High Prevalence of Ceftazidime-Resistant *Klebsiella pneumoniae* and Increase of Imipenem-Resistant *Pseudomonas aeruginosa* and *Acinetobacter* spp. in Korea: a KONSAR Program in 2004

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A nationwide antimicrobial resistance surveillance has been conducted since 1997 in Korea. In this study, susceptibility test data generated in 2004 by KONSAR group hospitals were analyzed and compared to those at a commercial laboratory. In hospitals, the rank orders of organisms in 2004 were identical to those in 2003. The most prevalent species was *Staphylococcus aureus* (20.2%) in hospitals, but *Escherichia coli* (29.7%) in the commercial laboratory. The proportions of *Enterococcus faecium* to all isolates of *Enterococcus faecalis* plus *E. faecium* were 47.2% in hospitals and 24.9% in the commercial laboratory. The mean resistance rates of significant antimicrobial-organism combinations in hospitals were: oxacillin-resistant *S. aureus* (68%), oxacillin-resistant (penicillin-nonsusceptible) *Streptococcus pneumoniae* (68%), vancomycin-resistant *E. faecium* (25%), cefotaxime-resistant *E. coli* (14%), ceftazidime- and cefoxitin-resistant *Klebsiella pneumon*iae (34% and 32%, respectively), and imipenem-resistant *Acinetobacter* spp. and *Pseudomonas aeruginosa* (17% and 24%, respectively). In conclusion, oxacillin-resistant staphylococci, expanded-spectrum cephalosporin-resistant *K. pneumoniae*, and imipenem-resistant *Acinetobacter* spp. and *P. aeruginosa* were prevalent in 2004. Increasing trends were observed for vancomycin-resistant *E. faecium*, cefoxitin-resistant *E. coli* and *K. pneumoniae*, and imipenem-resistant *Acinetobacter* spp. and *P. aeruginosa*. Certain antimicrobial-organism combinations were also prevalent among the commercial laboratory-tested strains.

INTRODUCTION

Alarming rises in the prevalence of certain pathogenic bacteria resistant to some antimicrobial agents has been noted worldwide. Antimicrobial selective pressures, which are the primary determining factors of the prevalence of resistant bacteria, differ significantly depending on the region and time. Therefore, monitoring resistance is necessary for empirical selection of the most appropriate antimicrobial agents to treat infected patients. Monitoring temporal trends of resistance is considered most beneficial for the detection of subtle changes in resistance.[1]

Antimicrobial resistance surveillance is also necessary to assess the extent of problems and determine the need for intervention.[2] Alexander, PROTEKT, SENTRY, and other programs[3,4] are good examples conducted internationally by collecting strains and testing by a reference laboratory. For example it was believed that the Alexander project had provided a resource for measuring trends in the susceptibility patterns of respiratory pathogens at the national, regional and global levels.[4] These type programs can provide the most accurate information. However, they are very costly. Analysis of routine suscep-

tibility test data at hospitals has inherent inaccuracies due to differences in methodology and interpretation, but does not require many additional resources.[3,5]

The KONSAR program in Korea was initiated in 1997,[6] based on a World Health Organization recommendation. Two surveillance methods have been used, which include the analysis of hospital-tested data, and the testing of collected strains by the coordinating laboratory. Analysis of test data in 2003[7] revealed a further increase of vancomycin-resistant *Enterococcus faecium*, fluoroquinolone-resistant *Klebsiella pneumoniae*, and imipenem-resistant *Acinetobacter* spp. The previous second program revealed wide dissemination of metallo-β-lactamase (MBL)-producing *Acinetobacter* spp. and *Pseudomonas* spp.,[8] and plasmid-mediated CMY-2 and DHA-1 allelepositive *Escherichia coli* and *K. pneumoniae*.[9]

Currently, more problematic antimicrobial agent-organism combinations worldwide include methicillin-resistant *Staphylococcus*, vancomycin-resistant *E. faecium*, expanded-spectrum cephalosporin-resistant *K. pneumoniae*,[10] multidrug resistant (MDR) *Acinetobacter* spp.[11] and imipenem-resistant *Pseudomonas aeruginosa*.[12]

The resistance rates of nosocomially-acquired bacteria are generally higher than those of community-acquired ones, necessitating differentiation of these two groups in the analysis. Yet, it is sometimes difficult to separate them satisfactorily. In the previous KONSAR program, data were collected from hospitals only, but in 2003, data were also collected from a commercial laboratory, which tested a large number of specimens which were submitted mostly from primary-care clinics in many parts of Korea.[7]

In the analysis of resistance data, NCCLS[13] recommends inclusion of the first isolate of a given species per patient per analysis period (e.g., year), irrespective of the antimicrobial susceptibility profile or other phenotypic characteristics. When multiple isolates of nosocomial pathogens from a patient are included, resistance rates become significantly higher, but elimination of duplicate isolates may result in the underestimation of resistance rates and mask trends in emerging resistance.[5]

In this study susceptibility test data generated

by the KONSAR group hospitals were analyzed, and the resistance rates at hospitals were compared to those at a commercial laboratory. In addition, the effects of excluding duplicate isolates of some selected species on resistance rates were analyzed using test data from the coordinating laboratory.

MATERIALS AND METHODS

Routine susceptibility test data on common aerobic bacteria isolated in 2004 were collected from 44 KONSAR group hospitals located both in large cities and in small provincial cities throughout Korea. Data were also obtained from one commercial laboratory, which tested specimens received mostly from primary clinics in many parts of the country. The data from eight hospitals were excluded from the analysis due to poor performance versus the WHO/CDC quality control program. Data were also excluded from the analysis when the numbers of isolates in a hospital were less than 10 for non-typhoidal *Salmonella*, or less than 20 for other species.

Three hospital groups, which were determined based on the location and bed capacity at the time of initiation of the program ($\geq$ 1000 beds countrywide, < 1000 beds in Seoul, and < 1000 beds in non-Seoul), were used to compare mean resistance rates, despite changes in bed capacity at some hospitals.

