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Changing Epidemiology of Pathogenic Bacteria Over the Past 20 Years in Korea

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ABSTRACT

Background: The epidemiology of pathogenic bacteria varies according to the socioeconomic status and antimicrobial resistance status. However, longitudinal epidemiological studies to evaluate the changes in species distribution and antimicrobial susceptibility of pathogenic bacteria nationwide are lacking. We retrospectively investigated the nationwide trends in species distribution and antimicrobial susceptibility of pathogenic bacteria over the last 20 years in Korea.

Methods: From 1997 to 2016, annual cumulative antimicrobial susceptibility and species distribution data were collected from 12 university hospitals in five provinces and four metropolitan cities in South Korea.

Results: The prevalence of *Staphylococcus aureus* was the highest (13.1%) until 2012 but decreased to 10.3% in 2016, consistent with the decrease in oxacillin resistance from 76.1% in 2008 to 62.5% in 2016. While the cefotaxime resistance of *Escherichia coli* increased from 9.0% in 1997 to 34.2% in 2016, *E. coli* became the most common species since 2013, accounting for 14.5% of all isolates in 2016. *Pseudomonas aeruginosa* and *Acinetobacter baumannii* rose to third and fifth places in 2008 and 2010, respectively, while imipenem resistance

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

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increased from 13.9% to 30.8% and 0.7% to 73.5% during the study period, respectively. *Streptococcus agalactiae* became the most common pathogenic streptococcal species in 2016, as the prevalence of *Streptococcus pneumoniae* decreased since 2010. During the same period, pneumococcal penicillin susceptibility decreased to 79.0%, and levofloxacin susceptibility of *S. agalactiae* decreased to 77.1% in 2016.

Conclusion: The epidemiology of pathogenic bacteria has changed significantly over the past 20 years according to trends in antimicrobial resistance in Korea. Efforts to confine antimicrobial resistance would change the epidemiology of pathogenic bacteria and, consequently, the diagnosis and treatment of infectious diseases.

Keywords: Epidemiology; Bacteria; Korea; Antimicrobial Resistance; MRSA; *Streptococcus agalactiae*

INTRODUCTION

The epidemiology of infectious diseases is influenced by many factors, such as the socioeconomic status, population composition, and healthcare practices, including antimicrobial usage.¹⁻³ Because many industrialized countries, including Korea, have experienced rapidly changing societal and medical circumstances, a change in the epidemiology of infectious diseases is presumed, and nationwide data are needed.

The emergence and transmission of antimicrobial-resistant bacteria have been one of the most significant medical issues in recent decades. From the worldwide spread of methicillin-resistant *Staphylococcus aureus* (MRSA)³ to the emergence of antimicrobial resistance, such as carbapenemase-producing *Enterobacteriales*,⁴ monitoring of antimicrobial resistance based on the epidemiology of pathogens has become a national public health issue designated by the World Health Organization.⁵

Since South Korea joined the Organisation for Economic Co-operation and Development in October 1996, its gross domestic product has tripled over 20 years. The age-standardized mortality rate from infectious diseases decreased from 43.5/100,000 in 1983 to 16.5/100,000 in 1996; however, it rose again to 44.6/100,000 in 2015.⁶ Despite the extreme decline in the incidence of tuberculosis and intestinal infections, an increase in the number of senior citizens aged 65 years and over has increased mortality in the last two decades. During the same period, the emergence of various multidrug-resistant pathogenic bacteria has threatened public health.⁵ Longitudinal epidemiological studies to understand the changes in species distribution and antimicrobial susceptibility of pathogenic bacteria nationwide are lacking. Thus, the aim of this study was to collect and retrospectively analyze data over 20 years from clinical microbiology laboratories of 12 university hospitals in South Korea.

METHODS

Participating laboratories

For this study, 12 clinical microbiology laboratories were recruited from 10 tertiary care hospitals and two secondary care hospitals so that each South Korean region could be evenly covered.

Microbiologic data

From 1997 to 2016, data on the number of isolates and patients and antimicrobial susceptibility for 11 species, including *S. aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterococcus faecium*, *Enterococcus faecalis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Haemophilus influenzae* were collected annually from the laboratory information system. All susceptibility data were analyzed except those for the surveillance isolates. Susceptibility data were interpreted based on Clinical and Laboratory Standards Institute M100-S27 using WHONET software.⁷ Susceptibility data were analyzed for the first isolate per patient when there were more than 30 patients per species in one laboratory. The susceptibility of *S. pneumoniae* to penicillin and cefotaxime was analyzed by dividing the cases according to meningitis or non-meningitis criteria.

Statistical analysis

For trend analysis, the ratios of the number of isolates of *E. coli* to *S. aureus* (E/S ratio) and *A. baumannii* to *P. aeruginosa* (A/P ratio), % cefotaxime-resistant *E. coli* to % oxacillin-resistant *S. aureus* (CREC/MRSA ratio), and % imipenem-resistant *A. baumannii* to % imipenem-resistant *P. aeruginosa* (IRAB/IRPA ratio) were compared annually. The correlation analysis between the ratios was performed using Spearman's rank correlation coefficient (ρ) using Statistical Package for the Social Sciences (ver. 18.0; SPSS, Chicago, IL, USA).

RESULTS

Data collection in participating laboratories

As the number of participating laboratories increased from 2 in 1997 to 12 in 2010, the data collection period varied from 7 to 20 years (**Supplementary Table 1**). The annual number of isolates was 42,800 in 1997 and 290,500 in 2010. In 2016, the number of isolates increased to 324,700. A total of 3,733,938 isolates were analyzed for each species or genus during the study period.

