Review Article

Antimicrobial resistance in South Korea: A report from the Korean global antimicrobial resistance surveillance system (Kor-GLASS) for 2017[☆]

Changseung Liu [a], Eun-Jeong Yoon [a], Dokyun Kim [a], Jong Hee Shin [b], Jeong Hwan Shin [c], Kyeong Seob Shin [d], Young Ah Kim [e], Young Uh [f], Hyun Soo Kim [g], Young Ree Kim [h], Seok Hoon Jeong [a, *]

[a] Department of Laboratory Medicine, Research Institute of Bacterial Resistance, Yonsei University College of Medicine, Seoul, South Korea
[b] Department of Laboratory Medicine, Chonnam National University School of Medicine, Gwangju, South Korea
[c] Department of Laboratory Medicine and Paik Institute for Clinical Research, Inje University College of Medicine, Busan, South Korea
[d] Department of Laboratory Medicine, Chungbuk National University College of Medicine, Cheongju, South Korea
[e] Department of Laboratory Medicine, National Health Insurance Service Ilsan Hospital, Goyang, South Korea
[f] Department of Laboratory Medicine, Yonsei University Wonju College of Medicine, Wonju, South Korea
[g] Department of Laboratory Medicine, Hallym University Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, South Korea
[h] Department of Laboratory Medicine, Jeju National University School of Medicine, Jeju, South Korea

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ABSTRACT

At the end of 2015, a global action plan on antimicrobial resistance (AMR) was proposed by the World Health Organization, and the Global AMR Surveillance System (GLASS) was subsequently initiated. The Centers for Disease Control and Prevention of South Korea established a customized AMR surveillance system for South Korea, called Kor-GLASS, in early 2016. A pilot phase of Kor-GLASS was operated from May to December 2016 with six sentinel hospitals, and phase I of Kor-GLASS started in January 2017 with eight sentinel hospitals. Previous surveillance data for overestimated AMR due to duplicate isolation of drug-resistant pathogens were corrected and error-free AMR data were compared with those from other countries. One-half (53.2%, 377/708) of *Staphylococcus aureus* blood strains exhibited resistance to cefoxitin, indicating methicillin-resistant *S. aureus*. Resistance to ampicillin in *Enterococcus faecalis* blood strains was rare (0.6%, 1/175), while the resistance rate to penicillin was 26.3% (46/175). Resistance to vancomycin (34.0%, 98/288) and teicoplanin (18.8%, 98/288) was frequently observed in *Enterococcus faecium* strains. The resistance rate of *Escherichia coli* strains to cefotaxime was 32.4% (574/1772), and that of *Klebsiella pneumoniae* strains was 26.1% (181/693). The resistance rates of *Pseudomonas aeruginosa* strains to imipenem and meropenem were 19.5% (29/149) and 18.1% (27/149), respectively. And 92.1% (187/203) of *Acinetobacter baumannii* strains were resistant to both imipenem and meropenem. The high incidence of bacteremia caused by major AMR pathogens among hospitalized patients especially in intensive care units emphasized the importance of hospital infection control and the need to improve the crowded hospitalization system in South Korea. The isolation rate of the *Salmonella* spp. is decreasing, reflecting the current socio-economic status of South Korea. The proportions of bacterial species in the blood strains were similar to those in other Asian countries with similar lifestyles.

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Contents

1. Kor-GLASS

At the end of 2015, a global action plan on Antimicrobial resistance (AMR) was proposed by the World Health Organization (WHO), and the Global AMR Surveillance System (GLASS) was subsequently initiated to gather the necessary evidence to guide further policy and decision making [1,2]. The GLASS protocol was generated to standardize the surveillance methods to enable a comparative overview of global AMR. With the advent of the new system in early 2016, the Centers for Disease Control and Prevention of South Korea (KCDC) established a customized AMR surveillance system for South Korea, the Korean GLASS (Kor-GLASS), replacing the existing laboratory-monitoring based surveillance system, the Korean AMR Monitoring System (KARMS) [3,4]. Following the principles of GLASS, including representativeness, specialization, harmonization, and localization, all non-duplicate clinical isolates of major pathogens were collected from sentinel hospitals across the Korean peninsula along with the clinical data of the patients. A pilot phase of Kor-GLASS was operated from May to December 2016 with six sentinel hospitals, and the established system received good reviews internationally as a desirable example of AMR surveillance [5,6].