As in the previous study, the mean resistance rates in each hospital groups were calculated from the resistance rates at each hospital to minimize the influence of a large numbers of isolates at some hospitals.[3,14] The data from the commercial laboratory were analyzed separately. Resistance rates, which did not include intermediate susceptibility, were calculated from all isolates, including duplicate ones. The effect of excluding duplicate isolates on the resistance rates was analyzed for some antimicrobial-species combinations using the WHONET 5 program.[15] Statistical significance of resistance trend was not determined as it was the common practice in the large scale continuous surveillance program.[4,16]

RESULTS

Rank order of isolates and methods of susceptibility testing

The number of isolates at hospitals in 2004 increased slightly compared to those in 2003, but the rank order remained the same in all 13 organisms (Table 1). The most prevalent species in hospitals was *Staphylococcus aureus* (20.2%), however it was *E. coli* (29.7%) at the commercial laboratory. The proportions of *E. faecium* to all isolates of *E. faecalis* plus *E. faecium* were 47.2% in hospitals and 24.9% at the commercial laboratory.

The responses to our questionnaire showed that the susceptibility test methods used for *E. coli* and *S. aureus* were the NCCLS disk diffusion method by 10 and 13 hospitals, the broth microdilution method (Vitek [bioMerieux, Marcy l'Etoile, France] or MicroScan [Dade MicroScan Inc., West Sacramento, CA, U.S.A.] system) by 21 and 17 hospitals, and a combination of the two by one and two hospitals, respectively. The fluoroquinolone susceptibility of gram-negative bacilli was mostly tested using ciprofloxacin, but some hospitals used levofloxacin instead. Kinds of antimicrobial agents used to test the susceptibility of *E. coli* and *S. aureus* were similar to those used in 2003 (data not shown).

Resistance rates of hospital isolates

The present surveillance showed that the mean oxacillin resistance rates of *S. aureus* and coagulase-negative staphylococci (CNS) in hospitals were 68% and 73%, respectively (Table 2). The resistance rate of *S. aureus* was much higher than that of CNS to fluoroquinolone (60% vs. 35%), but lower to cotrimoxazole (20% vs. 35%). Of *Streptococcus pneumoniae* tested, 68% were oxacillin-screening test positive, suggesting penicillin nonsusceptibility. The ampicillin resistance rate of *E. faecalis* was 2% in this study. Ampicillin and vancomycin resistance rates of *E. faecium* were 90% and 25%, respectively.

The resistance rates of *E. coli* to cefotaxime and *K. pneumoniae* to ceftazidime were 14% and 34%, respectively (Table 3). The resistance rates of *E.*

Table 1. Number, Proportion, and Rank Order of Isolates Tested in 2004

Organism	Hospitals		Commercial Lab.*	
	No. (%) of isolates	Rank	No. (%) of isolates	Rank
Escherichia coli	41,925 (17.7)	2	6,723 (29.7)	1
Klebsiella pneumoniae	25,320 (10.7)	5	2,513 (11.1)	4
Enterobacter cloacae	7,854 (3.3)	9	703 (3.1)	9
Serratia marcescens	5,743 (2.4)	10	1,068 (4.7)	8
Nontyphoidal *Salmonella*	545 (0.2)	13	164 (0.7)	12
Acinetobacter spp.	15,338 (6.5)	6	1,331 (5.9)	7
Pseudomonas aeruginosa	31,544 (13.3)	3	2,984 (13.2)	2
Haemophilus influenzae	954 (0.4)	12	138 (0.6)	13
Staphylococcus aureus	47,823 (20.2)	1	2,875 (12.7)	3
Coagulase-negative staphylococci	28,809 (12.1)	4	1,771 (7.8)	5
Enterococcus faecalis	14,795 (6.2)	7	1,509 (6.6)	6
E. faecium	13,211 (5.6)	8	500 (2.2)	10
Streptococcus pneumoniae	3,297 (1.4)	11	339 (1.5)	11
Total	237,158 (100)		22,618 (100)	

*Majority of the specimens were collected from primary care clinics in outside of Seoul.

Table 2. Antimicrobial Resistant Rates of Gram-Positive Cocci Tested at Hospitals and at a Commercial Laboratory

Antimicrobial agents	Percent of isolates resistant (No. of isolates tested)									
	S. aureus		CNS		*S. pneumoniae*		*E. faecalis*		*E. faecium*	
	Hospitals (47,823)	C-Lab (2,875)	Hospitals (28,809)	C-Lab (1,771)	Hospitals (3,297)	C-Lab (339)	Hospitals (14,795)	C-Lab (1,509)	Hospitals (13,211)	C-Lab (500)
Oxacillin	68	58	73	72	68*	40[†]	NT	NT	NT	NT
Penicillin/ampicillin[‡]	96	97	92	91	NT	NT	2	2	90	78
Clindamycin	37	42	37	21	NT	NT	NT	NT	NT	NT
Erythromycin	46	57	58	47	62	77	NT	NT	NT	NT
Cotrimoxazole	20	20	35	22	NT	NT	NT	NT	NT	NT
Tetracycline	32	47	34	39	NT	NT	80	87	13	21
Gentamicin	65	54	52	26	NT	NT	NT	NT	NT	NT
Fluoroquinolone[§]	60	NT	35	NT	NT	NT	34	27	91	69
Teicoplanin	0	0	0.5	0	NT	NT	1	0	20	8
Vancomycin	0	0	0	0	NT	NT	1	0	25	11

*Indicates proportion of penicillin-nonsusceptible isolates.
[†] Resistance determined by a broth microdilution test.
[‡] Resistance rates to penicillin for staphylococci and to ampicillin for enterococci.
[§]Majority of the laboratories used ciprofloxacin.
CNS, coagulase-negative staphylococci; C-Lab, commercial laboratory; NT, not tested.

coli and *K. pneumoniae* to cefoxitin were 8% and 32%, respectively (Table 3). The lowest resistance rates to cephalosporins shown by *Enterobacter cloacae* and *Serratia marcescens* were to cefepime, 8% and 17%, respectively. Imipenem-resistant *E. coli*, *K. pneumoniae*, *E. cloacae* and *S. marcescens* isolates existed, although the rates were very low (Table 3).

The resistance rates of *Acinetobacter* spp. were lower to imipenem (17%) and cefoperazone-sulbactam (19%) than to other antimicrobial agents, and those of *P. aeruginosa* were lower to ceftazidime (19%), and meropenem (20%), but slightly higher to imipenem (24%).

