Original Report

Antimicrobial Resistance among Community-Acquired Pneumonia Isolates in Europe: First Results from the SENTRY Antimicrobial Surveillance Program 1997

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ABSTRACT

Objective: The SENTRY antimicrobial surveillance program was established to monitor the occurrence and antimicrobial susceptibility of bacterial pathogens via an international network of sentinel hospitals.

Material and Methods: Microorganisms were forwarded to the reference laboratory for testing against various antimicrobial agents using broth microdilution. Twenty European hospitals referred 286 *Streptococcus pneumoniae*, 309 *Haemophilus influenzae*, and 167 *Moraxella catarrhalis* isolates during the first 10 months of the study, starting in April 1997.

Results: Seven percent of the *S. pneumoniae* isolates were highly resistant to penicillin, and 21% showed intermediate resistance. The highly resistant pneumococcal isolates came from Coimbra, Barcelona, Athens, and London, whereas the intermediate penicillin-resistant isolates were received from all participating countries. The incidence of intermediate penicillin-resistant pneumococci was lowest in Lausanne, Freiburg and Duesseldorf, London, and Utrecht and highest in southern European countries. Fifty-five percent of the penicillin-resistant *S. pneumoniae* were also resistant to erythromycin, and 35% to clindamycin. Sparfloxacin, trovafloxacin, levofloxacin, and vancomycin were fully active against pneumococcal isolates. *Haemophilus influenzae* isolates were generally highly susceptible to most of the antibiotics tested, and 92% of the *M. catarrhalis* isolates were resistant to penicillin. Susceptibility to cephalosporins, ciprofloxacin, levofloxacin, and rifampicin was 100%.

Conclusion: Penicillin may no longer be the first-choice drug for empirical treatment of pneumococcal infections. The newer fluoroquinolones may play a role in the empirical treatment of community-acquired pneumonia.

Key Words: *antibiotic, resistance, surveillance*

Int J Infect Dis 1999; 3:153–156.

Community-acquired respiratory tract infections are a major worldwide cause of morbidity and mortality. Chronic bronchitis affects more than 1 million people in the United Kingdom and more than 7 million in the United States.[1,2] Bacterial infections are responsible for approximately half of the acute exacerbations of this condition.[3] The incidence levels for community-acquired pneumonia are 3.6/1000 per year and 3.3/1000 per year for the United Kingdom and United States, respectively.[4,5] Severe community-acquired pneumonia is associated with high morbidity and mortality.[6,7] Treatment of these conditions is usually empirical, with penicillins normally being prescribed as the first-choice antibiotics for treatment, and erythromycin for patients allergic to penicillins. However, the increase in not only penicillin-resistant *Streptococcus pneumoniae* but also penicillin-resistant *Haemophilus influenzae* and *Moraxella catarrhalis* make the choice for empirical treatment more difficult. The use of fluoroquinolones, especially ciprofloxacin and ofloxacin, has limited value, because of their modest activity against *S. pneumoniae*. This continuously evolving threat of antimicrobial resistance warrants continuous antimicrobial surveillance.

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The SENTRY antimicrobial surveillance program was funded by an educational grant from Bristol-Myers Squibb Pharmaceutical Company (Princeton, NJ, USA). The European Network for Antimicrobial Resistance and Epidemiology (ENARE) received a grant (ERBCHRCT940554) from the European Union.

Received: November 18, 1998; Accepted: December 18, 1998.

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Several projects have been directed toward the study of respiratory tract infections, especially those caused by *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. The Surveillance Program of Antibiotic Resistance (SPAR) was one of these projects and was implemented in 10 European countries between December 1994 and April 1995. The isolates in that study were tested against six antibiotics at a national level, using local methods.[8] The Alexander Project, also directed at these organisms, started in 1992 to study isolates from Europe and the United States,[9] using standard methods. The SENTRY antimicrobial surveillance program was established in 1997 as a global longitudinal program to monitor the frequency and antimicrobial resistance of clinical isolates from blood infections, skin and soft tissue infections, urinary tract infections, nosocomial pneumonia, and community-acquired respiratory tract infections. These isolates are referred to key reference centers based in the Netherlands, the United States, and Australia. This report describes the isolation frequency and antimicrobial susceptibility of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* obtained from European patients with community-acquired respiratory tract infections during the first 2 months of the study, starting in April 1997.

