
Ciprofloxacin	≤0.015	≤0.015	99.9	≤0.015	≤0.015	100.0
Gatifloxacin	≤0.03	≤0.03	99.9	≤0.03	≤0.03	100.0
Levofloxacin	≤0.03	≤0.03	100.0	≤0.03	≤0.03	100.0
Moxifloxacin	≤0.03	≤0.03	99.9	≤0.03	≤0.03	100.0
Amoxicillin/Clavulanate	0.5	1	99.9	0.5	2	97.7
Azithromycin	1	2	99.8	1	2	99.6
Clarithromycin	8	16	89.2	8	16	83.7
Cefdinir	0.25	0.5	98.3	0.25	0.5	96.5
Cefpodoxime	0.06	0.12	100.0	0.06	0.12	99.6
Cefprozil	2	8	96.1	4	>16	79.8
Cefuroxime	1	2	98.4	1	2	97.0
Loracarbef	1	4	97.2	2	16	85.2
Chloramphenicol	≤2	≤2	99.7	≤2	≤2	94.7
Rifampin	≤1	≤1	99.7	≤1	≤1	99.7
Tetracycline	≤2	≤2	99.5	≤2	≤2	95.9
Trimethoprim/Sulfamethoxazole	≤0.5	>4	78.9	≤0.5	4	81.6

a. Susceptibility as defined by the NCCLS [2002].

INTRODUCTION

Community-acquired respiratory tract infections (CARTI) account for more than one-third of doctor's office visits and a majority of antimicrobial prescriptions are used for the treatment of this indication. Empiric oral therapy is most often used and therefore, broad-spectrum antimicrobials are most often preferred. During the last decade, several fluoroquinolones have been developed with a variety of molecular substitutions which have increased the activity against pathogens primarily suspected of causing CARTI. The increased utilization of quinolones in general has produced increasing resistance rates among several key human pathogens. To date, the prevalence of fastidious respiratory pathogens resistant to quinolones remains low. However, the resistance rates to older quinolones has increased and a continued trend of resistance to newer quinolones has been shown.

BMS284756 (formerly T-3811) is a des-fluoro(6)-quinolone with potent in vitro activity against many Gram-positive and -negative organisms. It's overall spectrum of activity is superior to older quinolones such as ciprofloxacin and levofloxacin and comparable to newer agents like moxifloxacin and gatifloxacin. In vivo studies have shown desfluoroquinolones have lower toxicity in mice and are high in bioavailability.

In this study, we compare the in vitro activity of BMS284756 to several orally administered agents including other quinolones, ß-lactams, macrolides, chloramphenicol, rifampin, tetracycline, and trimethoprim/sulfamethoxazole against a large collection of recent *Haemophilus influenzae* and *Moraxella catarrhalis*. These organisms were collected from patients diagnosed with CARTI in the SENTRY Antimicrobial Surveillance Program during 1999 and 2000 from medical centers throughout the world. All tests were performed using reference methods.

Table 2. Antimicrobial activity of BMS284756 and 17 other orally administered compounds tested against 4,195 *H. influenzae* strains isolated in SENTRY Antimicrobial Surveillance Program (1999-2000) medical centers in North America, Latin America, Europe, and Asia-Pacific.

	Region (no. tested)									
	North America (2,294)		Latin America (461)		Europe (892)		Asia-Pacific (548)		All (4,195)	
Antimicrobial agent	$MIC_{50/90}$ (µg/ml)	% susc.[a]	$MIC_{50/90}$ (µg/ml)	% susc.[a]	$MIC_{50/90}$ (µg/ml)	% susc.[a]	$MIC_{50/90}$ (µg/ml)	% susc.[a]	$MIC_{50/90}$ (µg/ml)	% susc.[a]
BMS284756	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0
Ciprofloxacin	≤0.015/≤0.015	99.9	≤0.015/≤0.015	100.0	≤0.015/≤0.015	100.0	≤0.015/≤0.015	100.0	≤0.015/≤0.015	99.9
Gatifloxacin	≤0.03/≤0.03	99.9	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	99.9
Levofloxacin	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0
Moxifloxacin	≤0.03/≤0.03	99.9	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	99.9
Amoxicillin/Clavulanate	0.5/1	100.0	0.5/1	100.0	0.5/1	99.6	0.5/2	98.5	0.5/1	99.7
Azithromycin	1/2	99.7	1/1	100.0	1/2	99.8	1/2	99.8	1/2	99.7
Clarithromycin	8/16	86.9	8/8	94.6	8/16	88.2	8/16	85.8	8/16	87.9
Cefdinir	0.25/0.5	99.0	0.25/0.5	99.6	0.25/1	97.9	0.5/1	91.2	0.25/1	97.7
Cefpodoxime	0.06/0.12	100.0	0.06/0.06	100.0	0.06/0.12	100.0	0.06/0.25	98.5	0.06/0.12	99.8
Cefprozil	2/8	91.7	2/4	98.0	2/8	94.3	4/16	86.3	2/8	92.2
Cefuroxime	1/2	98.7	1/2	99.6	1/2	97.6	1/4	93.2	1/2	97.9
Loracarbef	2/8	94.2	1/4	99.2	2/8	96.2	2/16	87.5	2/8	94.4
Chloramphenicol	≤2/≤2	99.7	≤2/≤2	98.3	≤2/≤2	98.5	≤2/≤2	94.0	≤2/≤2	98.6
Rifampin	≤1/≤1	99.9	≤1/≤1	99.8	≤1/≤1	99.4	≤1/≤1	99.5	≤1/≤1	99.7
Tetracycline	≤2/≤2	99.4	≤2/≤2	98.0	≤2/≤2	97.6	≤2/≤2	93.2	≤2/≤2	98.1
Trimethoprim/Sulfamethoxazole	≤0.5/>4	79.4	≤0.5/>4	62.5	≤0.5/>4	77.7	≤0.5/>4	83.0	≤0.5/>4	77.6