The resistance rates to gentamicin and tobramycin in this study were relatively high: in *E. coli* 24% and 20%, respectively, and in *K. pneumoniae* 26% and 36%, respectively. Amikacin resistance rates were 10% to 46%, except for *E. coli* (Table 3). *E. cloacae* was the species with the lowest resistance rate to fluoroquinolone, 11%, while *Acinetobacter* spp. was the species with the highest resistance rate of 56%.

The resistance rates of nontyphoidal *Salmonella* to ampicillin, cotrimoxazole, and fluoroquinolone were 44%, 7% and 0.7%, respectively (data not shown). Among the *Haemophilus influenzae* isolates 47% were resistant to ampicillin and 51% produced β-lactamase.

Resistance rates of commercial laboratory-tested isolates

The resistance rates of *S. aureus* to oxacillin (58%) and gentamicin (54%), and those of *E. faecium* to ampicillin (78%), fluoroquinolone (69%), and vancomycin (11%) at the commercial laboratory were lower than those in hospitals (Table 2). A comparison of the resistance rates of the commercial laboratory-tested gram-negative bacilli to those of hospital isolates showed that the cefotaxime resistance rates of *E. coli* were 12% and 14%, respectively, and cefoxitin resistance rates of *K. pneumoniae* were both 32%. However, cefotaxime, ticarcillin-clavulanic acid, and amikacin resistance rates of *E. cloacae* and *S. marcescens* were much

Table 3. Antimicrobial Resistance Rates of Gram-Negative Bacilli Tested at Hospitals and at a Commercial Laboratory

Antimicrobial agents	Percent of isolates resistant (No. of isolates tested)											
	E. coli		*K. pneumoniae*		*E. cloacae*		*S. marcescens*		*Acinetobacter*		*P. aeruginosa*	
	Hospitals (40,651)	C-Lab (6,723)	Hospitals (25,320)	C-Lab (2,513)	Hospitals (7,854)	C-Lab (703)	Hospitals (5,743)	C-Lab (1,068)	Hospitals (15,338)	C-Lab (1,331)	Hospitals (31,544)	C-Lab (2,984)
Ampicillin	65	70	-	-	-	-	-	-	-	-	-	-
Ampicillin-sulbactam	36	NT	42	NT	-	-	-	-	40	NT	-	-
Cephalothin	32	27	46	48	-	-	-	-	-	-	-	-
Cefotaxime	14	12	28	41	35	21	29	13	62	NT	57	NT
Ceftazidime	10	11	34	44	35	27	23	8	57	60	19	21
Aztreonam	11	NT	30	NT	33	NT	24	NT	72	79	26	22
Cefepime	11	NT	19	NT	8	NT	17	NT	49	42	23	20
Cefoperazone-sulbactam	6	NT	13	NT	8	NT	28	NT	19	NT	21	NT
Cefoxitin	8	7	32	32	NT	NT	NT	NT	NT	NT	NT	NT
Cefotetan	6	NT	18	NT	NT	NT	NT	NT	NT	NT	NT	NT
Piperacillin	60	NT	45	NT	28	NT	42	NT	55	65	36	30
Piperacillin-tazobactam	5	1	18	5	23	5	22	2	36	15	25	17
Ticarcillin-clavulanate	10	13	30	38	37	22	32	29	29	37	38	45
Imipenem	0.1	0	0.7	0	0.5	0	3	0	17	6	24	13
Meropenem	0	NT	0.1	NT	0.3	NT	9	NT	22	11	20	15
Amikacin	3	4	22	30	10	6	18	13	46	28	24	35
Gentamicin	24	29	26	35	23	26	39	43	59	62	37	45
Tobramycin	20	15	36	45	32	32	51	57	60	60	34	44
Fluoroquinolone*	32	33	31	41	11	9	18	16	56	68	38	48
Cotrimoxazole	35	15	36	32	26	30	21	29	57	54	95	100
Tetracycline	54	NT	16	NT	21	NT	69	NT	65	NT	95	NT

-Not applicable because of natural resistance.
*Majority of the laboratories used ciprofloxacin for testing.
NT, not tested.

lower. The imipenem and meropenem resistance rates of *P. aeruginosa*, 13% and 15%, respectively, were only slightly lower than those found in hospitals, but resistance rates of *Acinetobacter* spp., 6% and 11%, respectively, were much lower (Table 3).

The *E. coli* isolates tested by the commercial laboratory, and those by the hospitals, showed similar fluoroquinolone resistance rates, 33% and 32%, respectively. It is interesting to note that the commercial laboratory-tested *Acinetobacter* spp. and *P. aeruginosa* showed higher fluoroquinolone resistance rates than hospital isolates (Table 3).

