



Increasing Resistance to Extended-Spectrum Cephalosporins, Fluoroquinolone, and Carbapenem in Gram-Negative Bacilli and the Emergence of Carbapenem Non-Susceptibility in *Klebsiella pneumoniae*: Analysis of Korean Antimicrobial Resistance Monitoring System (KARMS) Data From 2013 to 2015

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Background: National surveillance of antimicrobial resistance becomes more important for the control of antimicrobial resistance and determination of treatment guidelines. We analyzed Korean Antimicrobial Resistance Monitoring System (KARMS) data collected from 2013 to 2015.

Methods: Of the KARMS participants, 16 secondary or tertiary hospitals consecutively reported antimicrobial resistance rates from 2013 to 2015. Data from duplicate isolates and institutions with fewer than 20 isolates were excluded. To determine the long-term trends, previous KARMS data from 2004 to 2012 were also considered.

Results: The prevalence of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium* from 2013 to 2015 was 66–72% and 29–31%, respectively. The resistance rates of *Escherichia coli* to cefotaxime and cefepime gradually increased to 35% and 31%, respectively, and fluoroquinolone resistance reached 48% in 2015. The resistance rates of *Klebsiella pneumoniae* to cefotaxime, cefepime, and carbapenem were 38–41%, 33–41%, and <0.1–2%, respectively, from 2013 to 2015. The carbapenem susceptibility rates of *E. coli* and *K. pneumoniae* decreased from 100% and 99.3% in 2011 to 99.0% and 97.0% in 2015, respectively. The resistance rate of *Pseudomonas aeruginosa* to carbapenem increased to 35% and the prevalence of carbapenem-resistant *Acinetobacter baumannii* increased from 77% in 2013 to 85% in 2015.

Conclusions: Between 2013 and 2015, the resistance rates of *E. coli* to third- and fourth-generation cephalosporins increased continuously, while carbapenem-susceptibility gradually decreased, particularly in *K. pneumoniae*. The prevalence of carbapenem-resistant *P. aeruginosa* and *A. baumannii* increased significantly; therefore, few treatment options remain for these resistant strains.

Key Words: Antimicrobial drug resistance, Surveillance, *Acinetobacter baumannii*, KARMS

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INTRODUCTION

The prevalence of antimicrobial-resistant bacteria has increased worldwide. In 2013, the Centers for Disease Control and Prevention in the United States reported that each year, at least two million people in the United States acquire serious infections due to resistant bacteria and that over 23,000 people die as a direct result of these antibiotic-resistant infections [1]. Resistance rates vary across countries because of differences in antimicrobial agent usage and systems for the prevention of antimicrobial resistant bacteria. In addition to resistance rates, modes of resistance also differ among countries and even among cities within the same country. Therefore, accurate nationwide surveillance of antimicrobial-resistant bacteria is becoming more important for the establishment of treatment guidelines for optimal applied therapies.

The spread of antimicrobial resistance is a major concern in Korea. In 2003, the prevalence of resistance in bacterial strains included 66% methicillin-resistant *Staphylococcus aureus* (MRSA), 22% vancomycin-resistant *Enterococcus faecium*, 14% ceftazidime-resistant *Klebsiella pneumoniae*, and 25% imipenem-resistant *Pseudomonas aeruginosa* [2]. Lee *et al* [3] reported that according to the Korean Nationwide Surveillance of Antimicrobial Resistance (KONSAR) study, the prevalence of ceftazidime-resistant *K. pneumoniae* and imipenem-resistant *Acinetobacter* species increased up to 47% and 22%, respectively. In 2009, the prevalence of imipenem-resistant *Acinetobacter* species increased to 57% [4]. Recently, carbapenem-resistant *Enterobacteriaceae* (CRE) have been increasingly reported in many hospitals in Korea, mostly associated with the clonal expansion of *K. pneumoniae* carbapenemase [5]. The Korean government has implicated six multidrug-resistant organisms, including MRSA, vancomycin-resistant *Staphylococcus aureus* (VRSA), vancomycin-resistant enterococci, multidrug-resistant *P. aeruginosa*, and multidrug-resistant *Acinetobacter baumannii* (MRAB), as the main agents of nosocomial infections. Since 2012, Korean hospitals are required to report infections by these organisms to the Korea Centers for Disease Control and Prevention (<http://www.cdc.go.kr/CDC/>). However, this program focuses solely on antimicrobial resistance rates and not on particular strain differences; further evaluation for elucidating the mode of resistance is not available through this program.