a. Susceptibility as defined by the NCCLS [2002].

MATERIALS AND METHODS

Organisms tested. The bacterial isolates tested in this study were collected by more than 60 medical centers in North America, Latin America, Europe and Asia-Pacific regions during 1999 and 2000 as part of the SENTRY Antimicrobial Surveillance Program. A total of 6,045 strains derived from patients diagnosed with community-acquired respiratory infections consisted of 4,195 *H. influenzae* (23.9% ampicillin-resistant, MIC, ≥ 2 µg/ml) and 1,850 *M. catarrhalis* (> 95% ß-lactamase-positive). These strains were forwarded to the monitoring sites (Iowa City, Iowa, USA and Adelaide, Australia) where ß-lactamase production was analyzed with the chromogenic cephalosporin test. In addition, butyrate and oxidase disk test reagents were utilized to confirm *M. catarrhalis* identifications.

Antimicrobial agents. BMS284756 was provided by Bristol-Myers Squibb (Princeton, NJ, USA) and the comparison compounds were obtained from their respective manufacturers.

Susceptibility testing. All strains were tested using the reference broth microdilution methods (NCCLS) in validated dry-form trays (TREK Diagnostics, Westlake, OH, USA). More than 30 antimicrobials were tested (17 - 18 reported here). After inoculation, the trays were incubated in ambient air at 35°C for 16 - 20 hours and minimum inhibitory concentration (MIC) endpoints were determined. NCCLS [2001] susceptibility interpretations were utilized for all comparison compounds and ≤ 4 µg/ml was applied for BMS284756 [Fung-Tomc et al., 2000]. Quality control was performed with the following strains: *H. influenzae* ATCC 49247, *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853 and *Enterococcus faecalis* ATCC 29212.

Table 3. Antimicrobial activity of BMS284756 and 15 other orally administered compounds tested against 1,850 *M. catarrhalis* strains isolated in the SENTRY Antimicrobial Surveillance Program 1999-2000 medical centers in Europe, North America, Latin America, and the Asia-Pacific.

	Penicillin susceptibility (no. tested)					
	Susceptible[a] (n=83)			Resistant[a] (n=1,767)		
Antimicrobial agent	MIC_{50}	MIC_{90}	% susc.[a]	MIC_{50}	MIC_{90}	% susc.[a]
BMS284756	≤0.03	≤0.03	100.0	≤0.03	≤0.03	100.0
Ciprofloxacin	0.03	0.03	100.0	0.03	0.03	100.0
Gatifloxacin	≤0.03	≤0.03	100.0	≤0.03	≤0.03	100.0
Levofloxacin	≤0.03	≤0.03	100.0	≤0.03	≤0.03	100.0
Moxifloxacin	0.06	0.06	100.0	0.06	0.06	100.0
Amoxicillin/Clavulanate	≤0.25	≤0.25	100.0	≤0.25	≤0.25	100.0
Erythromycin	≤0.25	≤0.25	100.0	≤0.25	≤0.25	94.2
Cefdinir	0.12	0.12	100.0	0.12	0.25	100.0
Cefpodoxime	0.12	0.12	100.0	0.5	1	100.0
Cefprozil	0.5	0.5	100.0	2	4	97.3
Cefuroxime	0.5	0.5	100.0	1	2	98.2
Loracarbef	≤0.25	≤0.25	100.0	0.5	2	98.0
Chloramphenicol	≤2	≤2	100.0	≤2	≤2	99.9
Rifampin	≤1	≤1	100.0	≤1	≤1	99.9
Tetracycline	≤2	≤2	100.0	≤2	≤2	98.4
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	100.0	≤0.5	≤0.5	97.3

a. Susceptibility as defined by the NCCLS [2002] for *H. influenzae* was used for all drugs except erythromycin where guidelines for *S. pneumoniae* were applied.
b. Penicillin MIC of ≤ 0.06 µg/ml correlates with a ß-lactamase-negative result.

