

Emergence and Spread of Antimicrobial Resistance of *Streptococcus pneumoniae* in Korea

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Pneumococcal resistance has become a global issue during the past three decades. One of the major foci of pneumococcal resistance worldwide is the Asian region including Korea, Japan, and Hong Kong. Korea had not been recognized as a focus of pneumococcal resistance until 1995, when serial reports documented the alarmingly high prevalence of penicillin resistance among clinical isolates. Serial reports on penicillin resistance among pneumococcal isolates in Korea ranged from 68% to 77% as of 1995. Multidrug resistance was also noted in 34% of Korean isolates. Penicillin-binding protein profile analysis, pulsed-field gel electrophoresis, ribotyping, and fingerprinting analysis of pbp genes showed that antibiotic-resistant pneumococci isolated in Korea were genetically related. Data documented the extensive spread of a resistant clone within Korea and between different countries. Besides the injudicious use of antimicrobial agents or the high prevalence of serotypes 23 and 19, the spread of a resistant clone may play an important role in the rapid increase of penicillin resistance in Korea.

Key Words: *Streptococcus pneumoniae*, antimicrobial resistance, spread of resistance

Streptococcus pneumoniae remains one of the leading pathogens causing significant morbidity and mortality. The clinical course of pneumococcal infection is affected by a number of factors including the site and severity of infection, underlying diseases, and the adequacy of antibiotic treatment. With the introduction of penicillin into clinical practice, the mortality associated with pneumococcal pneumonia, bacteremia, and meningitis dropped from 20% to 5%, from 50% to 20%, and from 80–100% to 30%, respectively (Tomasz, 1997). For many years, pneumococci were uniformly susceptible to penicillin until the first report of penicillin resistance

from a clinical specimen in 1967 by Hansman and Bullen. Their first resistant strain with a penicillin MIC of 0.6 µg/mL was isolated from the sputum of a patient with hypogammaglobulinemia and bronchiectasis. Between 1967 and 1977, anecdotal descriptions of penicillin resistance among pneumococcal isolates from clinical specimens began to appear in the literature (Hansman *et al.* 1971; Hansman, 1972). The next dramatic event in the epidemiology of antibiotic-resistant pneumococci was the outbreak of pneumococcal disease caused by multidrug-resistant strains in South Africa in 1977 (Jacobs *et al.* 1978). In contrast to the first isolate, South African strains isolated in 1977 were resistant to penicillin, tetracycline, chloramphenicol, erythromycin, clindamycin, and for some strains, rifampin. The extensive use of large numbers of antimicrobial agents has fueled the crisis in antibiotic resistance in the era of modern chemotherapy (Neu, 1992). Pneumococcal resistance had been regarded as one of the regional problems until 1991, when Munoz *et al.* first documented the intercontinental spread of a resistant clone from Spain to the United States.

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During the last two decades, the resistance of *S. pneumoniae* to penicillin has been rapidly increasing in many parts of the world. In the 1990s, pneumococcal resistance became a global issue. Furthermore, subsequent reports of treatment failure in pneumococcal meningitis caused by penicillin- or cephalosporin-resistant strains have made this emerging problem more significant in clinical practice (Sloas *et al.* 1992; Friedland and McCracken, 1994). In 1941, 10,000 units of penicillin administered four times a day for 4 days cured patients of pneumococcal pneumonia, while today a patient could receive 24 million units of penicillin a day and die of pneumococcal meningitis.

S. pneumoniae is defined as penicillin susceptible when the MIC is $\leq 0.06 \mu\text{g/mL}$. Penicillin MIC for *S. pneumoniae* $0.1-1 \mu\text{g/mL}$ is defined as intermediate and $>1 \mu\text{g/mL}$ as resistant (NCCLS, 1998). However, it is important to remember that these MIC breakpoints were selected on the basis of

the efficacy of penicillin in treating pneumococcal meningitis. Therefore, some investigators have questioned the relevance of penicillin-intermediate in the setting of non-meningeal infections. Extensive studies on the epidemiology of pneumococcal resistance and preventive or therapeutic strategies against resistant pneumococcal infections have been performed during the past 10 years.