Trends of significant resistance

The prevalence of oxacillin-resistant *S. aureus* and penicillin-nonsusceptible *S. pneumoniae* remained similar, but a further increase of ampicillin- and vancomycin-resistant *E. faecium* was observed
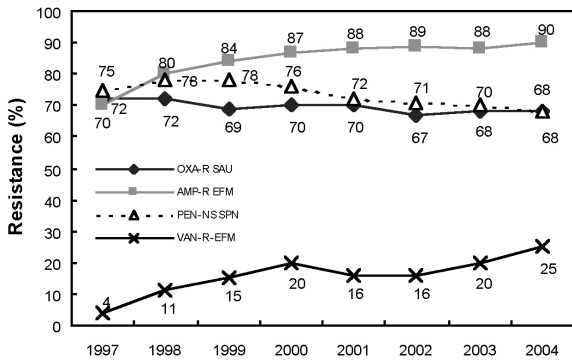
Fig. 1. Temporal changes of oxacillin-resistant *S. aureus*, ampicillin- and vancomycin-resistant *E. faecium* and penicillin-nonsusceptible *S. pneumoniae*. A continued increase of vancomycin-resistant *E. faecium* was observed. OXA, oxacillin; AMP, ampicillin; PEN, penicillin G; VAN, vancomycin; SAU, *Staphylococcus aureus*; EFM, *Enterococcus faecium*; SPN, *Streptococcus pneumoniae*; NS, nonsusceptible;. R, resistant.
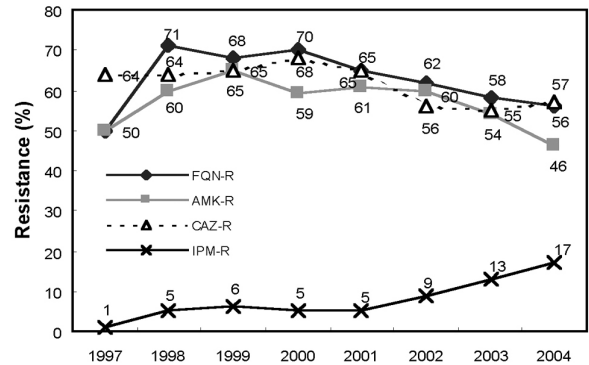
Fig. 3. Temporal changes of fluoroquinolone, amikacin, ceftazidime and imipenem resistance in *Acinetobacter* spp. A continued increase of imipenem resistance was observed. FQN, fluoroquinolone; AMK, amikacin; CAZ, ceftazidime; IPM, imipenem; R, resistant.
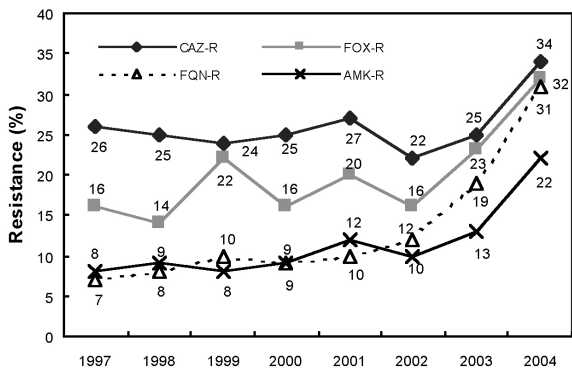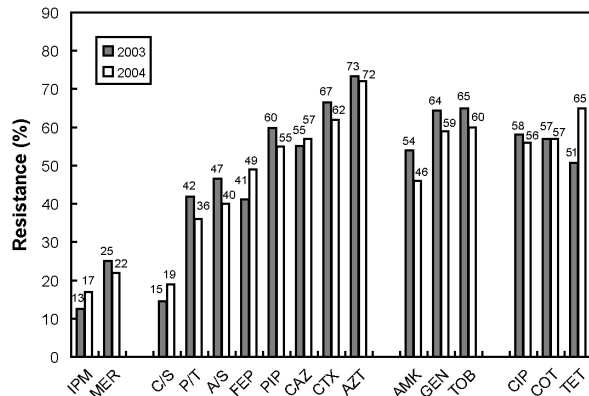

Fig. 2. Temporal changes of ceftazidime, cefoxitin, fluoroquinolone and amikacin resistance in *K. pneumoniae*. All of these resistances increased in 2004. CAZ, ceftazidime; FOX, cefoxitin; FQN, fluoroquinolone; AMK, amikacin; R, resistant.

Fig. 4. Comparison of antimicrobial resistance rates of *Acinetobacter* spp. isolated in 2003 and in 2004. Resistance rates to carbapenem and cefoperazone-sulbactam remained relatively low, but those to other antimicrobial agents were very high. IPM, imipenem; MER, meropenem; C/S, cefoperazone-sulbactam; P/T, piperacillin-sulbactam; A/S, ampicillin-sulbactam; FEP, cefepime; PIP, piperacillin; CAZ, ceftazidime; CTX, cefotaxime; AZT, aztreonam; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; CIP, ciprofloxacin; COT, cotrimoxazole; TET, tetracycline.

(Fig. 1). The resistance rates of *K. pneumoniae* to ceftazidime, cefoxitin, fluoroquinolone and amikacin also increased (Fig. 2).

Acinetobacter spp. showed a slight downward trend in resistance to fluoroquinolone, amikacin, and ceftazidime, but a steady upward trend in resistance to imipenem (Fig. 3). In the comparison of the resistance trends of the isolates in 2003 and 2004, the resistance rates to all three aminoglycosides, and to some β-lactams, decreased slightly, but the resistance to imipenem and cefoperazone-sulbactam was slightly increased (Fig. 4).

In the comparison of resistance rates by hospital

groups, isolates of vancomycin-resistant *E. faecium*, fluoroquinolone-resistant *E. coli*, cefoxitin-resitant *K. pneumoniae*, imipenem-resistant *P. aeruginosa* and *Acinetobacter* spp. were relatively more prevalent at the large hospital group than at the medium-size hospital group (Fig. 5). At the commercial laboratory, the rates of vancomycin-resistant *E. faecium*, imipenem-resistant *P. aeruginosa* and *Acinetobacter* spp. were lower, but the rate of
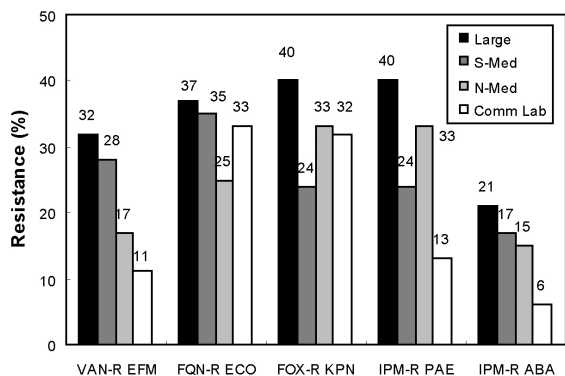
Fig. 5. Prevalence of problem antimicrobial-organism combinations in different hospital groups and at the commercial laboratory. Vancomycin-resistant *E. faecium*, and imipenem-resistant *P. aeruginosa* and *Acinetobacter* spp. were more prevalent among strain isolated from large hospitals than those tested at a commercial laboratory. S-Med, Seoul-medium; N-Med, non-Seoul-medium; Comm Lab, commercial laboratory; VAN, vancomycin; FQN, fluoroquinolone; FOX, cefoxitin; IMP, imipenem; EFM, *Enterococcus faecium*; ECO, *Escherichia coli*; KPN, *Klebsiella pneumoniae*; PAE, *Pseudomonas aeruginosa*; ABA, *Acinetobacter baumannii*; R, resistant.
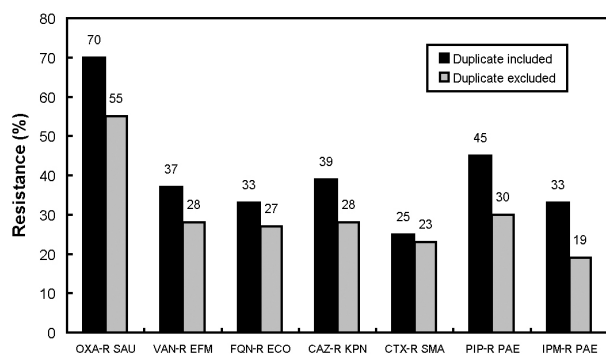