The Korean Antimicrobial Resistance Monitoring System (KARMS), which has been overseen by the Korea Centers for Disease Control and Prevention since 2002, is a surveillance program for collecting antimicrobial resistance data in Korea as well

as a limited number of resistant strain isolates. A total of 35 tertiary and secondary hospitals participate in this program by reporting the antimicrobial resistance rates of various bacteria once a year. In this study, we evaluated the antimicrobial resistance rates of the most commonly isolated bacteria, including *S. aureus*, *Enterococcus* species, *Streptococcus pneumoniae*, *Escherichia coli*, *K. pneumoniae*, *P. aeruginosa*, and *A. baumannii*, on the basis of the data from 16 hospitals that continuously reported to KARMS between 2013 and 2015.

METHODS

Antimicrobial resistance data was collected from 31 secondary or tertiary hospitals; 16 of these hospitals reported annually from 2013 to 2015. These 16 hospitals (620–1,356 beds) covered eight major cities and provinces in Korea, representing national antimicrobial resistance trends. The hospitals used their own hospital system or WHONET software [6] and duplicate isolates were excluded from the analysis. Antimicrobial susceptibility tests were performed by using disk diffusion or modified broth microdilution tests with the VITEK 2 automated system (bioMérieux, Marcy l'Etoile, France) or the MicroScan system (Beckman Coulter, Brea, CA, USA) according to the CLSI guidelines [7]. If the CLSI guideline threshold was not available, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) threshold was applied for the determination of susceptibility. To minimize size difference bias between the hospitals, data consisting of less than 20 isolates of an organism were excluded; resistance rates were calculated as the median and range because of the limited number of hospitals. The antimicrobial resistance of gram-negative bacilli was compared with previous results from 2004 to determine long-term trend changes [8–10].

RESULTS

1. Antimicrobial resistance in gram-positive cocci

The resistance rates of gram-positive cocci from 2013 to 2015 are summarized in Table 1. The prevalence of MRSA decreased from 72% in 2013 to 66% in 2015. The resistance rates of *S. aureus* isolates to other antibiotics also slightly decreased from 2013; 95% for penicillin, 54% for erythromycin, 54% for clindamycin, and 48% for ciprofloxacin in 2015. Over 97% of the isolates showed susceptibility to trimethoprim-sulfamethoxazole, while no vancomycin- and/or teicoplanin-resistant *S. aureus* were isolated. The rates of penicillin resistance in *S. pneumoniae* ranged from 11–14%; and 9–12% of isolates were re-