GLOBAL EPIDEMIOLOGY OF PNEUMOCOCCAL RESISTANCE

Penicillin resistance

Pneumococcal resistance is becoming a significant threat to public health worldwide. According to previous reports from various countries in the world, 10 main foci of pneumococcal resistance are located in the following areas (Table 1) (Baquero, 1995): 1) Asian countries (Korea, Japan, Vietnam, Thailand),

Table 1. Antibiotic resistance of pneumococcal isolates from selected geographic areas

Continent/Countries	Year	No. of strains	% of penicillin non-susceptible strains		
			I	R	I + R
Europe					
Spain (Barcelona)	1979 - 1990	865	13.9	7.9	21.8
(Madrid)	1988 - 1989	139	31.7	10.8	42.5
Hungary	1988 - 1989	135			58.5
	1995				47
France (Toulouse)	1991	644			16.9
United Kingdom	1990	394	20.6	8.4	29
America					
USA	1995	436	18	7	25
	1994 - 1995	1,527	14.1	9.5	23.6
Canada	1994 - 1995	1,089	8.4	3.3	11.7
Africa					
South Africa	1987 - 1990	4,597			12
	1996	83	31.3	3.6	34.9
Asia					
Japan (Nagasaki)	1988	23	4.3	4.3	8.6
	1992	41	26.8	9.8	36.6
	1996 - 1997	84	38.4	26.9	65.3
Hong Kong	1983	119			0
	1993 - 1995	204	9.3	19.6	28.9
Malaysia	1987	74			4.1
Singapore	1977 - 1986	186	0.5	0	0.5
	1996 - 1997	84	4.9	18.2	23.1
Taiwan	1990 - 1993	115			12.2
China (Beijing)	1997	79	11.4	2.5	13.9

2) Southwestern Europe (Spain, France, Portugal), 3) Central-eastern Europe (Hungary, Romania, Bulgaria, Turkey), 4) Northwest Russia, 5) South Africa, 6) Papua-New Guinea, 7) Alaska, 8) Southeastern United States, 9) Southwestern United States, and 10) South America.

Eastern Europe, and in particular Hungary, seemed to be the first European focus of penicillin-resistant pneumococci. Since the late 1970s, Hungary and Spain represented the only reported "hot spots" of European pneumococcal resistance for almost a decade (Fenoll *et al.* 1991). In Hungary, the current rates of penicillin resistance are 47% for infants, 24% for children (1–3 years old), and 18% for adults. However, it seems that Hungary has a stable situation with regard to the increase of penicillin resistance among pneumococcal isolates (Marton *et al.* 1991). In 1988, the rate of pneumococcal resistance began to increase in France, where penicillin resistance reached 20% in 1993. In Portugal, penicillin resistance had reached nearly 20% in 1993. Southeastern European countries have so far been rarely analyzed. Bulgaria and Romania, however, have detected resistance rates exceeding 25%, which can be extended to Turkey, where penicillin resistance approached nearly 50% in 1993 (Baquero, 1995). Northern European countries have low rates of penicillin resistance among pneumococcal isolates. Penicillin resistance in Britain, Denmark, Sweden, and Finland were reported to be less than 10%.

In Africa, South Africa may be the representative country where multiply resistant pneumococci were first detected in 1978. In Soweto, near Johannesburg, penicillin resistance among strains isolated from meningitis reached 40%, while recent data from Johannesburg has shown that 35% of pneumococcal isolates were not susceptible to penicillin (Koornhof *et al.* 1992).

In the United States, the first infection caused by penicillin-resistant pneumococci (MIC 0.25 µg/mL) was reported in a patient with pneumococcal meningitis and sickle cell anemia in 1974 (Naraqi *et al.* 1974). Until 1987, however, *S. pneumoniae* was uniformly susceptible to penicillin; since then, there has been increased identification of penicillin-non-susceptible pneumococci. Recent data from different parts of the United States showed that penicillin

resistance was 25–43% (Hofman *et al.* 1995; Doern *et al.* 1996; Borek *et al.* 1997). In Canada, 11.7% of pneumococcal isolates were not susceptible to penicillin between 1994 and 1995 (Simor *et al.* 1996).