Trends of species distribution

S. aureus was the most common species in 1997–2012 and the second most common in 2013–2016 (**Fig. 1A**). The number of *S. aureus* isolates was 38,000 in 2012 and then decreased to 33,000 in 2016. The frequency of *E. faecium* increased in rank from 18th in 1997 to 6th in 2016, whereas the frequency of *E. faecalis* increased more slowly than that of *E. faecium*.

E. coli was the second most common species in 2001–2012 and the most common species in 2013–2016 (**Fig. 1A**). The number of *K. pneumoniae* continued to increase to exceed the number of *P. aeruginosa* isolates in 2012 and has been the third most common species since 2013. The frequency of *P. aeruginosa* increased in the early decade, whereas that of *A. baumannii* rapidly increased from 2005 to 2010.

The number of *S. pneumoniae* isolates did not change since 2002, and the frequency rank decreased from 11th in 2002 to 18th in 2016 (**Fig. 1A**). The number of *S. agalactiae* isolates continued to increase to twice that of *S. pneumoniae* isolates in 2016. *H. influenzae* was ranked 25th during the study period.

The species distribution in blood isolates showed slightly different trends compared with the total species distribution. *E. coli* was the most common species isolated from blood

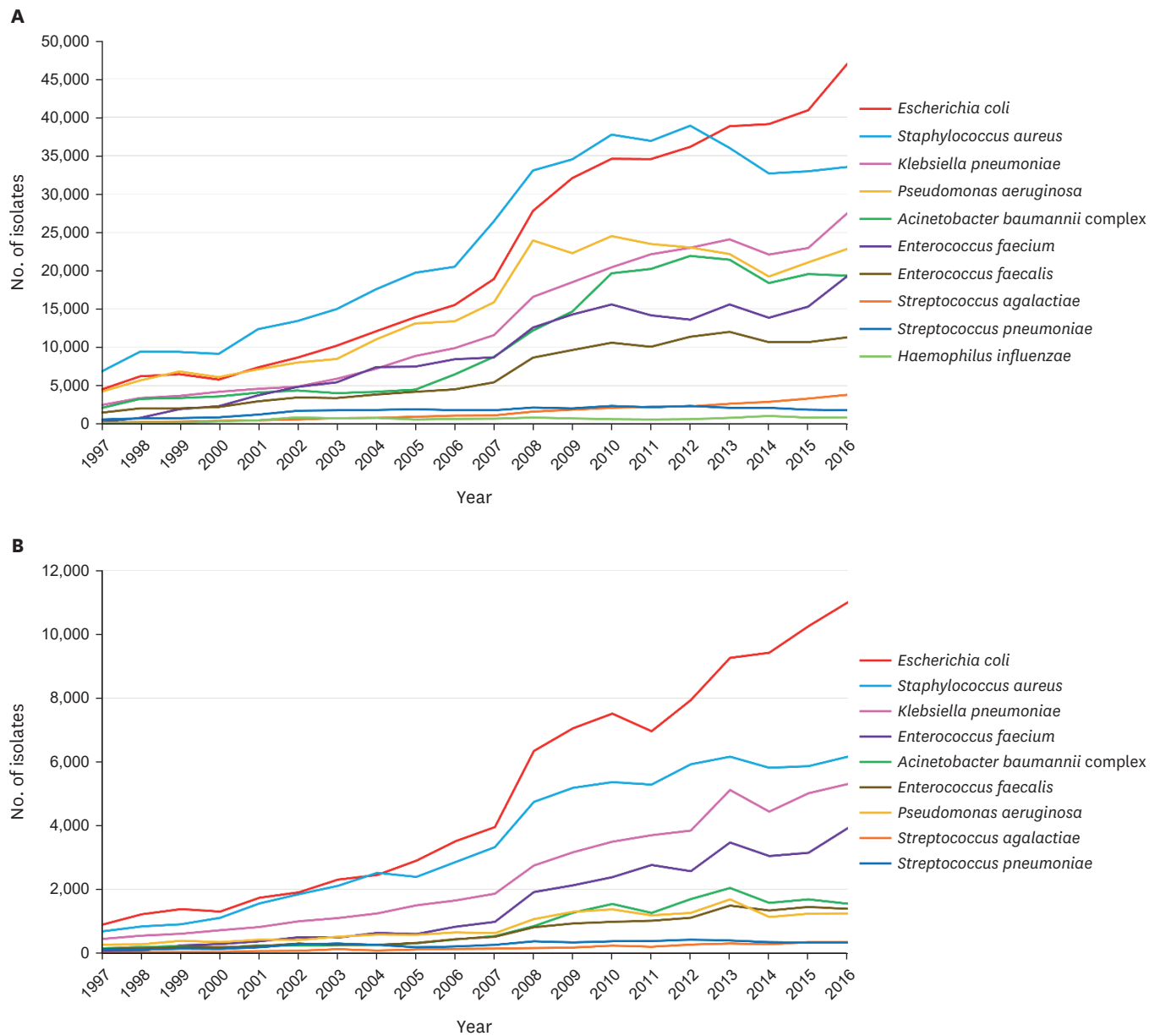


Fig. 1. Trend of species distribution of major pathogenic bacteria in (A) total isolates and (B) blood isolates for 20 years from 1997 to 2016.

during the entire study period, except in 2004, when *S. aureus* ranked first (Fig. 1B). While the frequencies of *P. aeruginosa* and *A. baumannii* showed a gradual increase among blood isolates during the entire study period. *E. faecium* was isolated more frequently than both *P. aeruginosa* and *A. baumannii* since 2004 and the frequency of *E. faecium* markedly increased to become greater than frequencies of the two combined in 2016.