Fig. 6. Comparison of resistance rates by including duplicate isolates and by including only the first isolate from a patient per year. The difference was relatively greater in piperacillin- and imipenem-resistant *P. aeruginosa*, and oxacillin-resistant *S. aureus*. OXA, oxacillin; VAN, vancomycin; FQN, fluoroquinolone; CAZ, ceftazidime; CTX, cefotaxime; PIP, piperacillin; IPM, imipenem; SAU, *Staphylococcus aureus*; EFM, *Enterococcus faecium*; ECO, *Escherichia coli*; KPN, *Klebsiella pneumoniae*; SMA, *Serratia marcescens*, PAE, *Pseudomonas aeruginosa*; R., resistant.

fluoroquinolone-resistant *E. coli* was similar.

Resistance rates excluding duplicate isolates

Coordinating laboratory data showed that the
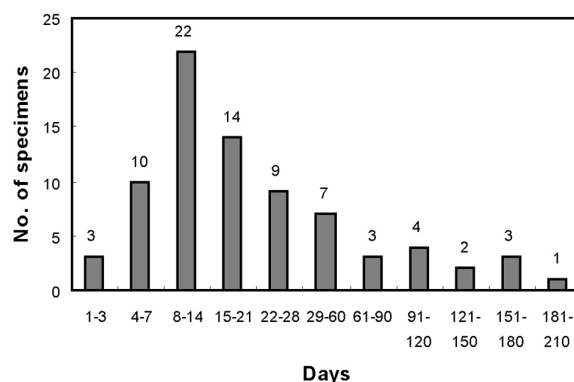
Fig. 7. The time (day) between the first isolation of an imipenem-susceptible strain and the subsequent isolation of an imipenem-resistant strain of *P. aeruginosa*. The first resistant strain was detected within 4 weeks in 58 of 78 (74%) patients.

resistance rates including all isolates were more than 5% higher compared to those including only the first isolate from a patient in oxacillin-resistant *S. aureus*, vancomycin-resistant *E. faecium* fluoroquinolone-resistant *E. coli*, ceftazidime-resistant *K. pneumoniae*, piperacillin- and imipenem-resistant *P. aeruginosa* (Fig. 6). The data from the coordinating laboratory were used to determine the time (day) between the first isolation of an imipenem-susceptible strain and the subsequent isolation of an imipenem-resistant strain of *P. aeruginosa* from same patients. The first resistant strain was detected within 4 weeks in 58 of 78 (74%) patients (Fig. 7). This suggested that, even in the monthly analysis of resistance rates, including the susceptibility of only the first isolate may result in the underestimation of the prevalence of some other resistances.

DISCUSSION

A comparison of total number of isolates tested in 2004 vs. 2003 showed a slight increase at hospitals, whereas there had been a significant decrease at the commercial laboratory (Table 1). The rank order remained the same for all 13 organisms in hospitals, but at the commercial laboratory, *K. pneumoniae* moved from the fifth to the fourth most prevalent, and coagulase-negative staphylococci dropped from the fourth to the fifth most prevalent.[7]

Kinds of antimicrobial agents used to test susceptibility of *E. coli* and *S. aureus* did not change significantly compared to those in 2003. With the increasing prevalence of CTX-M type extended-spectrum β-lactamase (ESBL) in Korea, testing the susceptibility of *E. coli*, *K. pneumoniae* and *Proteus mirabilis* to at least ceftazidime and cefotaxime became necessary for optimal detection of the enzymes,[17] but not all hospitals tested susceptibility to both of these antimicrobial agents.

The mean oxacillin resistance rates of *S. aureus* and coagulase-negative staphylococci (CNS) in hospitals were 68% and 73%, respectively (Table 2). Oxacillin-resistant *S. aureus* is now highly prevalent, not only in Japan,[18] but in other countries as well. Over 40% of *S. aureus* isolates in Greece, Italy, and United Kingdom were oxacillin-resistant, according to a surveillance study in 1999-2002.[19] The penicillin G breakpoint for *Streptococcus pneumoniae* is for the treatment of meningitis. A high penicillin G non-susceptible rate of pneumococci by oxacillin-disk screening test (68%) in this study suggests that empirical selection of penicillin G, without susceptibility testing, may result in a high rate of clinical failure in the treatment of meningitis. Penicillin-non-susceptible pneumococci are very prevalent in some other Asian countries, as well,[20] and increased penicillin resistance was also reported in the United States in the 1990s.[21]

The proportion of ampicillin-resistant *E. faecalis* was 2% in this study. Ampicillin-resistant *E. faecalis* was considered to be a misidentification of *E. faecium* in surveillance of the United Kingdom.[22] A thorough review of other unexpected antibiograms, such as < 100% vancomycin susceptibility for *S. aureus*, < 100% imipenem susceptibility for *Escherichia coli*, and > 0% ampicillin susceptibility for *K. pneumoniae*, was also recommended to improve the quality of surveillance data.[23] The vancomycin resistance rate of *E. faecium* was 25%. Difficulty in the control of vancomycin-resistant enterococci was shown by a high prevalence at a Chicago hospital,[24] where the proportion of vancomycin-resistant *E. faecium* isolates increased from 28.9% to 72.4%, between 1993 and 2002.