In South America, penicillin resistance has been detected at rates approaching 20% in Chile and Argentina, while Brazil had 24% penicillin resistance in the Sao Paulo area.

Multidrug resistance

Resistance to three or more classes of antibiotics can be defined as multidrug resistance (MDR). After the emergence of MDR strains in South Africa, a high prevalence of these organisms was documented in Spain. An epidemiologic pattern of MDR pneumococci in South Africa and Spain was initially similar; however, disease caused by MDR strains became a more significant problem in both children and adults in Spain. Data from Spain, South Africa, and the United States indicated that among pneumococcal isolates, 13.6%, 8.8%, and 2.2%, respectively (Friedland and Klugman, 1992; Linares *et al.* 1992; Welby *et al.* 1994). Recent data suggested a problem with MDR in Hungary, Romania, Pakistan, Taiwan, Hong Kong and Korea.

Serotype prevalence of resistant pneumococcal strains

Until 1995, the three countries with the highest reported incidence of penicillin-resistant pneumococci were South Africa, Spain, and Hungary. In South Africa, the predominant serotypes among resistant strains were 6, 14, 19, and 23 (Koornhof *et al.* 1992). In Spain, serotypes 6, 9, 19, 23 were the most common among isolates from blood cultures, while serotypes 19A, 6B, and 23F were the predominant ones in Hungary (Appelbaum, 1992). These data suggested that serotypes 23, 19, 14, 9 and 6 were the ones most frequently related to antibiotic resistance among pneumococci.

ASIAN EPIDEMIOLOGY OF PNEUMOCOCCAL RESISTANCE

Despite the serial reports from western countries, very little information has been available on the

epidemiology of antibiotic-resistant pneumococci in Asian countries where pneumococcal diseases are common and antibiotics are often used without prescription. However, reports from Korea and Hong Kong emphasized that pneumococcal resistance may be a serious problem in the Asian region. Among Asian countries, very few countries reported pneumococcal resistance in the English literature until 1995.

In Japan, penicillin resistance among pneumococcal isolates from sputum specimens from the Nagasaki region was 8.7% in 1988 and 36% in 1992 (Yoshida *et al.* 1995). Another report from the Nagasaki region showed 38% penicillin resistance between 1991 and 1994 (Rikitomi *et al.* 1996). However, recent data from the Asian Network for Surveillance of Resistant Pathogens (ANSORP) Study Group revealed a significantly increasing penicillin resistance to 65.3% of total isolates in the Nagasaki region in 1996–1997 (Song *et al.* 1998a). Since antimicrobial susceptibility tests were done in the same hospital by the same investigator in a different time period, current data clearly demonstrated the rapidly worsening situation in the Nagasaki region in Japan.

In China, 13.9% of pneumococcal isolates from clinical specimens were not susceptible to penicillin (including 2.5% of high-level resistance) in the Beijing area (Wang *et al.* 1998). ANSORP study done in Shanghai, China showed 9.8% (all were intermediate) penicillin non-susceptibility among clinical isolates.

In Hong Kong, however, pneumococcal resistance has been a serious problem since 1995. According to the report from Hong Kong in 1983, all pneumococcal isolates were susceptible to penicillin (Ling *et al.* 1983). However, in 1995, penicillin resistance rose up to 28.9% including 19.6% high-level resistance to penicillin (Kam *et al.* 1995). Further data from Hong Kong reported that penicillin resistance in Hong Kong was 55.8% in the second quarter of 1995 (Lyon *et al.* 1996). Based on these observations, Hong Kong may be the other major focus of pneumococcal resistance in the world along with Korea.

In Taiwan, a different pattern of pneumococcal resistance was noted. During the period from 1990 to 1993, penicillin resistance in Taiwan was 12.2%

among 115 clinical isolates from southern Taiwan, while 40.9% of all isolates showed multiple resistance to three or more classes of antibiotics (Hsueh *et al.* 1996). Resistance rates to erythromycin, tetracycline, and chloramphenicol were 62.2%, 71.3%, and 19.1%, respectively.