Table 4. Antimicrobial activity of BMS284756 and 16 other orally administered compounds tested against 1,850 *M. catarrhalis* strains isolated in SENTRY Antimicrobial Surveillance Program (1999-2000) medical centers in North America, Latin America, Europe, and Asia-Pacific.

	Region (no. tested)									
	North America (1,067)		Latin America (135)		Europe (376)		Asia-Pacific (272)		All (1,850)	
Antimicrobial agent	$MIC_{50/90}$ (µg/ml)	% susc.[a]	$MIC_{50/90}$ (µg/ml)	% susc.[a]	$MIC_{50/90}$ (µg/ml)	% susc.[a]	$MIC_{50/90}$ (µg/ml)	% susc.[a]	$MIC_{50/90}$ (µg/ml)	% susc.[a]
BMS284756	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0
Ciprofloxacin	0.03/0.03	100.0	0.03/0.03	100.0	0.03/0.03	100.0	0.03/0.03	100.0	0.03/0.03	100.0
Gatifloxacin	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0
Levofloxacin	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0	≤0.03/≤0.03	100.0
Moxifloxacin	0.06/0.06	100.0	0.06/0.06	100.0	0.06/0.06	100.0	0.06/0.06	100.0	0.06/0.06	100.0
Penicillin	>4/>4	5.0	4/>4	0.7	4/>4	4.8	>4/>4	4.0	>4/>4	4.5
Amoxicillin/Clavulanate	≤0.25/≤0.25	100.0	≤0.25/≤0.25	100.0	≤0.25/≤0.25	100.0	≤0.25/≤0.25	100.0	≤0.25/≤0.25	100.0
Erythromycina	≤0.25/≤0.25	95.7	≤0.25/≤0.25	95.6	≤0.25/≤0.25	96.5	≤0.25/0.5	86.0	≤0.25/≤0.25	94.4
Cefdinir	0.12/0.25	100.0	0.12/0.25	100.0	0.12/0.25	100.0	0.25/0.25	100.0	0.12/0.25	100.0
Cefpodoxime	0.5/1	99.8	0.5/0.5	100.0	0.5/0.5	100.0	0.5/1	100.0	0.5/1	99.9
Cefprozil	1/4	99.0	2/2	100.0	1/2	100.0	2/16	86.4	2/4	97.4
Cefuroxime	1/2	99.1	1/2	100.0	1/2	100.0	2/4	92.3	1/2	98.3
Loracarbef	0.5/2	99.6	0.5/1	100.0	0.5/1	100.0	1/16	89.3	1/2	98.1
Chloramphenicol	≤2/≤2	100.0	≤2/≤2	99.3	≤2/≤2	100.0	≤2/≤2	100.0	≤2/≤2	99.9
Ritampin	≤1/≤1	100.0	≤1/≤1	99.3	≤1/≤1	100.0	≤1/≤1	100.0	≤1/≤1	99.9
Tetracycline	≤2/≤2	99.3	≤2/≤2	100.0	≤2/≤2	97.1	≤2/≤2	96.3	≤2/≤2	98.5
Trimethoprim/Sulfamethoxazole	≤0.5/≤0.5	97.9	≤0.5/≤0.5	96.3	≤0.5/≤0.5	95.7	≤0.5/≤0.5	98.2	≤0.5/≤0.5	97.4

a. Susceptibility as defined by the NCCLS [2002].

RESULTS

- ß-lactamase-mediated resistances in *H. influenzae* were similar between years with the highest rate seen in North America (28 - 31%; data not shown).
- A decrease (-) in *H. influenzae* susceptibility to clarithromycin was noted across regions and ranged from -4% in North America to -7% in Europe.
- *M. catarrhalis* strains were generally very susceptible to all tested agents (≥ 94.4%) except ß-lactamase-labile penicillins such as penicillin and ampicillin. ß-lactamase production was detected in > 95% of isolates (MICs, > 0.06 µg/ml).
- BMS284756 and the comparison quinolones exhibited potent activity (MIC_{90}s, ≤0.03 µg/ml) against *H. influenzae* and *M. catarrhalis* during 1999 and 2000.
- Isolates less susceptible to quinolones (ciprofloxacin MIC, ≥ 0.12 µg/ml) were detected in *H. influenzae* and *M. catarrhalis* in 1999 (one in APAC region) and 2000 (eight in three regions).

CONCLUSIONS

- BMS284756 appears to be a potent fluoroquinolone and compares favorably with compounds in its class against *H. influenzae* and *M. catarrhalis*.
- Based on these results, current commonly prescribed oral agents continue to be effective against *H. influenzae*. However, the variability of ß-lactamase producing strains among different geographic regions as well as differences in tetracycline and trimethoprim/sulfamethoxazole requires the monitoring of key oral agents world-wide.
- The activity of fluoroquinolones, oral cephalosporins and macrolides do not appear to be compromised among *M. catarrhalis* isolates in any geographic regions.
- The potency of BMS284756 against key respiratory pathogens which cause CARTI provides another therapeutic option in the treatment of this indication.

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