Cumulative antimicrobial susceptibility

S. aureus and *Enterococcus* species

The susceptibility of *S. aureus* to ciprofloxacin, clindamycin, erythromycin, gentamicin, and penicillin increased in parallel with oxacillin susceptibility during the last decade (Table 1). Trimethoprim/sulfamethoxazole susceptibility was the lowest at 78.0% in 2003 but rebounded

Table 1. Antimicrobial susceptibility of *Staphylococcus aureus* and *Enterococcus* species

Organism/Antimicrobial agents	% Susceptibility in each year																				
	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	
<i>S. aureus</i> , No. tested	39	50	52	49	66	71	78	82	93	109	142	170	173	167	187	169	164	164	165	180	
Ciprofloxacin	34.7	38.4	40.6	40.7	31.0	37.4	38.7	39.5	39.4	39.9	36.4	37.8	37.9	38.0	36.2	41.5	45.9	45.4	47.9	51.9	
Clindamycin	33.7	39.0	39.0	44.8	36.6	37.3	37.3	42.6	41.9	42.0	36.8	39.2	40.2	36.1	36.3	37.4	41.5	42.1	45.8	54.0	
Erythromycin	24.2	27.7	29.2	30.4	22.2	27.3	29.2	29.0	28.9	30.1	27.1	28.8	30.3	30.9	32.6	34.1	37.4	37.9	40.2	44.7	
Gentamicin	38.1	39.4	39.4	39.5	33.8	38.5	38.0	39.4	42.8	45.2	47.4	47.8	48.5	46.1	48.1	45.6	49.4	48.3	50.9	57.7	
Oxacillin	30.6	34.4	37.3	34.4	27.2	33.2	33.4	31.1	28.7	28.4	24.2	23.9	25.7	26.9	28.5	28.5	32.1	31.8	33.0	37.5	
Penicillin	2.7	2.7	2.8	2.6	1.7	2.9	3.2	3.6	3.8	3.7	3.2	3.2	3.6	3.3	3.7	7.5	7.4	4.9	4.6	6.5	
Trimethoprim/Sulfamethoxazole	98.1	97.8	96.3	91.4	85.3	80.9	78.0	83.7	87.7	89.9	90.7	92.9	96.1	96.7	98.1	98.0	98.0	97.8	97.9	98.2	
<i>Enterococcus faecium</i> , No. tested	6	12	13	13	20	20	22	27	32	35	39	55	56	52	58	48	54	55	60	66	
Ampicillin	35.8	22.0	11.4	6.4	12.6	12.2	12.8	8.4	8.0	8.6	7.5	7.5	7.6	9.0	8.6	8.4	9.0	8.8	10.3	8.9	
Gentamicin, high level	24.4	15.6	13.7	18.0	21.7	21.4	24.2	20.8	22.4	16.8	25.3	27.8	27.8	32.9	36.9	41.5	47.1	46.1	48.1	59.7	
Streptomycin, high level					50.0	50.0	45.1	59.0	55.6	68.8	65.7	71.9	79.3	72.0	71.8	69.9	73.8	74.8	78.7	85.5	
Teicoplanin					92.7	68.4	68.9	69.5	73.8	70.2	71.0	64.6	65.8	74.4	70.8	72.2	71.4	73.5	74.5	70.9	71.0
Tetracycline	56.0	67.2	72.2	78.5	80.9	84.8	87.4	86.8	84.5	85.4	82.0	78.2	73.3	70.0	66.0	68.4	69.2	71.3	76.3	76.3	
Vancomycin	92.2	85.6	72.1	69.4	71.6	73.3	72.1	68.9	60.6	55.8	68.4	65.6	68.5	67.6	68.8	65.8	65.8	59.5	59.6	59.0	
<i>Enterococcus faecalis</i> , No. tested	11	16	16	17	22	21	22	24	28	32	38	61	68	68	70	72	78	72	72	71	
Ampicillin	94.3	95.9	95.4	96.2	89.7	95.5	96.8	98.3	97.3	98.4	98.7	98.8	96.1	91.6	92.4	89.6	90.1	91.1	91.8	97.2	
Gentamicin, high level	41.5	29.8	36.1	39.6	38.0	48.7	51.2	45.7	50.0	44.6	45.1	45.1	45.1	44.4	44.7	43.1	44.9	44.8	43.8	44.7	
Streptomycin, high level					65.2	75.2	70.1	73.1	73.4	70.7	70.6	71.9	73.2	74.2	73.6	75.0	78.3	81.5	83.8	86.2	
Teicoplanin					99.8	99.0	87.9	89.6	97.7	98.3	99.3	99.4	99.5	99.4	99.0	99.0	97.5	99.3	99.2	99.5	
Tetracycline	17.0	20.9	24.0	19.9	21.9	21.0	24.1	23.6	23.8	21.0	19.2	16.7	15.6	15.7	14.4	13.5	14.1	13.9	15.1	16.4	
Vancomycin	98.6	94.1	99.1	98.9	89.0	88.9	97.4	98.2	98.6	98.1	99.0	99.0	98.7	99.2	99.0	98.8	98.7	99.3	99.0	99.5	

No. tested = the number of tested isolates ($\times 100$).

to 98.2% in 2016. Among *E. faecium* isolates, vancomycin susceptibility decreased from 92.2% in 1998 to 59.0% in 2016, and susceptibility to both high-level gentamicin and high-level streptomycin significantly increased during the same period. The proportion of vancomycin-resistant *E. faecalis* was consistently low at less than 2%, except in 2000 and 2001, but susceptibility to high-dose streptomycin increased from 65.2% in 2001 to 86.2% in 2016.

Streptococcus species and H. influenzae

Among *S. pneumoniae* isolates, penicillin susceptibility decreased from 93.2% in 2009 to 79.0% in 2016, and cefotaxime, erythromycin, levofloxacin, and clindamycin susceptibility also decreased (Table 2). However, *S. pyogenes* was consistently susceptible to penicillin, and susceptibility to erythromycin and clindamycin recovered during the late decade from 87.6% and 92.2% in 2008 to 91.0% and 94.1% in 2016, respectively. The susceptibility of *S. agalactiae* to levofloxacin decreased from 98.5% in 2001 to 77.1% in 2016. The susceptibility of *H. influenzae* to amoxicillin/clavulanic acid and cefuroxime decreased from 98.1% and 95.6% in 2006 to 58.1% and 46.8% in 2016, respectively.