In Singapore, penicillin resistance was 0.5% (all were intermediate) during the period from 1977 to 1986 (Ling and Tay, 1990). However, a recent study revealed a 50-fold increase of penicillin non-susceptibility in Singapore with 21% high-level resistance to penicillin among clinical isolates (Song *et al.* 1998a).

Although these data represented the status of pneumococcal resistance in Asia, a more thorough epidemiological investigation is warranted in the region.

PNEUMOCOCCAL RESISTANCE IN KOREA

Antimicrobial susceptibility patterns among Korean isolates

Korea was not recognized as a focus of pneumococcal resistance until 1995, when serial reports documented the alarmingly high prevalence of penicillin resistance among clinical isolates from Korea. Lee *et al.* reported that 70% of pneumococcal isolates were not susceptible to penicillin (37% intermediate, 33% high-level resistance) in 1995. Chong *et al.* also reported 77% penicillin resistance among pneumococcal isolates in 1993. More importantly, this report documented the rapid increase of penicillin resistance in Korea from 29% in 1988 to 77% in 1993. Both reports showed that the major serotypes in Korean isolates were 23F, 19F, 6B, and 14. Further data from Korea supported these observations that 78% of pneumococcal isolates which were collected from 1989 to 1993 were not susceptible to penicillin (Kim *et al.* 1996). When this author tested 173 isolates of *S. pneumoniae* which were collected during the period from 1989 to 1995 in two tertiary-care hospitals in Seoul, Korea, penicillin resistance was 68%, while resistance to other antibiotics was as follows; cefotaxime (57.7%), ceftriaxone (58.2%), cefuroxime (62.9%),

Table 2. Antimicrobial susceptibilities of 173 isolates of *S. pneumoniae* in Korea between 1989 and 1995

Antimicrobial agents	MIC ($\mu\text{g/mL}$)			% of strains		
	Range	50%	90%	S	I	R
Penicillin	0.015–4	2	4	32.2	8.2	59.6
Cefotaxime	0.015–2	1	2	42.3	39.1	18.5
Ceftriaxone	0.12–2	1	2	41.8	21.2	36.9
Cefuroxime	0.12–8	4	8	37.1	3.6	59.3
Imipenem	0.03–2	1	1	42.5	56.9	0.5
Erythromycin	0.25–16	0.25	8	47.9	15.4	36.7
Tetracycline	0.5–32	4	16	35.5	16.2	48.2
Chloramphenicol	1–16	8	16	27.7	54.6	17.7
Vancomycin	<0.25	<0.25	<0.25	100	0	0

imipenem (57.5%), erythromycin (52.1%), tetracycline (64.5%), chloramphenicol (72.3%), and vancomycin (0%) (Table 2) (Song *et al.* 1996). Multidrug-resistance to three or more classes of antibiotics was 34%.

These reports clearly showed that Korea is an area with the most serious problem worldwide with regard to pneumococcal resistance. At present, no other country has shown penicillin resistance higher than 70% among clinical isolates. Penicillin resistance in Korean hospitals seems to be worsening in recent years. Some tertiary-care hospitals in Seoul, Korea observed 80–90% penicillin resistance among clinical isolates in 1998. Recent data from the ANSORP study also showed that penicillin resistance in Seoul was 79.7%.

The major reasons for the unusually high rate of resistance in Korea may be multifaceted. Basically, injudicious use of antimicrobial agents, particularly oral cephalosporins, may be the major factor which has resulted in heavy selective pressure on antimicrobial agents. A survey conducted in Korea revealed that 75% of private practitioners prescribed antibiotics for infections of the upper respiratory tract (Lee *et al.* 1991). Ampicillin was the drug most frequently prescribed, and erythromycin and oral cephalosporins were the next most commonly administered. Another important factor for antibiotic abuse may be the policy of selling all kinds of antibiotics on an over-the-counter basis without regulation. Overcrowded conditions in Korea, in conjunction with excessive use of antimicrobials, may also contribute to the maintenance and spread