Table 1. Antimicrobial resistance rates (%) of gram-positive cocci

Organism	Antimicrobial agent	Antimicrobial resistance rate, median (range)		
		2013	2014	2015
<i>Staphylococcus aureus</i>	N of tested isolates	18,461	13,017	10,770
	Penicillin	95 (84–99)	95 (93–98)	95 (90–100)
	Oxacillin	72 (54–80)	70 (46–85)	66 (40–84)
	Erythromycin	63 (44–73)	61 (41–73)	54 (38–70)
	Clindamycin	63 (31–72)	56 (32–71)	54 (30–71)
	Gentamicin	49 (29–60)	48 (24–65)	42 (25–67)
	Ciprofloxacin	59 (28–67)	54 (28–68)	48 (24–66)
	Tetracycline	54 (30–70)	54 (25–66)	48 (27–68)
	Trimethoprim-sulfamethoxazole	2 (0.4–4)	3 (1–6)	3 (1–4)
	Vancomycin	0	0	0
	Teicoplanin	0	0	0
Linezolid	<0.1 (0–0.6)	<0.1 (0–3)	<0.1 (0–1)	
<i>Streptococcus pneumoniae</i>	N of tested isolates	1,007	865	890
	Penicillin G	12 (0–16)	14 (3–18)	11 (0–18)
	Erythromycin	80 (65–87)	81 (68–91)	82 (67–100)
	Fluoroquinolone	9 (0–24)	12 (4–22)	11 (0–24)
<i>Enterococcus faecalis</i>	N of tested isolates	7,799	5,590	4,945
	Ampicillin	1 (0–3)	2 (0–6)	0 (0–6)
	High-level gentamicin*	62 (31–67)	59 (33–67)	61 (52–68)
	High-level streptomycin*	22 (18–35)	19 (13–30)	18 (7–26)
	Ciprofloxacin	36 (18–47)	34 (19–47)	36 (17–64)
	Tetracycline	88 (92–93)	88 (79–92)	89 (83–96)
	Vancomycin	1 (0–8)	1 (0–7)	0.8 (0–16)
	Teicoplanin	0.9 (0–10)	1 (0–7)	0.9 (0–6)
	Linezolid	0.3 (0–2.0)	0.6 (0–2.0)	0.6 (0–2)
<i>Enterococcus faecium</i>	N of tested isolates	5,536	4,539	4,392
	Ampicillin	94 (89–97)	93 (76–99)	93 (82–98)
	High-level gentamicin*	58 (32–74)	59 (42–75)	53 (40–80)
	High-level streptomycin*	34 (16–44)	23 (16–51)	24 (11–34)
	Ciprofloxacin	94 (90–99)	95 (77–99)	95 (84–98)
	Tetracycline	36 (21–54)	31 (23–50)	31 (17–55)
	Vancomycin	29 (12–68)	31 (19–46)	30 (15–49)
	Teicoplanin	23 (9–56)	28 (15–69)	26 (12–45)
	Linezolid	0.2 (0–4.0)	0.0 (0–1.0)	0.0 (0–2.0)
	Quinupristin-dalfopristin	1.0 (0–4.0)	0.6 (0–5.0)	0.6 (0–11.0)

*High level resistance of gentamicin and streptomycin were defined as above the minimum inhibitory concentration (MIC) of 500 and 1,000 µg/mL, respectively.

sistant to levofloxacin. In *Enterococcus faecalis*, ampicillin resistance was low (0–2%); however, 61% and 18% of isolates were resistant to high-level gentamicin (minimum inhibitory concentration [MIC] >500 µg/mL) and high-level streptomycin (MIC

>1,000 µg/mL), respectively. The rates of vancomycin resistance were 0.8–1% in both 2013 and 2015. In contrast, ampicillin resistance was widespread in *E. faecium* (93–94%) and 29–31% of isolates exhibited vancomycin resistance during the test period.

2. Antimicrobial resistance in *Enterobacteriaceae*

The antimicrobial resistance rates of *Enterobacteriaceae* are detailed in Table 2. The resistance rates of *E. coli* isolates were 69–

72% to ampicillin, 29–35% for cefotaxime, 30–31% for ceftazidime, 28–31% for cefepime, and 9–10% for cefoxitin from 2013 to 2015, respectively. The resistance rates to fluoroquinolone in-

Table 2. Antimicrobial resistance rates (%) of *Escherichia coli* and *Klebsiella pneumoniae* in Korea from 2013 to 2015*

Antimicrobial agent	<i>E. coli</i>			<i>K. pneumoniae</i>		
	2013 (26,339)	2014 (18,317)	2015 (16,262)	2013 (10,548)	2014 (7,867)	2015 (6,571)
Ampicillin	70 (66–79)	69 (16–82)	72 (51–79)	NT	NT	NT
Piperacillin	79 (74–84)	69 (67–74)	68 (67–69)	NT	NT	NT
Ampicillin-sulbactam	40 (27–69)	44 (29–53)	45 (13–48)	NT	NT	NT
Piperacillin-tazobactam	6 (4–9)	5 (2–10)	5 (2–9)	22 (10–38)	20 (6–36)	21 (2–36)
Cefotaxime	29 (21–41)	32 (24–44)	35 (23–46)	40 (22–62)	41 (20–57)	38 (25–60)
Ceftazidime	30 (9–42)	31 (13–45)	31 (11–46)	40 (15–62)	41 (18–57)	36 (21–60)
Cefepime	28 (5–42)	30 (6–42)	31 (41)	38 (6–61)	41 (6–57)	33 (11–59)
Aztreonam	30 (13–42)	30 (13–45)	30 (14–47)	39 (17–62)	38 (17–57)	35 (24–60)
Cefoxitin	9 (6–14)	10 (6–13)	9 (6–16)	17 (11–29)	12 (9–26)	14 (10–25)
Imipenem	<0.1 (0–1)	<0.1 (0–1)	<0.1 (0–1)	<0.1 (0–3)	1 (0–10)	1 (0–10)
Meropenem	<0.1 (0–6)	<0.1 (0–2)	<0.1 (0–2)	<0.1 (0–3)	1 (0–11)	1 (0–10)
Amikacin	1 (0–2)	1 (0–2)	1 (0–1)	7 (2–16)	5 (1–31)	5 (1–25)
Gentamicin	29 (25–39)	30 (22–42)	29 (25–36)	19 (11–32)	20 (8–34)	19 (8–32)
Fluoroquinolone	42 (32–59)	45 (32–55)	48 (34–57)	34 (16–55)	35 (16–46)	34 (18–50)
Cotrimoxazole	38 (34–45)	38 (34–40)	39 (34–46)	21 (9–42)	24 (18–73)	30 (23–45)
Tigecycline	NT	NT	NT	5 (1–15)	6 (4–14)	8 (0–22)