Enterobacteriales and nonfermenting gram-negative bacilli

Although cefotaxime and ciprofloxacin susceptibility significantly decreased in both *E. coli* and *K. pneumoniae* during the study period, this trend was more pronounced in *K. pneumoniae* in the early decade and *E. coli* in the late decade (Table 3). The susceptibility of *P. aeruginosa* to imipenem and ceftazidime decreased markedly during the first decade and remained in the range of 60–70% in the second decade, whereas the susceptibility of *A. baumannii* to imipenem and ampicillin/sulbactam markedly decreased. Susceptibility of *A. baumannii* to imipenem decreased from 98.6% in 1997 to 19.5% in 2016, and susceptibility to ampicillin/sulbactam decreased from 54.6% in 2008 to 20.4% in 2016. In contrast, gentamicin susceptibility continuously increased from 35.0% in 1997 to 69.8% in 2016 in *P. aeruginosa*, whereas it showed no significant change at approximately 30% in *A. baumannii*.

Correlation between species distribution and antimicrobial resistance

The E/S ratio was below 0.69 until 2001 and then increased to 1.4 in 2016 (Fig. 2A). The CREC/MRSA ratio was below 0.2 until 2001 and then increased to 0.55 in 2016. The E/S and CREC/MRSA ratios were strongly correlated ($\rho = 0.947$). The A/P ratio was within the range of 0.49 to 0.59 until 2000, gradually decreased to 0.34 in 2005, and then increased rapidly to 0.97 in 2013 (Fig. 2B). The A/P and IRAB/IRPA ratios were moderately correlated ($\rho = 0.698$). The E/S and A/P ratios from the blood isolates also showed moderate correlation with the CREC/MRSA and IRAB/IRPA ratios, as shown in the total isolates ($\rho = 0.740$ and 0.777 , respectively) (Fig. 2).

DISCUSSION

We investigated the changes in species distribution and antimicrobial susceptibility of major pathogenic bacteria over the past 20 years in South Korea. Among the epidemiological changes during the study period, the most prominent finding was that the frequency of *S. aureus* and MRSA decreased over the last 10 years. The MRSA surveillance program in the United States also reported a decrease in the incidence of invasive MRSA infections between 2009 and 2016.⁸ MRSA is one of the most important targets for infection control, and various interventions, including national surveillance, have been implemented. The prevalence of MRSA bloodstream infections (BSI) increased between 2005 and 2008 and decreased till 2013–2016 among hospital-onset and community-acquired BSI in a 20-year global study of

Table 2. Antimicrobial susceptibility of *Streptococcus* species and *Haemophilus influenzae*