The success of the pilot phase of Kor-GLASS encouraged the KCDC to expand the system by increasing the number of sentinel hospitals from six in the pilot phase to eight in phase I (2017–2019) and 10 in phase II (2020–2022). During the pilot phase, Kor-GLASS was reinforced by establishing two supplemental structures: (i) a quality control center for ensuring the accuracy of the results from the analysis center by performing parallel tests and (ii) a web-based data-managing constitution for clinical data from sentinel hospitals, laboratory data from the analysis center, and parallel test results from the quality control center. The phase I of Kor-GLASS started in January 2017 with eight sentinel hospitals and is now in its third year. Here, we report on the blood isolates from the one-year assessment in 2017 to mainly present their characteristics and the clinical information of the patients with bacteremia caused by nine major pathogens.
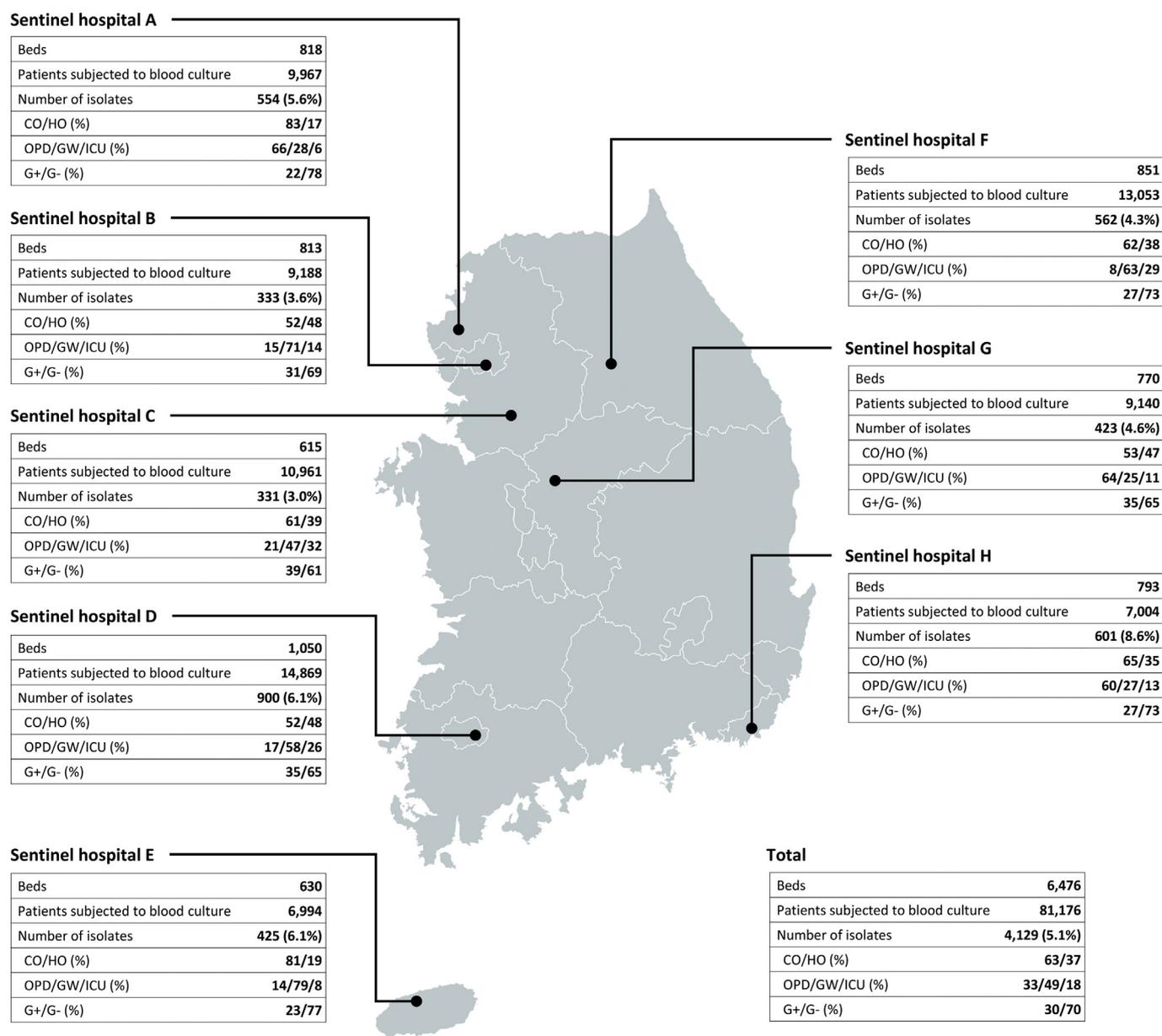
2. Collection of blood isolates and patient data at each sentinel hospital

All non-duplicated blood isolates of *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella* spp., *Pseudomonas aeruginosa*, and *Acinetobacter* spp. recovered through enrichment cultures of blood specimens were collected from 8 sentinel hospitals (Fig. 1). Each isolate was inoculated in a cryotube containing 20% (w/v) skimmed milk and then stored at −80 °C [7]. The collected blood isolates were transferred to an analysis center twice a month through a cold chain delivery system. For the transferred clinical isolates, purity and viability were verified by sub-culture. If an isolate did not grow or had been contaminated, the sentinel hospital was asked to resend the isolate. Feedback was given in cases of contamination and no growth to improve the performance in sentinel hospitals.