*Antimicrobial resistance rates are presented as median (whole range). Abbreviation: NT, not tested.

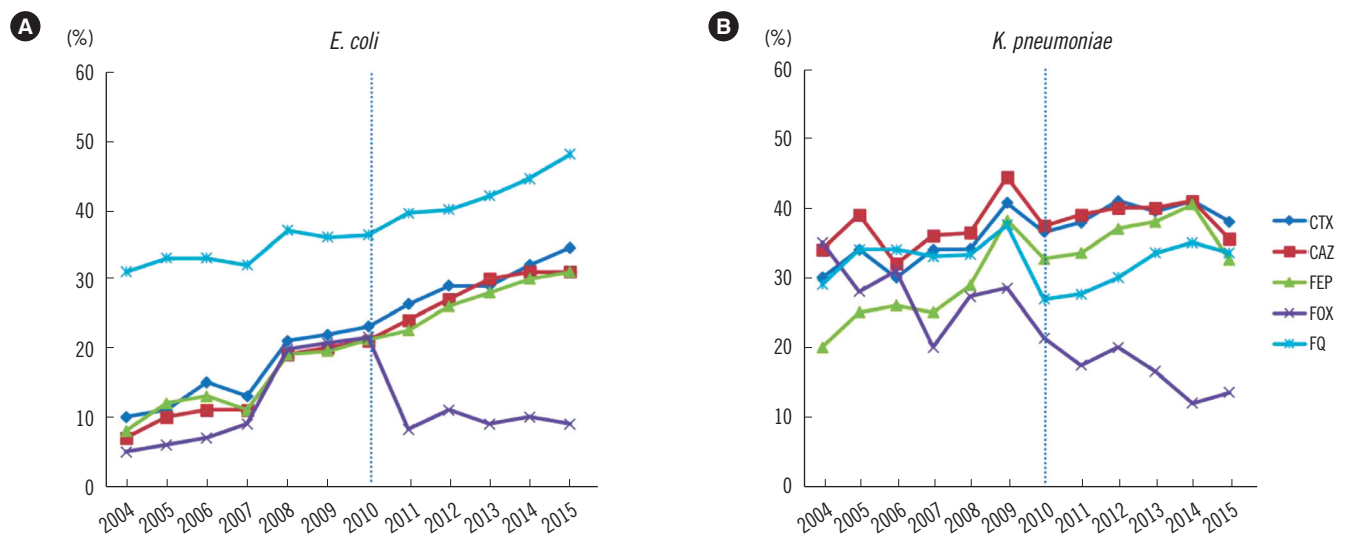


Fig. 1. Antimicrobial resistance rates (%) of *Escherichia coli* and *Klebsiella pneumoniae* from 2004 to 2015. The resistance rates from 2004 to 2012 were from the previous publication of the KARMS [8-10]. The resistance rates of *E. coli* to fluoroquinolone, third- and fourth-generation cephalosporins (CAZ, CTX, FEP) gradually increased since 2004. However, the resistance rates of *E. coli* and *K. pneumoniae* to cephamycin decreased. The vertical dotted lines indicate the application of the lowered cefotaxime and ceftazidime breakpoints according to changes in the CLSI guideline in 2010.