Organism/Antimicrobial agents	% Susceptibility in each year																			
	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16
<i>Streptococcus pneumoniae</i> , No. tested	203	307	295	308	867	839	1,342	1,231	1,398	1,350	1,028	1,603	1,541	1,578	1,540	1,664	1,433	1,524	1,490	1,305
Cefotaxime (non-meningitis)						89.5	88.2	94.8	94.6	93.1	86.4	93.4	92.8	85.2	83.2	79.6	79.5	81.7	79.4	77.8
Cefotaxime (meningitis)	42.9					52.3	36.6	57.0	51.8	44.1	50.4	47.0	56.5	47.6	43.2	48.2	51.4	50.5	53.0	45.3
Clindamycin	24.7	20.8	18.6	14.9	20.1	27.8	26.7	26.8	24.2	25.0	28.1	22.9	22.8	18.4	18.6	18.4	19.6	17.1	16.5	13.7
Erythromycin				98.4	97.1	97.4	95.5	97.0	97.8	92.5	95.6	95.9	93.6	94.3	93.5	91.5	91.2	88.4	90.4	92.0
Levofloxacin	71.6	90.0	94.3	93.4	89.4	88.8	90.4	86.6	84.8	67.4	54.7	91.0	93.2	90.3	87.9	77.6	79.6	82.5	81.8	79.0
Penicillin (non-meningitis)	34.8	23.8	23.8	26.0	30.3	33.6	30.7	32.3	28.8	28.1	31.5	25.7	24.0	18.9	20.1	18.9	16.9	14.9	21.2	17.6
Penicillin (meningitis)	21.8	15.9	18.8	16.9	17.3	22.4	22.0	22.2	23.1	20.4	24.0	25.5	24.4	20.3	22.7	22.7	23.6	22.8	21.3	20.2
Tetracycline	31.8	37.2	32.6	20.0	32.4	42.5	36.3	38.6	35.6	33.2	36.8	34.1	30.0	31.3	42.2	36.7	40.3	45.5	46.0	46.3
Trimethoprim/Sulfamethoxazole																				
<i>Streptococcus pyogenes</i> , No. tested	59	83	36	125	204	182	244	206	213	442	234	193	159	104	220	127	159	170	188	321
Clindamycin	94.9	75.9	83.3	84.8	83.3	82.4	91.4	94.6	89.7	68.6	84.9	92.2	88.7	94.2	95.0	91.3	92.4	90.0	89.4	94.1
Erythromycin	94.9	94.0	77.8	72.0	74.0	76.9	88.5	88.3	85.0	71.3	77.4	87.6	84.3	90.4	90.5	92.0	87.4	88.2	88.3	91.0
Levofloxacin					100	95.8	100	99.3	96.4	100	92.3	98.2	94.3	97.7	97.3	93.5	93.0	91.0	92.3	95.0
Penicillin	94.9	98.8	97.2	98.4	99.5	98.4	99.2	98.1	99.1	99.3	98.1	97.7	94.6	94.8	97.1	96.0	97.5	98.8	98.9	99.4
Tetracycline	71.8			66.1							61.1		92.6	86.0	94.7	85.7	86.7	84.4	84.1	87.4
<i>Streptococcus agalactiae</i> , No. tested	139	174	240	338	358	460	567	616	676	822	970	925	978	1,097	1,184	1,241	1,355	1,569	1,829	2,236
Cefotaxime						78.9	96.9	90.6		94.5	67.6	93.0	90.1	98.3	99.3	98.6	99.3	99.6	99.8	99.2
Clindamycin	61.9	55.7	56.7	50.7	55.8	44.7	47.8	48.1	48.1	50.9	53.1	55.6	60.6	62.8	69.7	67.7	73.1	72.9	72.4	73.1
Erythromycin	62.6	67.8	76.7	66.9	62.8	57.2	56.3	58.9	57.2	60.9	64.0	64.9	69.1	66.6	72.3	68.7	71.7	70.0	69.6	68.8
Levofloxacin					98.5	100	97.1	98.0	96.4	97.5	93.7	94.1	88.4	87.5	85.3	80.7	76.9	74.4	77.1	77.1
Meropenem													99.1	99.7	99.5	99.6	99.6	99.7	100	99.9
Penicillin	74.1	85.6	84.6	87.4	98.8	97.2	97.9	95.3	96.8	98.0	92.6	97.0	93.7	98.3	98.6	98.8	99.0	99.2	96.9	99.4
Tetracycline	1.2			7.4		9.3	9.7	8.8	11.1	15.3	27.6	20.3	30.1	31.7	28.9	36.3	46.0	49.9	53.4	56.0
<i>Haemophilus influenzae</i> , No. tested	124	141	141	303	329	653	472	534	431	515	515	571	518	465	436	489	613	838	649	689
Amoxicillin/Clavulanic acid	69.4	88.6	90.4	93.8	90.9	90.0	95.2	94.6	98.1	89.0	91.6	85.7	88.6	82.7	86.1	77.6	65.5	61.4	58.1	58.1
Ampicillin	37.4	30.5	30.5	35.0	38.6	47.8	46.6	49.4	46.4	51.7	58.0	51.8	52.3	54.2	47.0	43.8	39.5	35.6	38.4	31.9
Azithromycin					100	99.8	99.6	99.6	100	100	99.7	99.7	99.7	99.7	99.6	99.6	99.6	97.5	98.1	96.5
Ceftriaxone					100	99.3	100	99.2	99.7	97.7	97.8	96.8	92.0	93.2	89.2	95.0	92.0	88.8	80.3	87.4
Cefuroxime	85.7	83.7	96.7	96.7	99.3	99.1	96.3	98.1	94.6	95.6	89.3	88.9	85.3	84.7	83.3	75.5	65.6	53.4	49.4	46.8
Trimethoprim/Sulfamethoxazole	46.0	54.0	51.7	45.9	54.0	60.9	61.2	62.4	55.3	60.2	59.5	60.7	63.3	55.7	50.6	54.6	50.3	51.2	45.1	45.1

No. tested = the number of tested isolates.

Table 3. Antimicrobial susceptibility of Enterobacteriales and nonfermenting gram-negative bacilli