MATERIAL AND METHODS

The SENTRY Antimicrobial Surveillance Program Design

SENTRY was established to monitor the occurrence and antimicrobial susceptibility of both nosocomial and community-acquired bacterial pathogens via an international network of sentinel hospitals, distributed roughly equally by size and location. In this program consecutive bacterial or fungal isolates, deemed clinically significant by local criteria, are forwarded to the regional reference laboratories to monitor those isolates associated with bloodstream infections, pneumonia, skin or soft tissue infections, urinary tract infections in hospitalized patients, and community-acquired respiratory tract infections due to fastidious organisms (*S. pneumoniae*, *H. influenzae*, and *M. cattarhalis*). These regional reference laboratories are located at the University Hospital Utrecht, Utrecht, the Netherlands (for Europe), the University of Iowa College of Medicine, Iowa City, IA, USA (for North and South America), and Women's and Children's Hospital, North Adelaide, Australia (for Australasia). Currently, 24 hospitals, in 12 European countries are referring isolates to the European SENTRY reference laboratory.

Referral of Isolates

Each participating hospital was requested to refer those *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* isolates judged clinically to be the cause of community-acquired pneumonia, each calendar month. Only one isolate was permitted per patient. Each isolate was speciated at the source, according to the routine methodology used at the referring hospital, and sent to the Eijkman-Winkler Institute for Microbiology, Infectious Diseases, and Inflammation at the University Hospital Utrecht, using Amies charcoal medium transport swabs (Difco, Chicago, IL, USA) as the transport medium. Each isolate was accompanied by relevant epidemiologic data, including genus and species name, method of identification, date of patient's birth, ward, etc. Upon receipt, isolates were subcultured onto blood agar to ensure purity. Isolate identity was confirmed, if necessary. Isolates were snap-frozen in brain-heart infusion broth (Oxoid, Chicago, IL, USA) with 15% glycerol, using liquid nitrogen, and banked at -70°C until needed.

Antimicrobial Agents and Susceptibility Testing

Minimum inhibitory concentrations (MICs) were determined against a range of antibiotics, using a broth microdilution method and following standard methods defined by the National Committee for Clinical Laboratory Standards (NCCLS, 1998).[10] Cation-adjusted Mueller-Hinton broth with lysed horse blood (5%) was used as the growth medium for *S. pneumoniae* or *Haemophilus* test medium broth for *H. influenzae,* throughout the study (Dade International, Sacramento, CA, USA). The final bacterial inoculum concentration was approximately 5×10^5 colony forming units (CFU)/mL. Trays were incubated for 20 to 24 hours at 35°C in ambient air, prior to determining MIC values. National Committee for Clinical Laboratory Standards breakpoints were used to interpret MIC data. Broth microdilution plates were designed specifically for the SENTRY study and contained extended-range dilutions of the following antibiotics: penicillin, amoxicillin, amoxicillin-clavulanate, cefotaxime, cefepime, ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin, gatifloxacin, trovafloxacin, erythromycin, clindamycin, azithromycin, clarithromycin, quinopristin-dalfopristin, chloramphenicol, rifampin, tetracycline, vancomycin, and trimethoprim-sulfamethoxazole. Appropriate quality control was performed using *S. pneumoniae* ATCC 49619 and *H. influenzae.*

RESULTS AND DISCUSSION

Frequency of Isolation

During the first 10 months of the program, 20 European hospitals referred a total of 286 *S. pneumoniae*, 309 *H. influenzae*, and 167 *M. catarrhalis* isolates to the European SENTRY reference laboratory.