Abbreviations: CAZ, ceftazidime; CTX, cefotaxime; FEP, cefepime; FOX, cefoxitin; FQ, fluoroquinolone.

creased from 42% in 2013 to 48% in 2015, while the resistance rate to trimethoprim-sulfamethoxazole remained stable at 38–39%. In *K. pneumoniae*, the resistance rates to third- and fourth-generation cephalosporins were 36–41% and 33–41%, respectively. The resistance rates were 12–17% for ceftazidime, 34–35% for fluoroquinolone, and 21–30% for trimethoprim-sulfamethoxazole. Over the last decade, the rates of resistance to the third- and fourth-generation cephalosporins and fluoroquinolone have steadily increased, except resistance to ceftazidime, which decreased significantly (Fig. 1). The resistance rate to carbapenems in *E. coli* and *K. pneumoniae* was 0.1% in 2013 and 0.1% and 1%, respectively, in 2015. However, the susceptibility rates in both species decreased from 99.7% and 98.7% in 2013 to 99.3% and 97.0% in 2015, respectively (Fig. 2).

3. Antimicrobial resistance in glucose non-fermenting gram-negative bacilli

The antimicrobial resistance rates of *A. baumannii* and *P. aeruginosa* are shown in Table 3. The resistance rates of *A. baumannii* were 77–86% for extended-spectrum cephalosporins, 77–85% for carbapenems, 84–88% for fluoroquinolone, 45–60% for amikacin, and 73–76% for gentamicin. The resistance rate to ampicillin-sulbactam decreased from 57% in 2013 to 46% in 2015. The resistance rates were 2–5% for tigecycline and less

than 0.1% for colistin. In *P. aeruginosa*, the resistance rates to ceftazidime, cefepime, amikacin, and gentamicin were 19–21%, 18–20%, 12–13%, and 18–20%, respectively. The resistance rate of carbapenem-resistant *P. aeruginosa* from 2013 to 2015

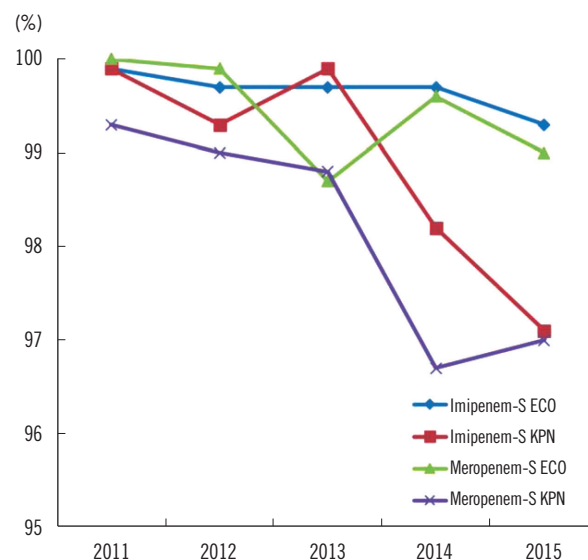


Fig. 2. Carbapenem susceptibility rates of *Escherichia coli* and *Klebsiella pneumoniae* from 2011 to 2015. The resistance rates from 2011 to 2012 were from the previous publication of the KARMS [10]. Abbreviations: ECO, *E. coli*; KPN, *K. pneumoniae*; S, susceptible.

Table 3. Antimicrobial resistance rates (%) of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in Korea from 2013 to 2015*