Table 3. Serotype distribution of 122 isolates of *S. pneumoniae* in Korea

Serotype	No. (%) of strains	No. of strains with susceptibility to penicillin		
		S	I	R
19	54 (44.3)	12	6	36
23	47 (38.5)	12	6	29
6	10 (8.2)	3	2	5
3	2 (1.6)	2	0	0
Others	9 (7.4)	2	2	5

of resistant strains. Another reason for the resistance crisis in Korea is the high prevalence of serotypes 23F and 19F, which accounted for 50–80% of pneumococcal isolates from Korea (Table 3). Pneumococcal strains with these serotypes tend to be more likely to be resistant to antimicrobial agents. Still, these factors may not be enough to explain the rapid increase of penicillin resistance during such a short period in Korea. More importantly, the spread of resistant clones within Korea can be an alternative reason for the rapid surge of pneumococcal resistance.

Spread of resistant clones in Korea

The emergence of penicillin resistance among pneumococci is the result of at least three distinct events: 1) the introduction of foreign genes, presumably via transformation and recombination

into at least one bacterial clone; 2) the spread of resistant clones; and 3) the distribution of the mosaic resistant gene from the resistant clone into other clones. PBP-mediated resistance to penicillin can spread either by the dissemination of resistant organisms (clonal spread) or by the dissemination of mosaic *pbp* genes (horizontal spread) (Coffey *et al.* 1995). Molecular epidemiological methods are required to distinguish clonal spread from horizontal spread.

There have been many reports which have demonstrated the spread of resistance between different countries or within a certain region since the intercontinental spread of a multiresistant clone of serotype 23F *S. pneumoniae* between Spain and Cleveland, USA was first reported in 1991 (Munoz *et al.* 1991). Those strains from Cleveland and Spain had the same serotype, shared identical PBP profiles, had the same multilocus enzyme genotype, as well as the identical DNA fingerprints for two of the chromosomal genes known to contribute to penicillin resistance. Serotype 23F Spanish clone has also been reported to spread to many other parts of the world, including France, South Africa, eastern European countries, and Asian countries. Besides the serotype 23F clone, the multiresistant clone of serotype 6B was imported to Iceland from Spain in the late 1980s (Soares *et al.* 1993). Regional spread of a resistant pneumococcal clone was also documented in Canada (Waltman *et al.* 1992). As of 1998, at least 11 worldwide epidemic resistant clones were identified, from the Spanish 23F clone to the Slovakian 19A clone. Therefore, spread of a resistant clone within a certain region or between different countries is a common phenomenon.

In Korea, several lines of evidence based on molecular epidemiologic techniques have strongly suggested that spread of resistant clones has occurred in Korea. PBP profile analysis using H³-benzylpenicillin showed that most Korean MDR pneumococcal strains shared a common PBP profile with decreased affinity of PBPs 1a, 2x, and 2b. It represented a PBP family of common clonal origin (Song *et al.* 1997b).

Pulsed-field gel electrophoresis (PFGE) showed that 29 out of 35 Korean MDR pneumococci exhibited uniform DNA restriction patterns with *Sma* I or *Apa* I digestion (type A pattern), while

several strains showed a unique restriction pattern (type B pattern) (Song *et al.* 1996). The strains with identical PFGE pattern belonged to serotype 23F, 19F, or 6B with a different antimicrobial susceptibility pattern to non- β -lactam agents. Interestingly, a Spanish 23F resistant strain, which is thought to be an international epidemic clone, showed an identical type A pattern with Korean MDR strains, while the Iceland clone of serotype 6B or the French clone of serotype 14 showed quite different PFGE patterns from those of Korean strains. Recent data documented that PFGE patterns of serotype 19F and 23F multidrug-resistant pneumococcal isolates from Korea were indistinguishable from those shown by representative multiresistant 23F clones from Croatia, Portugal and New York City (Tarasi *et al.* 1997). These findings suggest that the Spanish 23F clone had been introduced to Korea as it had to many other parts of the world (Song *et al.* 1998a).