Organism/Antimicrobial agents	% Susceptibility in each year																			
	97	98	99	00	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16
<i>Escherichia coli</i> , No. tested	32	43	42	35	43	50	62	67	78	88	107	158	181	187	184	213	211	229	237	260
Ampicillin	20.1	24.4	22.9	26.2	27.9	29.1	31.6	31.6	31.1	30.0	29.9	28.5	29.9	29.4	30.5	29.2	30.5	29.4	30.1	28.7
Cefotaxime	83.9	82.7	85.5	89.1	89.9	86.5	85.4	85.4	85.6	84.2	81.7	78.8	78.9	77.8	76.6	73.3	71.6	70.2	67.1	64.8
Ciprofloxacin	79.1	76.0	75.6	75.2	70.1	66.9	66.3	66.9	64.7	64.4	63.4	61.7	61.0	58.4	57.9	56.6	56.0	55.5	54.0	53.7
Gentamicin	66.0	65.7	67.6	72.4	73.2	72.0	72.3	72.0	73.7	72.5	70.6	70.7	71.1	70.9	71.6	71.6	72.9	71.8	71.6	71.0
Imipenem	99.9	99.9	99.6	99.6	100	99.7	99.8	99.9	99.7	99.9	99.9	99.9	99.9	99.8	99.9	99.9	99.8	99.9	99.9	99.9
Tetracycline									50.1	47.1	49.4	47.4	49.4	53.1	54.3	53.4	56.6	57.4	58.8	56.8
Trimethoprim/Sulfamethoxazole	43.3	45.4	46.5	50.0	53.7	56.0	59.7	61.1	61.1	62.1	62.7	60.2	62.0	60.4	60.7	61.1	62.6	62.7	63.0	62.1
<i>Klebsiella pneumoniae</i> , No. tested	14	20	22	23	25	28	31	39	46	56	66	92	100	102	119	116	123	115	116	130
Cefotaxime	71.3	71.0	70.5	61.1	72.5	73.7	70.0	58.3	60.8	63.2	64.8	68.2	64.4	65.8	61.6	62.0	62.1	63.7	63.7	63.0
Ciprofloxacin	92.8	91.2	86.2	77.5	79.2	82.3	79.7	66.8	67.0	63.9	69.0	69.2	65.7	66.1	65.6	66.3	65.5	66.7	65.8	65.3
Gentamicin	78.2	76.5	73.6	69.7	81.0	80.5	83.8	72.9	70.8	71.0	74.2	77.6	76.2	78.1	77.2	80.2	80.4	80.8	81.3	83.5
Imipenem	99.9	99.9	99.6	99.7	99.8	99.7	99.8	99.5	99.6	99.2	99.3	99.4	99.1	99.1	99.1	99.2	99.2	99.0	98.4	98.1
Tetracycline									69.4	70.0	70.1	72.2	71.6	77.5	73.5	73.9	68.6	67.6	67.2	69.5
Trimethoprim/Sulfamethoxazole	78.7	75.6	68.8	72.2	80.4	76.2	73.0	64.0	67.8	69.0	73.7	75.0	72.7	74.3	70.8	73.0	70.8	72.2	70.1	69.2
<i>Pseudomonas aeruginosa</i> , No. tested	29	35	39	31	34	41	39	43	53	65	82	103	101	96	99	91	95	90	93	96
Cefepime					66.7	69.1	67.8	63.5	62.7	59.9	56.0	58.9	61.7	65.1	72.3	67.3	67.1	68.7	67.5	68.3
Ceftazidime	78.2	75.4	71.1	68.1	72.3	77.2	78.5	73.2	72.7	68.0	62.2	65.0	68.3	68.2	72.2	69.4	66.8	69.5	69.8	69.2
Ciprofloxacin	50.5	57.0	58.0	53.6	57.3	62.1	61.6	61.5	61.9	54.8	59.2	61.1	58.6	60.8	64.2	58.5	61.4	62.2	61.1	61.9
Gentamicin	35.0	42.7	45.8	44.3	50.2	55.5	58.5	57.3	59.6	54.0	53.4	59.6	59.7	61.8	68.2	65.5	67.3	70.4	68.5	69.8
Imipenem	82.5	85.4	80.6	74.6	79.1	83.1	75.3	68.6	71.4	66.2	57.6	62.1	61.6	63.7	70.8	67.7	67.6	66.5	64.2	65.5
Piperacillin/Tazobactam	80.3	72.6	59.9	65.0	70.6	70.1	67.5	67.5	71.9	69.9	63.1	66.3	65.7	68.1	75.4	70.8	69.2	65.1	63.9	63.9
<i>Acinetobacter baumannii</i> , No. tested	12	19	19	17	20	22	17	16	20	25	32	45	57	70	87	84	88	85	87	81
Ampicillin/Sulbactam												54.6	42.2	36.1	33.7	30.2	25.2	20.0	21.7	20.4
Ceftazidime	32.1	28.0	31.7	28.3	28.8	29.0	35.0	35.0	35.0	34.1	30.1	36.9	26.4	24.5	21.7	20.1	21.7	24.1	25.6	20.4
Ciprofloxacin	30.7	36.9	38.7	32.0	33.5	33.0	40.9	41.2	42.6	33.4	30.0	36.3	29.1	26.2	21.4	18.0	17.8	14.5	16.1	17.5
Gentamicin	23.4	28.5	30.1	28.4	29.2	30.1	37.2	40.6	52.9	36.3	32.1	36.7	27.7	25.4	23.8	23.9	31.4	34.0	31.0	31.4
Imipenem	98.6	97.5	94.5	87.0	81.8	72.1	72.2	80.1	70.7	70.5	61.3	55.4	36.4	29.6	25.1	24.3	22.0	17.1	17.4	19.5
Trimethoprim/Sulfamethoxazole	45.3	48.2	54.4	57.2	61.0	55.5	57.2	57.8	53.1	41.3	40.5	42.3	30.9	27.1	26.8	32.3	25.6	31.3	35.5	39.7

No. tested = the number of tested isolates (× 100).