Antimicrobial agent	<i>A. baumannii</i>			<i>P. aeruginosa</i>		
	2013 (11,117)	2014 (10,288)	2015 (9,345)	2013 (9,703)	2014 (6,919)	2015 (5,259)
Piperacillin	82 (60–100)	87 (66–97)	86 (76–97)	30 (14–49)	26 (14–46)	27 (16–46)
Ampicillin-sulbactam	57 (16–76)	50 (24–91)	46 (16–75)	NT	NT	NT
Piperacillin-tazobactam	81 (56–100)	86 (71–100)	82 (69–96)	29 (2–54)	28 (14–50)	25 (7–45)
Cefotaxime	79 (56–100)	86 (71–97)	84 (65–100)	NT	NT	NT
Ceftazidime	77 (51–93)	84 (55–97)	83 (56–96)	21 (6–39)	21 (8–37)	19 (9–40)
Cefepime	78 (55–93)	85 (70–97)	83 (67–96)	20 (6–34)	20 (7–37)	18 (6–37)
Aztreonam	NT	NT	NT	23 (13–51)	33 (10–68)	23 (13–38)
Imipenem	77 (54–92)	84 (70–96)	85 (73–97)	32 (12–57)	35 (16–50)	35 (15–47)
Meropenem	77 (55–93)	85 (66–96)	84 (67–96)	24 (10–46)	27 (12–40)	25 (15–45)
Amikacin	45 (3–79)	52 (12–83)	60 (8–89)	13 (4–25)	12 (6–59)	13 (6–47)
Gentamicin	73 (42–88)	76 (52–89)	75 (42–90)	19 (7–32)	20 (7–37)	18 (5–37)
Ciprofloxacin	84 (59–96)	88 (74–98)	87 (75–97)	36 (15–53)	30 (20–48)	34 (17–47)
Cotrimoxazole	74 (43–97)	75 (58–88)	64 (52–75)	NT	NT	NT
Tigecycline	5 (0–12)	2 (1–7)	4 (0–7)	NT	NT	NT
Colistin	<0.1 (0–2)	<0.1 (0–1)	<0.1 (0–1)	1 (0–5)	1 (0–9)	<0.1 (0–3)

*Antimicrobial resistance rates are presented as median (whole range). Abbreviation: NT, not tested.

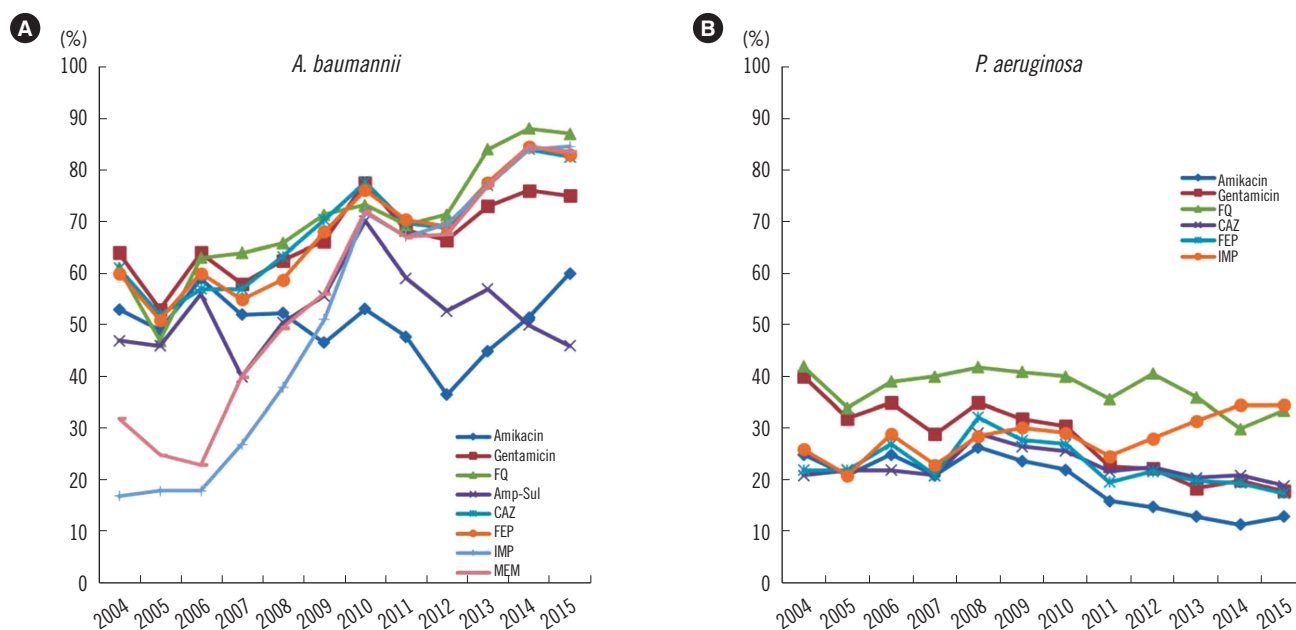


Fig. 3. Antimicrobial resistance rates (%) of *Acinetobacter baumannii* and *Pseudomonas aeruginosa* from 2004 to 2015. The resistance rates from 2004 to 2012 were from the previous publication of the KARMS [8–10]. Abbreviations: CAZ, ceftazidime; FEP, cefepime; FQ, fluoroquinolone; IMP, imipenem; MEM, meropenem; Amp-Sul, ampicillin-sulbactam.

was 32–35% for imipenem and 24–27% for meropenem (Fig. 3). The resistance rates of *A. baumannii* showed a steady increase, except for ampicillin-sulbactam, while the resistance rates of *P. aeruginosa* exhibited a decrease, except for imipenem.