Ribotyping of 42 MDR pneumococcal isolates from Korea, Spain, and the United States which was performed with the restriction enzyme *Pvu* II by using a [α -³²P]dCTP-labeled gene probe from *Escherichia coli* 16S+23S RNA, showed that 19 out of 33 Korean MDR strains, 3 of 4 strains from the United States, and 4 of 5 Spanish strains shared the same ribopattern (Song *et al.* 1997a). Data from ribotyping also strongly supported the genetic relatedness of resistant pneumococci isolated from Korea.

Fingerprinting analysis of *pbp* genes 1a, 2x, and 2b of MDR pneumococci from Korea was also performed. A total of 22 pneumococcal strains isolated from clinical specimens in two university-affiliated hospitals during the period from 1989 to 1996 were tested. Genes encoding PBP 1A, 2X, and 2B were amplified from chromosomal DNA by the polymerase chain reaction and the amplified products were digested with *Hinf* I or *Mse* I+*Dde* I. Fingerprinting analysis of PBP 1A, 2X, and 2B genes digested with *Hinf* I showed that 17 out of 22 strains had almost identical fingerprints. Dendrogram showed clusters with greater than 90% similarities existed in 77%, 77%, and 82% of strains with *pbp* 1a, *pbp* 2x, and *pbp* 2b genes, respectively (Song *et al.* 1998b). Fingerprinting patterns with *Mse* I+*Dde* I were the same as those with *Hinf* I.

All these evidences strongly suggest the ex-

tensive spread of resistant pneumococcal clones within Korea and between different countries, which can partly explain the rapid increase of pneumococcal resistance during such a short period in Korea.

CONCLUSION

Based on published reports and current observations, Korea may be the "hottest spot" in the world with regard to the penicillin resistance among *S. pneumoniae*. Data from molecular epidemiologic studies have documented the spread of resistant clones within Korea and between Korea and other countries. More thorough epidemiologic investigation and regular follow-up of resistance status in Korea is warranted in the future.