Antimicrobial Susceptibility of *S. pneumonia*

Of the *S. pneumoniae* isolates tested, 7.0% were highly resistant to penicillin and 21.3% showed intermediate

Table 1. Antimicrobial Susceptibility and Activity Spectrum ($MIC_{50/90}$) of Antimicrobials Tested against *S. pneumoniae, H. influenzae,* and *M. catarrhalis* Isolates Implicated in Community-Acquired Respiratory Tract Infections

	PS-S. pneumoniae (*n* = 205)		*PI*-S. pneumoniae (*n* = 61)		*PR*-S. pneumoniae (*n* = 20)		H. influenzae (*n* = 309)		M. catarrhalis (*n* = 167)	
	$MIC_{50/90}$	Susceptible (%)	$MIC_{50/90}$	Susceptible (%)	$MIC_{50/90}$	Susceptible (%)	$MIC_{50/90}$	Susceptible (%)	$MIC_{50/90}$	Susceptible (%)
Amoxycillin	≤0.06/≤0.06	100	0.25/2	68.9	4/8	0	0.5/8	NA	1/4	NA
Amoxycillin/clavulanate	≤0.06/≤0.06	100	0.25/2	68.9	4/8	0	0.5/2	99.4	≤0.06/0.25	94.6
Cefotaxime	0.015/0.03	100	0.25/1	86.9	1/1	30.0	0.015/0.06	100	0.12/0.5	100
Cefepime	≤0.06/≤0.06	100	0.25/1	75.4	2/2	5	0.12/0.25	100	0.5/2	100
Ciprofloxacin	1/1	NA	1/2	NA	1/1	NA	≤0.015/≤0.015	100	≤0.012/0.03	100
Levofloxacin	1/1	100	1/2	100	1/1	100	<0.05/≤0.05	100	≤0.5/≤0.5	100
Sparfloxacin	≤0.25/0.5	98.5	0.25/0.5	98.4	0.25/0.5	100	≤0.12/≤0.12	100	≤0.12/≤0.12	99.4
Gatifloxacin*	0.25/0.5	NA	0.25/0.5	NA	0.25/0.5	NA	≤0.03/≤0.03	NA	≤0.03/≤0.03	NA
Trovafloxacin*	0.25/0.5	100	0.25/0.5	100	0.25/0.5	100	≤0.03/≤0.03	100	≤0.03/≤0.03	NA
Erythromycin	≤0.25/≤0.25	90.2	≤0.25/>32	67.2	0.5/>32	45.0	2/4	–	≤0.25/0.5	95.2
Clindamycin	≤0.06/≤0.06	96.1	≤0.06/>8	68.9	≤0.06/>8	65.0	4/8	NA	1/2	31.1
Azithromycin	≤0.12/0.25	94.6	≤0.12/>16	68.9	≤0.12/>16	65.0	1/2	99.4	≤0.12/≤0.12	99.4
Clarithromycin	NT	NA	NT	NA	NT	NA	4/8	90.9	≤0.25/≤0.25	98.2
Quinopristin-dalfopristin*	0.5/1	NA	0.5/2	NA	0.5/1	NA	4/8	NA	0.5/0.5	NA
Chloramphenicol	≤2/≤2	97.1	≤2/8	77.1	≤2/8	55.0	≤2/≤2	97.4	≤2/≤2	99.4
Rifampin	≤1/≤1	99.5	≤1/≤1	100	≤1/≤1	95.0	≤1/≤1	97.4	≤1/≤1	98.2
Tetracycline	≤2/16	85.4	≤2/>16	55.7	4/>16	45.0	≤2/≤2	96.4	≤2/≤2	98.2
Vancomycin	0.25/0.5	100	0.25/0.5	100	0.25/0.5	100	>16/>16	NA	>16/>16	NA
Trimethoprim-sulfamethoxazole	≤0.25/1	NA	2/4	NA	4/4	–	≤0.25/8	NA	≤0.03/≤0.03	NA

*Investigational drug.
NA = No susceptibility breakpoints are available for this drug (NCCLS,1998); NT = not tested; PS = penicillin-susceptible; PI = intermediate penicillin-resistant; PR = penicillin-resistant.