DISCUSSION

The prevalence of antimicrobial-resistant organisms varies greatly among hospitals and countries. Moreover, changes in resistance rates differ greatly depending on time and region. For example, Scandinavian countries, such as Sweden, show low MRSA levels (<1%) [11]. However, the rates of MRSA in other European countries, Japan, and Korea are as high as 40–60% [4, 12]. Therefore, national surveillance systems are becoming more important for guiding clinicians in terms of empirical treatment for suspected infections and the control of antimicrobial resistance dissemination. KARMS data allowed us to analyze national trends of antimicrobial resistance and detect the emergence of new resistances in Korea.

MRSA is the one of the most important resistant pathogens; we found that the rate of MRSA slightly decreased from a peak of 75% in 2009 to 66% (55% in blood isolates, data not shown) in 2015 [4]. The prevalence of MRSA infection could be affected by carriage rate and healthcare-associated infection control; in addition, this decrease might be due to the introduction of the

decolonization and hand-hygiene program (the most common transmission route of MRSA [13]) for controlling infection in health-care-associated settings in Korea [14]. Vancomycin and teicoplanin are drugs commonly used for MRSA treatment; however, none of the *S. aureus* isolates showed vancomycin resistance between 2013 and 2015 and most isolates exhibited susceptibility to linezolid.

In *S. pneumoniae*, the resistance rate to penicillin G ranged from 11% to 14% during 2014 and 2015, which is similar to previous results following the application of a new breakpoint [15]. However, the resistance rate to erythromycin remained high (>80%) in 2015. A recent survey of the empirical treatment of community-acquired pneumonia in Korea reported that 13.4% of local clinic doctors still prescribe macrolide monotherapy [16]; increased resistance to erythromycin could be the result of treatment failure due to this regimen. The resistance rate to fluoroquinolone was as low as 9–12%; however, this did represent an increase from the 2–5% reported in 2005 and 2006 [17]. Previous use of fluoroquinolones, cerebrovascular disease, and healthcare-associated infection have been significantly associated with levofloxacin resistance in *S. pneumoniae* [18]; thus, antimicrobial stewardship and an infection control program are required to prevent the spread of fluoroquinolone-resistance.

Resistance rates varied among *Enterococcus* species. In *E. faecalis*, the resistance rates were extremely low, 0–2% to ampi-

cillin and 1% to vancomycin, which is consistent with previous results since 2004 [8-10]. *E. faecium* showed a high prevalence of ampicillin resistance (> 90%) and the resistance rates to vancomycin and teicoplanin were 30% and 26%, respectively. The similarity in the resistance rates to teicoplanin and vancomycin might indicate that most isolates contain *vanA* gene clusters; the small discrepancy could be related to the presence of the *vanA* gene with a VanB phenotype [19]. The resistance rates of *E. faecium* to linezolid and quinupristin/dalfopristin did not increase during the surveillance period. The linezolid susceptibility of most isolates can be explained by the fact that the most common mechanism of linezolid resistance is a mutation in the linezolid binding site, which cannot be spread by horizontal transfer, in contrast to the acquisition of the *cfz* gene. Persistent daptomycin susceptibility (data not shown) might be caused by the unavailability of this antimicrobial agent in Korea. Indeed, increased minimal inhibitory concentrations of daptomycin have been associated with treatment failure in other countries [20].