REFERENCES

- Appelbaum PC: Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. *Clin Infect Dis* 15: 77-83, 1992
- Baquero F: Pneumococcal resistance to β -lactam antibiotics: a global geographic overview. *Microb Drug Resist* 1: 115-120, 1995
- Borek AP, Dressel DC, Hussong J, Peterson LR: Evolving clinical problems with *Streptococcus pneumoniae*: increasing resistance to antimicrobial resistance to antimicrobial agents, and failure of traditional optochin identification in Chicago, Illinois, between 1993 and 1996. *Diagn Microbiol Infect Dis* 29: 209-214, 1997
- Chong Y, Lee K, Kwon OH, Henrichsen J: Capsular types and antimicrobial resistance of *Streptococcus pneumoniae* isolated in Korea. *Eur J Clin Microbiol Infect Dis* 14: 528-531, 1995
- Coffey TJ, Dowson CG, Daniels M, Spratt BG: Genetics and molecular biology of β -lactam-resistant pneumococci. *Microb Drug Resist* 1: 29-34, 1995
- Doern G, Brueggemann A, Holley HP, Rauch AM: Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients in the United States during the winter months of 1994 to 1995: results of a 30-center national surveillance study. *Antimicrob Agents Chemother* 40: 1208-1213, 1996
- Fenoll A, Bourgon CM, Munoz R, Vicioso D, Casal J: Serotype distribution and antimicrobial resistance of *Streptococcus pneumoniae* isolates causing systemic infections in Spain, 1979-1989. *Rev Infect Dis* 13: 56-60, 1991
- Friedland IR, Klugman KP: Antibiotic-resistant pneumococcal disease in South African children. *Am J Dis Child* 146: 920-923, 1992
- Friedland IR, McCracken GH: Management of infections caused by antibiotic-resistant *Streptococcus pneumoniae*. *N Engl J Med* 331: 377-382, 1994
- Hansman D: Type distribution and antibiotic sensitivity of pneumococci from carriers in Kiriwana, Trobriand Islands (New Guinea). *Med J Aust* 2: 771-773, 1972
- Hansman D, Bullen MM: A resistant pneumococcus. *Lancet* 2: 264-265, 1967
- Hansman D, Glasgow H, Stuart J, Devitt HL, Douglas R: Increased resistance to penicillin of pneumococci isolated from man. *N Engl J Med* 284: 175-177, 1971
- Hofman J, Cetron MS, Farley MM, Baughman WS, Facklam RR, Elliot JA, Deaver KA, Freiman RF: The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. *N Engl J Med* 333: 481-486, 1995
- Hsueh PR, Chen HM, Lu YC, Wu JJ: Antimicrobial resistance and serotype distribution of *Streptococcus pneumoniae* strains isolated in southern Taiwan. *J Formos Med Assoc* 95: 364-371, 1996
- Jacobs MR, Koornhof HJ, Robins-Browne RM, Stevenson CM, Vermaak ZA, Freiman I, Miller GB, Witcomb MA, Isaacson M, Ward J, Austrian R: Emergence of multiply resistant pneumococci. *N Engl J Med* 299: 735-740, 1978
- Kam KM, Luey KY, Fung SM, Yiu PP, Harden TJ, Cheung MM: Emergence of multiple-antibiotic-resistant *Streptococcus pneumoniae* in Hong Kong. *Antimicrob Agents Chemother* 39: 2667-2670, 1995
- Kim SN, Kim SW, Choi IH, Pyo SN, Rhee DK: High incidence of multidrug-resistant *Streptococcus pneumoniae* in South Korea. *Microb Drug Resist* 2: 401-406, 1996
- Koornhof HJ, Wasas A, Klugman KP: Antimicrobial resistance in *Streptococcus pneumoniae*: a South African perspective. *Clin Infect Dis* 15: 84-94, 1992
- Lee HJ, Park JY, Jang SH, Kim JH, Kim EC, Choi KW: High incidence of resistance to multiple antimicrobials in clinical isolates of *Streptococcus pneumoniae* from a university hospital in Korea. *Clin Infect Dis* 20: 826-835, 1995
- Lee YS, Kim MK, Kim YI, Shin YS, Lee HJ, Ahn HS: Private practitioners' antimicrobial prescription patterns for acute respiratory tract infections in children. *J Korean Public Health Assoc* 17: 3-19, 1991
- Linares J, Pallares R, Alonso T, Perez JL, Ayats J, Guidol F, Viladrich PF, Martin R: Trends in antimicrobial resistance of clinical isolates of *Streptococcus pneumoniae* in Bellvitge Hospital, Barcelona, Spain (1979-1990). *Clin Infect Dis* 15: 99-105, 1992