The resistance rates of *E. coli* to cefotaxime and

K. pneumoniae to ceftazidime were 14% and 34%, respectively (Table 3). *E. coli* and *K. pneumoniae* often acquire ESBL genes. In Korea, TEM-, SHV-, CTX-M-type ESBLs were reported.[25-27] An analysis of *K. pneumoniae* strains collected between 1998 and 2002 from Asian countries[28] showed that ESBL-producing isolates were particularly prevalent in Singapore (35.6%), China (30.7%), and the Philippines (21.9%). Increased prevalence of ESBL-producing *E. coli* and *Klebsiella* spp. over time was also reported in Europe.[29]

The cefoxitin resistance rate of *K. pneumoniae* was 32% (Table 3). A majority of the resistant isolates likely produced plasmid-mediated AmpC β-lactamases. DHA-1 and CMY-2 enzymes were reported to be the prevalent plasmid-mediated AmpC enzymes in Korea.[9,30,31] Dissemination of *E. coli* and *K. pneumoniae* strains producing plasmid-mediated AmpC β-lactamases has become a worldwide problem,[32] since the enzymes confer resistance not only to cephalosporins and cephamycins, but also to carbapenems when the mechanism is combined with porin loss.[33]

Imipenem-resistant *E. coli*, *K. pneumoniae*, *E. cloacae* and *S. marcescens* isolates existed, although the rates were very low (Table 3). MBL-producing *E. cloacae*,[34,35] and *S. marcescens* and *Citrobacter freundii*[35] were reported in Korea. The resistance rates of *Acinetobacter* spp. were lower to imipenem (17%) and cefoperazone-sulbactam (19%) than to other antimicrobial agents. Higgins et al.[36] reported that *in vitro* activity of β-lactam-β-lactamase inhibitor combinations against *A. baumannii* are mainly determined by the intrinsic activity of the inhibitors alone. It was reported that sulbactam has a good intrinsic activity against MDR *Acinetobacter* strains at concentrations readily achievable in human serum and may therefore have some therapeutic implications in the treatment of infections caused by MDR *A. baumannii* infections. Smolyakov et al.[37] reported that ampicillin-sulbactam appeared to be one of the last effective and safe empirical resorts for the treatment of MDR *A. baumannii* bloodstream infections, but in our present study, the resistance rate to this combination was not low (40%).

Increasing resistance of *P. aeruginosa* and *Acinetobacter* spp. to carbapenems is the most serious problem, as it is the only class of β-lactam

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active against ESBL- and derepressed AmpC enzyme-producing organisms.[38] Various mechanisms are involved in carbapenem resistance.[12] In Korea, VIM-2 and IMP-1 type acquired metallo-β-lactamases (MBLs) were reported in these organisms.[8,39-41] Certain types of OXA enzymes can hydrolyze carbapenem. Carbapenem-hydrolyzing OXA-23 enzyme was detected in outbreak strains of imipenem-resistant *A. baumannii*, which involved 36 patients at a university hospital in 2003.[42] In Brazilian hospitals, resistance rates of *Acinetobacter* spp. to carbapenem have reached 12% or higher.[43] Thus, more toxic agents, such as polymyxin, have been used, and as a consequence, it was found that 5 out of 100 blood isolates of *Acinetobacter* spp. were resistant to this drug.

Increasing amikacin resistance in some species of gram-negative bacilli (Table 3) suggest that empirical selection of this aminoglycoside has also became difficult. Fluoroquinolones are frequently used, as they are one of the three major broad-spectrum classes of antimicrobial agents,[44] but 56% of *Acinetobacter* spp. isolates were resistant to this drug.

Compared to the previous report of ampicillin and cotrimoxazole resistance rates (both 34%) of *Salmonella enterica* serovar Typhymurium DT104,[45] the resistance rate to ampicillin was higher, but the rate to cotrimoxazole was much lower. Nontyphoidal *Salmonella* infections are mostly acquired in communities rather than in hospitals. Therefore, an increase of ampicillin-resistant isolates may suggest prevalence of this resistance in the community. The fluoroquinolone-resistance rate remained very low, but this low rate may not be useful to predict clinical efficacy for the treatment of extra-intestinal *Salmonella* infections, because low-level quinolone resistance is clinically relevant but not detectable by using fluoroquinolones. A similar ampicillin resistance rate of 47% and β-lactamase production rate of 51% in *Haemophilus influenzae* isolates in this study suggests that β-lactamase-negative ampicillin-resistant (BNAR) *H. influenzae* remain rare in Korea, although it has been a prevalent type in Japan.[46]

In general, resistant bacteria are more prevalent among hospital isolates. However the cefotaxime resistance rate of *E. coli* (12%) at the commercial laboratory was similar to that in hospitals (14%), suggesting a spread of ESBL-producing strains to the community or to small hospitals. Presence of imipenem-resistant *P. aeruginosa* and *Acinetobacter* spp. at the commercial laboratory also suggests a spread of this resistance to small hospitals. The similar fluoroquinolone resistance rates of *E. coli* at the commercial laboratory (33%) and in hospitals (32%) suggest the presence of fluoroquinolone-resistant *E. coli* in the community (Table 3). In a Taiwanese surveillance study in 2000, fluoroquinolone resistance is found among isolates from both inpatients and outpatients, not only in medical centers, but also at regional hospitals throughout the country.[47]

A further increase of cefoxitin-resistant *K. pneumoniae* was observed in this study (Fig. 2). A previous KONSAR study showed that plasmid-mediated CMY-2 and DHA-1 AmpC-producing *K. pneumoniae* isolates were prevalent in Korea.[8] It is a concern that plasmid-mediated AmpC can confer resistance to imipenem when combined with porin loss.

Acinetobacter spp. showed slight decreased resistance to fluoroquinolone, amikacin, and ceftazidime, but a steady upward trend of resistance to imipenem (Fig. 3). A recent increase in carbapenem usage probably caused these two different trends. In the 2003 KONSAR study,[8] many isolates of *Acinetobacter* spp. showed MDR patterns.

The lower rates of vancomycin resistance in *E. faecium*, imipenem resistance in *P. aeruginosa* and *Acinetobacter* spp., but the similar rate of fluoroquinolone resistance in *E. coli* at the commercial laboratory in this study, may be due to less use of vancomycin and imipenem, but frequent use of fluoroquinolones in the community or at clinics. Diekema et al.[48] analyzed the American Hospital Association annual survey data, and reported a greater prevalence of oxacillin-resistant *S. aureus*, vancomycin-resistant enterococci, fluoroquinolone-resistant *E. coli*, and ESBL-producing *K. pneumoniae* in teaching hospitals than non-teaching hospitals, and in > 199-bed hospitals than smaller hospitals.

In conclusion, oxacillin-resistant staphylococci, expanded-spectrum cephalosporin-resistant *K.*

pneumoniae and fluoroquinolone-resistant *E. coli*, *Acinetobacter* spp., and *P. aeruginosa* were highly prevalent problem organisms in Korea in 2004. Increasing trends were observed for vancomycin-resistant *E. faecium*, cefoxitin-resistant *E. coli* and *K. pneumoniae*, and imipenem-resistant *P. aeruginosa* and *Acinetobacter* spp. Some antimicrobial-organisms combinations were also prevalent among the commercial laboratory-tested strains.