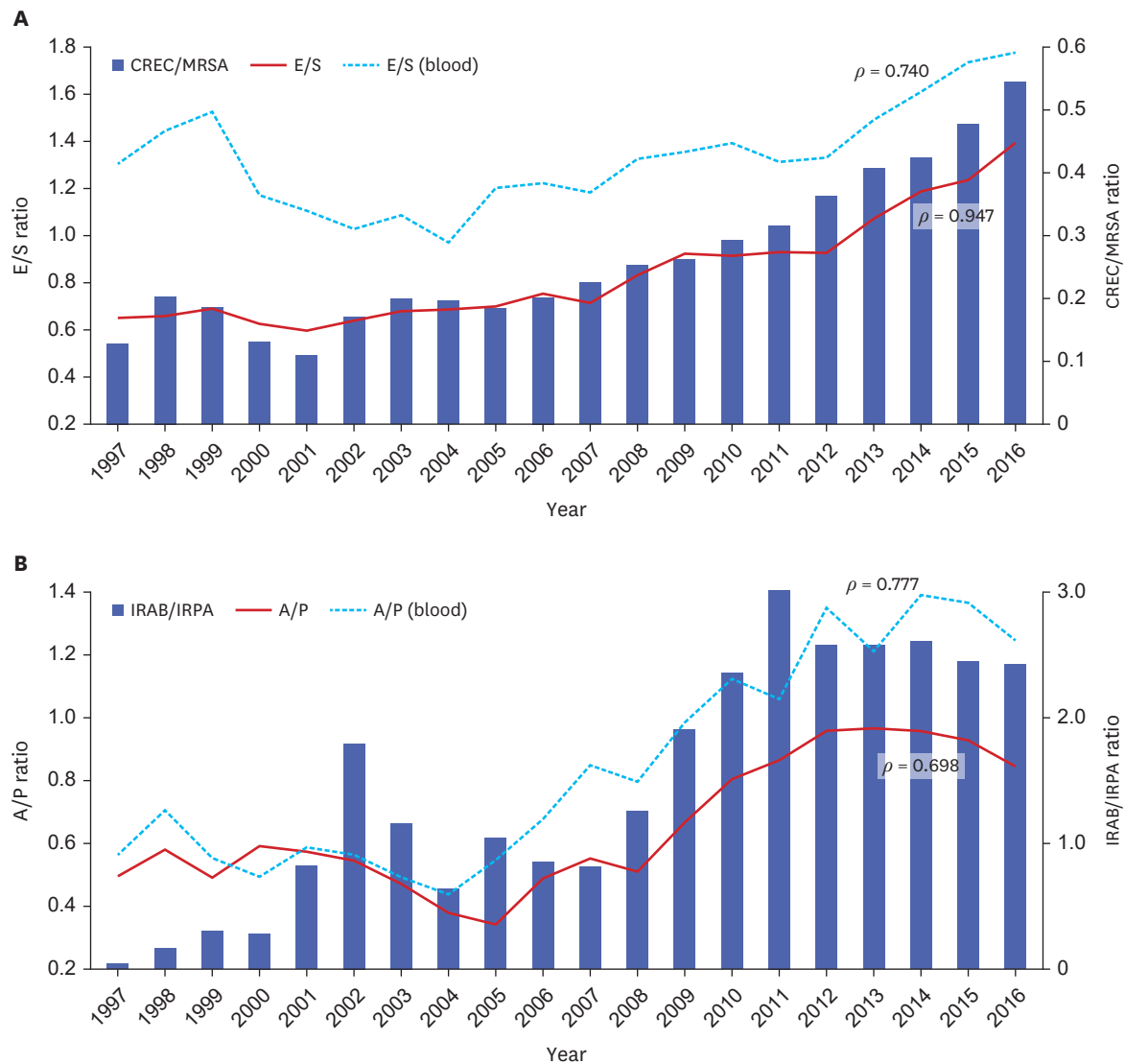


Fig. 2. Correlation between species distribution and antimicrobial resistance of four most prevalent species. **(A)** Correlation analysis of the E/S ratio and the CREC/MRSA ratio showed strong correlation in total isolates ($\rho = 0.947$) and blood isolates ($\rho = 0.740$). **(B)** The A/P ratio and the IRAB/IRPA ratio showed moderate correlations in both total ($\rho = 0.698$) and blood isolates ($\rho = 0.777$).

E/S ratio = ratio of the number of isolates of *Escherichia coli* to those of *Staphylococcus aureus*, CREC/MRSA ratio = ratio of % cefotaxime-resistant *E. coli* to % oxacillin-resistant *S. aureus*, A/P ratio = ratio of the number of isolates of *Acinetobacter baumannii* to those of *Pseudomonas aeruginosa*, IRAB/IRPA ratio = ratio of % imipenem-resistant *A. baumannii* to % imipenem-resistant *P. aeruginosa*.

SENTRY.⁹ The rate of device-associated MRSA infections in intensive care units (ICUs) has been reported to decrease slightly from 95.0% in 2006 to 90.2% in 2013.¹⁰ The trends of decreasing MRSA rates were more prominent when more community-related isolates were included, changing from 69% in 2009 to 66% in 2011 in the Korean Nationwide Surveillance of Antimicrobial Resistance program (KONSAR)^{11,12} and from 72% in 2013 to 66% in 2015 in the Korean Antimicrobial Resistance Monitoring System.¹³ A laboratory in Daejeon which is one of the participating laboratories reported a 20% annual decline in the incidence density of ICU-acquired MRSA bacteremia over a decade (2009–2018), primarily due to reductions in the incidence of catheter-related infections.¹⁴ Therefore, the frequency of total *S. aureus* and the decreased MRSA rate seems to be a national trend in South Korea.

E. coli became the most prevalent pathogen since 2012 in this study. It has consistently been the most abundant pathogen in the KONSAR study since 2007,¹¹ and SENTRY reported that *E. coli* was the most common pathogen worldwide, causing BSI from 2005 to 2016.⁹ The simultaneous decrease in the frequency of *S. aureus* and increase in that of *E. coli* appears to be due to antimicrobial resistance when inferring a strong correlation between the E/S ratio and the CREC/MRSA ratio in this study. Cefotaxime is the most sensitive indicator of extended-spectrum β -lactamase (ESBL) *E. coli* in Korea because type of ESBL is mainly CTX-M-14 or M-15 among ESBL-producing *E. coli*.¹⁵ The CREC rate correlated with the ESBL-producing rate in *E. coli*. The predominant strain of antimicrobial-resistant *E. coli* was ST131 in the early 2000s worldwide¹⁶ and in Korea, as shown in a previous multicenter study analyzing ciprofloxacin-resistant *E. coli* isolated in 2006–2007.¹⁷ ST131 is also a major clone in ESBL-producing *E. coli* in the community and healthcare settings in Korea.¹⁸ The domestic spread of this clone may explain its decreased susceptibility to ciprofloxacin and cefotaxime in the late decade. In this study, *K. pneumoniae* was always more resistant than *E. coli* to imipenem and cefotaxime. Classical *K. pneumoniae* is a pathogen that causes healthcare-associated infections driven by multidrug resistance (MDR) rather than higher virulence.¹⁹ Therefore, it is noteworthy that the imipenem susceptibility of *E. coli* remained unchanged for 20 years, whereas the imipenem resistance of *K. pneumoniae* increased to 2% in 2016. Carbapenem-resistant *Enterobacterales* (CRE) is an emerging threat to public health worldwide.⁹ The number of carbapenem-nonsusceptible *Enterobacterales* isolates increased approximately 1.5-fold per year as per the national laboratory surveillance of Korea conducted from 2011 to 2015.²⁰ The most serious concern is that carbapenem resistance in *K. pneumoniae* is mediated by plasmids carrying carbapenemase genes encoding KPC, NDM, VIM, OXA-48, and IMP, among others.²¹ Therefore, close monitoring and thorough infection control of CRE are required, as CRE is considered to affect the epidemiology of pathogenic bacteria in the near future.