- Ling J, Chau PY, Leung YK, Ng WS, So SY: Antibiotic susceptibility of pneumococci and *Haemophilus influenzae* isolated from patients with acute exacerbation of chronic bronchitis: prevalence of tetracycline-resistant strains in Hong Kong. *J Infect* 6: 33-37, 1983
- Ling ML, Tay L: Epidemiology of pneumococcal infection in Singapore (1977-1986). *Ann Acad Med Singapore* 19: 777-780, 1990
- Lyon DJ, Scheel O, Fung KS, Cheng AF, Henrichsen J: Rapid emergence of penicillin-resistant pneumococci in Hong Kong. *Scand J Infect Dis* 28: 375-376, 1996
- Marton A, Gulyaas M, Munoz R, Tomasz A: Extremely high incidence of antibiotic resistance in clinical isolates of *Streptococcus pneumoniae* in Hungary. *J Infect Dis* 163: 542-548, 1991
- Munoz R, Coffey TJ, Daniels M, Dowson CG, Laible G, Casal J, Hakenbeck R, Jacobs M, Musser JM, Spratt BG, Tomasz A: Intercontinental spread of a multiresistant clone of serotype 23F *Streptococcus pneumoniae*. *J Infect Dis* 164: 302-306, 1991
- Naraqi S, Kirkpatrick GP, Kabins S: Relapsing pneumococcal meningitis: isolation of an organism with decreased susceptibility to penicillin. *J Pediatr* 85: 671-673, 1974
- National Committee for Clinical Laboratory Standards: Performance standards for antimicrobial susceptibility testing: eighth informational supplement. NCCLS document M100-S8. Wayne, Pa, National Committee for Clinical Laboratory Standards, 1998
- Neu HC: The crisis in antibiotic resistance. *Science* 257: 1064-1073, 1992
- Rikitomi N, Sow PS, Watanabe K, Nunez DS, Martinez G, Nagatake T: Rapid increase of pneumococcal resistance to beta-lactam and other antibiotics in isolates from respiratory tract (Nagasaki, Japan: 1975-1994). *Microbiol Immunol* 40: 899-905, 1996
- Simor AE, Louie M, Low D: Canadian national survey of prevalence of antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 40: 2190-2193, 1996
- Sloas MM, Barrett FF, Chesney PJ, English BK, Hill BC, Tenover FC, Leggiadro RJ: Cephalosporin treatment failure in penicillin- and cephalosporin-resistant *Streptococcus pneumoniae* meningitis. *Pediatr Infect Dis J* 11: 662-666, 1992
- Soares S, Kristinsson KG, Musser JM: Evidence for the introduction of a multiresistant clone of serotype 6B *Streptococcus pneumoniae* from Spain to Iceland in the late 1980s. *J Infect Dis* 168: 158-163, 1993
- Song JH, Lee NY, Ichiyama S and the Asian Network for Surveillance of Resistant Pathogens (ANSORP) Study Group: Spread of drug-resistant *Streptococcus pneumoniae* in Asian countries: Asian Network for Surveillance of Resistant Pathogens (ANSORP) study. *Clin Infect Dis* (submitted, 1998a)
- Song JH, Yang JW, Jin JH, Peck KR, Kim S, Lee H, Lee NY: PCR fingerprinting analysis of genes encoding penicillin-binding proteins of multidrug-resistant *Streptococcus pneumoniae* isolated from Korea. *Korean J Infect Dis* 30: 117-125, 1998b
- Song JH, Yang JW, Jin JH, Peck KR, Kim S, Lee NY: Ribotyping of multidrug-resistant *Streptococcus pneumoniae* from Korea and other countries. *Korean J Infect Dis* 29: 469-476, 1997a
- Song JH, Yang JW, Lee NY, Peck KR, Kim S, Pai CH: Antimicrobial resistance of *Streptococcus pneumoniae* in Korea: evidence for a clonal origin of multidrug-resistant strains. *Korean J Infect Dis* 28: 393-404, 1996
- Song JH, Yang JW, Peck KR, Kim S, Lee NY, Jacobs MR, Appelbaum PC, Pai CH: Spread of multidrug-resistant *Streptococcus pneumoniae* in South Korea. *Clin Infect Dis* 25: 747-749, 1997b
- Tarasi A, Chong Y, Lee K, Tomasz A: Spread of the serotype 23F multidrug-resistant *Streptococcus pneumoniae* clone to South Korea. *Microb Drug Resist* 3: 105-109, 1997
- Tomasz A: Antibiotic resistance in *Streptococcus pneumoniae*. *Clin Infect Dis* 24(suppl 1): 85-88, 1997
- Waltman WD, Talkington DF, Lipinski AE, Crain MJ, Dixon JMS, Briles DE: Evidence of a clonal origin of relative penicillin resistance among type 9L pneumococci in Northwestern Canada. *J Infect Dis* 165: 671-675, 1992
- Wang H, Huebner R, Chen M, Klugman K: Antibiotic susceptibility patterns of *Streptococcus pneumoniae* in China and comparison of MICs by agar dilution and E-test methods. *Antimicrob Agents Chemother* 42: 2633-2636, 1998
- Welby PL, Keller DS, Cromien JL, Tebas P, Storch GA: Resistance to penicillin and non-beta-lactam antibiotics of *Streptococcus pneumoniae* at a children's hospital. *Pediatr Infect Dis J* 13: 281-287, 1994
- Yoshida R, Kaku M, Kohno S, Ishida K, Mizukane R, Takemura H, Tanaka H, Usui T, Tomono K, Koga H, Hara K: Trends in antimicrobial resistance of *Streptococcus pneumoniae* in Japan. *Antimicrob Agents Chemother* 39: 1196-1197, 1995