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REFERENCES

1. Morris AK, Masterton RG. Antibiotic resistance surveillance: action for international studies. J Antimicrob Chemother 2002;49:7-10.
2. Bax R, Bywater R, Cornaglia G, Goossens H, Hunter P, Isham V, et al. Surveillance of antimicrobial resistance-what, how and whither? Clin Microbiol Infect 2001;7: 316-25.
3. Van Beneden CA, Lexau C, Baughman W, Barnes B, Bennett N, Cassidy PM, et al. Aggregated antibiograms and monitoring of drug-resistant *Streptococcus pneumoniae*. Emerg Infect Dis 2003;9:1089-95.
4. Felmingham D, White AR, Jacobs MR, Appelbaum PC, Poupard J, Miller LA, et al. The Alexander Project: the benefit from a decade of surveillance. J Antimicrob Chemother 2005;56 (Suppl 2):ii3-ii21.
5. Cornaglia G, Hryniewicz W, Jarlier V, Kahlmeter G, Mittermayer H, Stratchounski L, et al. European recommendations for antimicrobial resistance surveillance. Clin Microbiol Infect 2004;10:349-83.
6. Chong Y, Lee K, Park YJ, Jeon DS, Lee MH, Kim MY, et al. Korean nationwide surveillance of antimicrobial resistance of bacteria in 1997. Yonsei Med J 1998;39: 569-77.
7. Lee K, Park KH, Jeong SH, Lim HS, Shin JH, Yong D, et al. Further increase of vancomycin-resistant *Enterococcus faecium*, amikacin- and fluoroquinolone-resistant *Klebsiella pneumoniae*, and imipenem-resistant *Acinetobacter* spp. in Korea: 2003 KONSAR surveillance. Yonsei Med J 2006;47:43-54.
8. Lee K, Lee WG, Uh Y, Ha GY, Cho J, Chong Y, et al. VIM- and IMP-type metallo-β-lactamase-producing *Pseudomonas* spp. and *Acinetobacter* spp. in Korean hospitals. Emerg Infect Dis 2003;9:868-71.
9. Lee K, Lee M, Shin JH, Lee MH, Kang SH, Park AJ, et

al. Prevalence of plasmid-mediated AmpC β-Lactamases in *Escherichia coli* and *Klebsiella pneumoniae* in Korea. Microb Drug Resist 2006;12:44-9.

10. Gniadkowski M. Evolution and epidemiology of extended-spectrum β-lactamases (ESBLs) and ESBL-producing microorganisms. Clin Microbiol Infect 2001;7: 597-608.

11. Urban C, Segal-Maurer S, Rahal JJ. Considerations in control and treatment of nosocomial infections due to multidrug-resistant *Acinetobacter* baumannii. Clin Infect Dis 2003;36:1268-74.

12. Walsh TR, Toleman MA, Poirel L, Nordmann P. Metallo-β-lactamases: the quiet before the storm? Clin Microbiol Rev 2005;18:306-25.

13. National Committee for Clinical Laboratory Standards. Analysis and presentation of cumulative antimicrobial susceptibility test data. Approved guideline M39-A. Wayne, PA: NCCLS; 2002.

14. Fridkin SK, Hill HA, Volkova NV, Edwards JR, Lawton RM, Gaynes RP, et al. Temporal changes in prevalence of antimicrobial resistance in 23 U.S. hospitals. Emerg Infect Dis 2002;8:697-701.

15. Stelling JM, O'Brien TF. Surveillance of antimicrobial resistance: the WHONET program. Clin Infect Dis 1997; 24 Suppl 1:157-68.

16. Sahm DF, Marsilio MK, Piazza G. Antimicrobial resistance in key bloodstream bacterial isolates: electronic surveillance with the Surveillance Network Database-USA. Clin Infect Dis 1999;29:259-63.

17. National Committee for Clinical Laboratory Standards. Performance Standards for antimicrobial susceptibility testing: fourteenth informational supplement. Wayne, PA: NCCLS; 2004.

18. Yasunaka K, Kono K. Epidemiological study of methicillin-resistant *Staphylococcus aureus* at Fukuoka University Hospital. Microb Drug Resist 1999;5:207-13.

19. Tiemersma EW, Bronzwaer SL, Lyytikainen O, Degener JE, Schrijnemakers P, Bruinsma N, et al. Methicillin-resistant *Staphylococcus aureus* in Europe, 1999-2002. Emerg Infect Dis 2004;10:1627-34.

20. Song JH, Jung SI, Ko KS, Kim NY, Son JS, Chang HH, et al. High prevalence of antimicrobial resistance among clinical *Streptococcus pneumoniae* isolates in Asia (an ANSORP Study). Antimicrob Agents Chemother 2004;48:2101-7.

21. Mera RM, Miller LA, Daniels JJ, Weil JG, White AR. Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States over a 10-year period: Alexander Project. Diagn Microbiol Infect Dis 2005;51: 195-200.

22. Hunter PA, Reeves DS. The current status of surveillance of resistance to antimicrobial agents: report on a meeting. J Antimicrob Chemother 2002;49:17-23.

23. Zapantis A, Lacy MK, Horvat RT, Grauer D, Barnes BJ, O'Neal B, et al. Nationwide antibiogram analysis using NCCLS M39-A guidelines. J Clin Microbiol 2005;43: 2629-34.

24. Treitman AN, Yarnold PR, Warren J, Noskin GA.

25. Emerging incidence of *Enterococcus faecium* among hospital isolates (1993 to 2002). J Clin Microbiol 2005;43: 462-3.

25. Pai H, Choi EH, Lee HJ, Hong JY, Jacoby GA. Identification of CTX-M-14 extended-spectrum β-lactamase in clinical isolates of *Shigella sonnei*, *Escherichia coli*, and *Klebsiella pneumoniae* in Korea. J Clin Microbiol 2001;39: 3747-9.

26. Jeong SH, Bae IK, Lee JH, Sohn SG, Kang GH, Jeon GJ, et al. Molecular characterization of extended-spectrum beta-lactamases produced by clinical isolates of *Klebsiella pneumoniae* and *Escherichia coli* from a Korean nationwide survey. J Clin Microbiol 2004;42:2902-6.