Concurrent increases in imipenem resistance and the frequency of *P. aeruginosa* and *A. baumannii* continued until 2008 and 2011, respectively. The frequency of meropenem-nonsusceptible *Acinetobacter* spp. markedly increased from 13.6% to 78.8% in the Asia-Pacific region from 1997–1998 to 2015–2016, while the frequency of meropenem-nonsusceptible *P. aeruginosa* fluctuated between 20% and 30% over 20 years.^{22,23} According to previous studies, the increase in carbapenem resistance in *P. aeruginosa* and *A. baumannii* in South Korea is similar to a global trend.^{12,13} In this study, the increase in the prevalence of carbapenem-resistant *A. baumannii* was primarily explained by the spread of a clone carrying the *bla*_{oxa-23}-like gene since 2007 in South Korea.²⁴ Compared to *A. baumannii*, carbapenem resistance in *P. aeruginosa* is mediated more by the induction of multifaceted resistance mechanisms against antimicrobial usage than by plasmid-mediated carbapenemases.^{25–27} Given the impact of carbapenem resistance mechanisms on the epidemiology of *P. aeruginosa* and *A. baumannii*, *K. pneumoniae* will become the most problematic pathogen in the near future through their carbapenemase-mediated resistant mechanism.

This study showed that vancomycin resistance in *E. faecium* was as high as 40–50% and that *E. faecalis* was still susceptible to vancomycin independent of the hospital size and region in Korea. These findings are consistent with those of previous global and Korean studies.^{12,28} *E. faecium* is intrinsically more resistant than *E. faecalis*, a well-known virulence factor that increases the incidence of *E. faecium* infections in healthcare-associated settings.²⁹ In this study, the number of isolates of *E. faecium* first outnumbered that of *E. faecalis* in 2000 among all isolates and in 1999 among blood isolates. Since then, the incidence of these two *Enterococcus* species fluctuated. However, the number of patients was consistently higher with

E. faecalis than with *E. faecium*, except from 2004 to 2006. A transient increase in the frequency of *E. faecium* is often associated with the prevalence of vancomycin-resistant *E. faecium*; in 2001–2002, two laboratories showed very high vancomycin resistance rates of up to 29.0%. Therefore, *Enterococcus* species are representative organisms in which antimicrobial resistance affects epidemiology; thus, if there is a sudden change in the isolation frequency, it should always be interpreted concerning antimicrobial susceptibility.

The relative frequency of *S. pneumoniae* infection decreased since 2002. Considering that pneumococcal vaccines were started in 2003 in Korea, which caused a decline in the frequency of pathogenic serotypes,^{30,31} this finding is not surprising. The prevalence of multidrug-resistant *S. pneumoniae*, including those resistant to penicillin, continuously increased during the study period. There is a strong correlation between antimicrobial resistance and serotype, and the representative non-PCV13 serotype 11A that most frequently causes infection after pneumococcal vaccination has a MDR rate of 80.9% and the next most frequent serotype 19A is also an MDR strain in South Korea.^{31,32} Unlike other species, the increase in MDR with a decrease in the incidence of *S. pneumoniae* infections can be explained by the vaccine effect.

The frequency of *S. agalactiae* showed a 19-fold increase over 20 years, and it became the most common pathogenic *Streptococcus* species since 2013. It was also the most common pathogenic *Streptococcus* isolated from blood cultures since 2015. *S. agalactiae* is a well-known pathogen that causes meningitis and pneumonia in infants < 3 months of age.³³ However, the prevalence of *S. agalactiae* skin/soft tissue infections and bacteremia in adults with underlying diseases has increased.^{34–36} *S. agalactiae* showed low susceptibility to erythromycin and clindamycin at 56.3–72.3% and 44.7–73.1%, respectively, from the beginning of this study. Levofloxacin susceptibility remained high but declined to 77.1% in 2016 over the past decade. The increasing trend in levofloxacin resistance is supported by a previous report that showed an increase from 5.6% in 2005 to 10.6% in 2008 among clinical isolates of *S. agalactiae* in a university hospital.³⁷ Reduced levofloxacin and macrolide susceptibility exacerbates the problem associated with the increased incidence of *S. agalactiae* infections. The guidelines for community-acquired pneumonia published in 2009 recommend β -lactam \pm macrolide or respiratory fluoroquinolone as the first choice of antimicrobial agents for outpatients in Korea.³⁸ Therefore, the increased incidence of *S. agalactiae* infections and increased resistance to levofloxacin and macrolide may be associated with the greater use of macrolide and levofloxacin in the community. For the same reason, *S. agalactiae* is likely to become a more serious problem over a considerable period.

This study has a few important limitations. This study aimed to collect comprehensive national data for the last 20 years; however, the minimal inhibitory concentration (MIC) test panel differed according to the laboratory; therefore, some antimicrobials were not included in the analysis. Second, not all laboratories participated during the study period because each participating laboratory's data collection period was different. Third, the participating laboratories were mainly from university and tertiary care hospitals; therefore, the conclusions of this study cannot be generalized to community hospitals. However, the homogeneity of the participating laboratories had an advantage in terms of test performance and MIC data quality.

In conclusion, the epidemiology of pathogenic bacteria has greatly changed according to the trends of antimicrobial resistance rates over the past two decades in Korea. An increase

in antimicrobial resistance is associated with the trend of an increasing frequency of certain species. National trend analysis of species distribution and antimicrobial resistance of pathogenic bacteria helps to predict epidemiologic changes in the near future and highlights interventions for infection control and antimicrobial agent usage to prevent the further spread of antimicrobial resistance.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Number of isolates tested in 12 participating laboratories

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