Resistance to third- and fourth-generation cephalosporins in *E. coli* has increased since 2004 (Fig. 1). The resistance rate to cefotaxime was slightly higher than that to ceftazidime, which is consistent with a previous report on the dissemination of CTX-M type extended spectrum β -lactamase (ESBL) rather than TEM- or SHV- type ESBL [21]. As fluoroquinolone-resistant *E. coli* also increased to 48%, the empirical use of fluoroquinolone for urinary tract infections caused primarily by *E. coli* should be avoided, as previously reported [22]. The reason underlying the continual increase in fluoroquinolone resistance is unclear; it might be related to mutation of the *gyrA* or topoisomerase IV genes including *qyrA*, *gyrB*, *parC* and *parE* [23]. Moreover, the spread of plasmid-mediated fluoroquinolone-resistance, such as the *qnr* gene, should also be considered [24]. Further evaluations are required to determine the mode of resistance. Interestingly, only the resistance rate to cefoxitin decreased to 9%. This finding might indicate the reduced prevalence of plasmid-mediated AmpC β -lactamase genes, such as *DHA-1* and *CMY-1* [25], due to lowered selective pressure for cephamycin. In *K. pneumoniae*, the resistance rates to most antimicrobial agents, including third- and fourth-generation cephalosporins and fluoroquinolone, remained similar to previous results, except for decreased resistance to cefoxitin. The rates in CRE remained at <1% in 2015; however, the susceptibility rates to carbapenem (especially meropenem) in *Enterobacteriaceae*, including *E. coli* and *K. pneumoniae*, decreased from 100% and 99.3 in 2011 to 99.0% and 97.0% in 2015, respectively. Furthermore, carbapenem non-susceptible *E. coli* were reported in 75.0% of hospitals in 2015,

which was higher than in 2013 (43.8%), and carbapenem non-susceptible *K. pneumoniae* were reported in all participating hospitals from 2013 to 2015. Therefore, appropriate surveillance using rapid detection and infection control strategies for CRE should be mandated to prevent the spread of CRE, especially carbapenemase-producing organisms. Furthermore, molecular genetic studies of multidrug-resistant *Enterobacteriaceae* should be conducted to elucidate the mechanisms of resistance and dissemination.

P. aeruginosa and *A. baumannii* are important pathogens in healthcare-associated infections. The emergence of multidrug-resistant *P. aeruginosa* and multidrug-resistant *A. baumannii* is a major concern in Korea, because few drugs, except for polymyxins, are available for the treatment of these infections. The incidence of carbapenem-resistant *P. aeruginosa* was 35% in 2015, higher than the rate reported by Lee *et al* in 2009 (23%) [4]. Surprisingly, the resistance rates of *P. aeruginosa* to third- and fourth-generation cephalosporins, amikacin, and gentamicin decreased significantly with the increased resistance rate to carbapenem, similar to observations in France from the last 4 years; however, the mechanism underlying this phenomenon remains unclear [11]. Another remarkable change in *P. aeruginosa* carbapenem resistance is the emergence of ST235 bearing the IMP-6 metallo- β -lactamase since the early 2010s. Although the reason for the transition from the VIM-2 to IMP-6 phenotype is not clear [26, 27], the increased use of meropenem may be associated with the dissemination of IMP-6, because IMP-6 can hydrolyze meropenem more efficiently than VIM-2 [28]. In addition, the rate of carbapenem-resistant *A. baumannii* gradually increased to >80%. This finding can be explained by the horizontal spread of *A. baumannii* carrying the *bla*_{OXA-23}-like gene, which is the most common type of carbapenem resistance in Korea [29]. In contrast, the resistance rate to ampicillin-sulbactam decreased to 46% in 2015. Therefore, ampicillin-sulbactam could constitute a treatment option for MRAB in combination with colistin [30]. The resistance rate of *A. baumannii* to tigecycline remained at <5% in 2015, when the breakpoint for *Enterobacteriaceae* was applied. However, several studies have demonstrated the inefficacy of tigecycline for the treatment of MRAB because of rapid distribution to the tissue, which results in increased all-cause mortality [31].

In conclusion, we analyzed KARMS data from 16 hospitals from 2013 to 2015 with respect to antimicrobial resistance trends. The resistance rate of *E. coli* to third- and fourth-generation cephalosporins and fluoroquinolone increased significantly and carbapenem-non-susceptible *Enterobacteriaceae* are becoming a

more common clinical isolate. The prevalence of carbapenem-resistant *P. aeruginosa* and *A. baumannii* increased significantly, leaving few remaining treatment options for these infections. Furthermore, nationwide antimicrobial susceptibility surveillance should be improved in order to standardize the quality of data and meet global needs.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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