27. Ryoo NH, Kim EC, Hong SG, Park YJ, Lee K, Bae IK, et al. Dissemination of SHV-12 and CTX-M-type extended-spectrum β-lactamases among clinical isolates of *Escherichia coli* and *Klebsiella pneumoniae* and emergence of GES-3 in Korea. J Antimicrob Chemother 2005;56:698-702.

28. Hirakata Y, Matsuda J, Miyazaki Y, Kamihira S, Kawakami S, Miyazawa Y, et al. Regional variation in the prevalence of extended-spectrum β-lactamase-producing clinical isolates in the Asia-Pacific region (SENTRY 1998-2002). Diagn Microbiol Infect Dis 2005; 52:323-9.

29. Goossens H, Grabein B. Prevalence and antimicrobial susceptibility data for extended-spectrum (-lactamase- and AmpC-producing Enterobacteriaceae from the MYSTIC Program in Europe and the United States (1997-2004). Diagn Microbiol Infect Dis 2005;53:257-64.

30. Song W, Kim JS, Kim MN, Kim EC, Park YJ, Yong D, et al. Occurrence and genotypic distribution of plasmid-mediated AmpC β-lactamase-producing Eshcherichia coli and *Klebsiella pneumoniae* in Korea. Korean J Lab Med 2002;22:410-6.

31. Yong D, Lim Y, Song W, Choi YS, Park DY, Lee H, et al. Plasmid-mediated, inducible AmpC β-lactamase (DHA-1)-producing Enterobacteriaceae at a Korean hospital: wide dissemination in *Klebsiella pneumoniae* and Klebsiella oxytoca and emergence in Proteus mirabilis. Diagn Microbiol Infect Dis 2005;53:65-70.

32. Philippon A, Arlet G, Jacoby GA. Plasmid-determined AmpC-type beta-lactamases. Antimicrob Agents Chemother 2002;46:1-11.

33. Bidet P, Burghoffer B, Gautier V, Brahimi N, Mariani-Kurkdjian P, El-Ghoneimi A, et al. *In vivo* transfer of plasmid-encoded ACC-1 AmpC from *Klebsiella pneumoniae* to *Escherichia coli* in an infant and selection of impermeability to imipenem in *K. pneumoniae*. Antimicrob Agents Chemother 2005;49:3562-5.

34. Jeong SH, Lee K, Chong Y, Yum JH, Lee SH, Choi HJ, et al. Characterization of a new integron containing VIM-2, a metallo-β-lactamase gene cassette, in a clinical isolate of Enterobacter cloacae. J Antimicrob Chemother 2003;51:397-400.

35. Lee HK, Park YJ, Kim JY, Chang E, Cho SG, Chae HS, et al. Prevalence of decreased susceptibility to carbapenems among *Serratia marcescens*, *Enterobacter cloacae*,

and *Citrobacter freundii* and investigation of carbapenemases. Diagn Microbiol Infect Dis 2005;52:331-6.

36. Higgins PG, Wisplinghoff H, Stefanik D, Seifert H. *In vitro* activities of the beta-lactamase inhibitors clavulanic acid, sulbactam, and tazobactam alone or in combination with beta-lactams against epidemiologically characterized multidrug-resistant *Acinetobacter baumannii* strains. Antimicrob Agents Chemother 2004;48:1586-92.

37. Smolyakov R, Borer A, Riesenberg K, Schlaeffer F, Alkan M, Porath A, et al. Nosocomial multi-drug resistant *Acinetobacter baumannii* bloodstream infection: risk factors and outcome with ampicillin-sulbactam treatment. J Hosp Infect 2003;54:32-8.

38. Livermore DM, Woodford N. Carbapenemases: a problem in waiting? Curr Opin Microbiol 2000;3:489-95.

39. Kim IS, Oh WI, Song JH, Lee NY. Screening and identification of metallo-β-lactamase gene in clinical isolates of imipenem-resistant *Pseudomonas aeruginosa*. Korean J Lab Med 2004;24:177-82.

40. Kim IS, Lee NY, Ki CS, Oh WS, Peck KR, Song JH. Increasing prevalence of imipenem-resistant *Pseudomonas aeruginosa* and molecular typing of metallo-β-lactamase producers in a Korean hospital. Microb Drug Resist 2005;11:355-9.

41. Shin KS, Han K, Lee J, Hong SB, Son BS, Youn SJ, et al. Imipenem-resistant *Achromobacter xylosoxidans* carrying *bla*VIM-2-containing class 1 integron. Diagn Microbiol Infect Dis 2005;53:215-20.

42. Jeon BC, Jeong SH, Bae IK, Kwon SB, Lee K, Young D, et al. Investigation of a nosocomial outbreak of imipenem-resistant *Acinetobacter baumannii* producing the OXA-23 β-lactamase in Korea. J Clin Microbiol 2005; 43:2241-5.

43. Reis AO, Luz DAM, Tognim MCB, Sader HS, Gales AC. Polymyxin-resistant *Acinetobacter* spp. isolates; what is next? Emerg Infect Dis 2003;9:1025-7.

44. Hooper DC. The future of the quinolones. APUA Newsletter 2001;19:1-5.

45. Park MS, Kang YH, Lee SJ, Song CY, Lee BK. Characteristics of epidemic multidrugresistant *Salmonella enterica* serovar Typhimurium DT104 strains first isolated in Korea. Korean J Infect Dis 2002;34:1-8.

46. Hasegawa K, Chiba N, Kobayashi R, Murayama Y, Iwata S, Sunakawa K, et al. Rapidly increasing prevalence of β-lactamase-nonproducing, ampicillin-resistant *Haemophilus influenzae* type b in patients with meningitis. Antimicrob Agents Chemother 2004;48: 1509-14.

47. Lauderdale TL, McDonald LC, Shiau YR, Chen PC, Wang HY, Lai JF, et al. The status of antimicrobial resistance in Taiwan among gram-negative pathogens: the Taiwan surveillance of antimicrobial resistance (TSAR) program, 2000. Diagn Microbiol Infect Dis 2004; 48:211-9.

48. Diekema DJ, BootsMiller BJ, Vaughn TE , Woolson RF, Yankey JW, Ernst EJ, et al. Antimicrobial resistance trends and outbreak frequency in United States hospitals. Clin Infect Dis 2004;38:78-85.