resistance. The percentage of highly resistant isolates was somewhat lower than that observed in both the Alexander Project and SPAR, whereas that of isolates with intermediate resistance was higher.[8,11] This discrepancy may have been caused by the somewhat different distribution of centers across Europe. The highly resistant isolates were obtained from Spain, Portugal, Greece, and France. Isolates with intermediate resistance to penicillin were obtained from all participating countries, although most were obtained from those countries where highly penicillin-resistant pneumococci were isolated. The incidence of intermediate penicillin-resistant pneumococci was below 12% in Utrecht (the Netherlands), Lausanne (Switzerland), Freiburg and Dusseldorf (Germany), and London (England). These data more or less reflect the data presented in the Alexander Project.[11]

Highly and intermediate penicillin-resistant *S. pneumoniae* isolates also showed relatively high levels of resistance to macrolide antibiotics like erythromycin. The susceptibility of penicillin-susceptible isolates for erythromycin was approximately 90%. This relation between resistance to penicillin and resistance to macrolide antibiotics also was noted in the Alexander Project.[11] Clindamycin has been considered for the eradication of community-acquired penicillin-resistant *S. pneumoniae*, although it was not active against *H. influenzae* or other respiratory tract infections. Jones et al investigated cross-resistance between erythromycin and clindamycin and showed that a substantial number of isolates were resistant only to the former antibiotic.[12] In this study, the data indicate that the total levels of susceptibility to erythromycin and to clindamycin were roughly equal, demonstrating that the so-called M-phenotype is not prevalent (Table 1).

The fluoroquinolones performed rather well against all pneumococci, independent from their resistance to penicillin. Susceptibility to sparfloxacin was more than 98% for penicillin-susceptible isolates and those with intermediate resistance, whereas all highly resistant isolates were susceptible. Although no breakpoints have been defined for the other quinolones tested, $MIC_{50/90}$ data suggest that trovafloxacin and the investigational drug gatifloxacin performed equally well, but the performance of ciprofloxacin and levofloxacin was less than that of sparfloxacin. These data are comparable for those obtained in SPAR for sparfloxacin and ciprofloxacin. The data for ciprofloxacin in the Alexander Project indicated a somewhat higher level of resistance (MIC_{90} was 2 μg/mL).[11] The role of quinolones in the treatment of respiratory tract infections recently was discussed by Geddes and Grossman.[13,14] These authors argue that quinolones may be beneficial for the treatment of respiratory tract infections. Data in the present study indicate

that at least the newer quinolones may have potential in the treatment of these infections.

The pneumococcal isolates showed good susceptibility to the investigational drug quinopristin-dalfopristin and to older drugs, such as rifampin. All isolates were susceptible to vancomycin.

Antimicrobial Susceptibility of *H. influenzae*

Haemophilus influenzae isolates were generally highly susceptible to all antibiotics tested (more than 96% susceptibility), although there were a few exceptions (e.g., clarithromycin, with 91% susceptibility) (see Table 1). Susceptibility to amoxicillin-clavulanate was 99% and to cefepime, cefotaxime, and the fluoroquinolones was 100%. These results are in general agreement with data from SPAR and the Alexander Project.[8,11]

Antimicrobial Susceptibility of *M. catarrhalis*

All *M. catarrhalis* isolates were fully susceptible to cefepime, cefotaxime, trimethoprim-sulfamethoxazole, ciprofloxacin, and levofloxacin (see Table 1). More than 99% of the isolates were susceptible to sparfloxacin and azithromycin. In contrast, susceptibility to penicillin, vancomycin, and clindamycin was poor (8%, 7%, and 31% susceptibility, respectively). Results from SPAR and the Alexander Project were comparable to present results.[8,11]

CONCLUSION

Penicillins used to be first-choice antibiotics for the empirical treatment of pneumococcal infections. However, the emergence of penicillin-resistant *S. pneumoniae* in some parts of Europe requires more regional protocols for empirical treatment. The newer fluoroquinolones may play a role in the empirical treatment of *S. pneumoniae*, especially when penicillin resistance is expected. These newer fluoroquinolones along with macrolides also may play a role in the empirical treatment of *H. influenzae* and *M. catarrhalis* infections

ACKNOWLEDGMENTS

The authors thank Marita Hautvast, Miriam Klootwijk, Carlijn Kusters, and Stefan de Vaal for their expert technical assistance.

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