Demographic data (age and sex), infection origin [hospital origin (HO) or community origin (CO)], and admission type [outpatient department (OPD), general ward (GW), or intensive care unit (ICU)] of all patients for whom blood cultures were performed during the study period were recorded at each sentinel hospital. An infection of HO was defined when a blood specimen was taken from an inpatient hospitalized for ≥2 calendar days, including the hospitalization days in another healthcare facility before transfer. An infection of CO was defined when a blood specimen was taken either from an outpatient or from an inpatient hospitalized for <2 calendar days.

3. Microbiological analyses at the analysis center

Bacterial species were confirmed in the analysis center using a matrix-assisted laser desorption/ionization time-of-flight mass spectrometer (Bruker Biotyper, Bruker Daltonics GmbH, Bremen, Germany). And we selectively used the VITEK 2 system (bio-Mérieux, Marcy l'Etoile, France) for the identification of *S. pneumoniae*. Additional sequence analyses of the *rpoB* gene were performed to identify the *Acinetobacter* species, and species

Sentinel hospital A

Beds	818
Patients subjected to blood culture	9,967
Number of isolates	554 (5.6%)
CO/HO (%)	83/17
OPD/GW/ICU (%)	66/28/6
G+/G- (%)	22/78

Sentinel hospital B

Beds	813
Patients subjected to blood culture	9,188
Number of isolates	333 (3.6%)
CO/HO (%)	52/48
OPD/GW/ICU (%)	15/71/14
G+/G- (%)	31/69

Sentinel hospital C

Beds	615
Patients subjected to blood culture	10,961
Number of isolates	331 (3.0%)
CO/HO (%)	61/39
OPD/GW/ICU (%)	21/47/32
G+/G- (%)	39/61

Sentinel hospital D

Beds	1,050
Patients subjected to blood culture	14,869
Number of isolates	900 (6.1%)
CO/HO (%)	52/48
OPD/GW/ICU (%)	17/58/26
G+/G- (%)	35/65

Sentinel hospital E

Beds	630
Patients subjected to blood culture	6,994
Number of isolates	425 (6.1%)
CO/HO (%)	81/19
OPD/GW/ICU (%)	14/79/8
G+/G- (%)	23/77

Sentinel hospital F

Beds	851
Patients subjected to blood culture	13,053
Number of isolates	562 (4.3%)
CO/HO (%)	62/38
OPD/GW/ICU (%)	8/63/29
G+/G- (%)	27/73

Sentinel hospital G

Beds	770
Patients subjected to blood culture	9,140
Number of isolates	423 (4.6%)
CO/HO (%)	53/47
OPD/GW/ICU (%)	64/25/11
G+/G- (%)	35/65

Sentinel hospital H

Beds	793
Patients subjected to blood culture	7,004
Number of isolates	601 (8.6%)
CO/HO (%)	65/35
OPD/GW/ICU (%)	60/27/13
G+/G- (%)	27/73

Total

Beds	6,476
Patients subjected to blood culture	81,176
Number of isolates	4,129 (5.1%)
CO/HO (%)	63/37
OPD/GW/ICU (%)	33/49/18
G+/G- (%)	30/70

Fig. 1. Location of the sentinel hospitals in South Korea and the number of blood isolates collected by each hospital. Abbreviations: CO, community origin; G+, Gram-positive; G-, Gram-negative; GW, general ward; HO, hospital origin; ICU, intensive care unit; OPD, outpatient department.

identification discrepancy between methods or between sentinel hospitals and the analysis center was confirmed by 16S rDNA sequencing. Antimicrobial susceptibility testing (AST) was performed using the disk diffusion and broth microdilution methods following the guidelines of the Clinical and Laboratory Standards Institute [8].

Drug resistance was categorized following Magiorakos et al. [9] with a few modifications: susceptible to all tested drugs (drug-susceptible, DS); non-susceptible to one or two drug classes (drug-resistant, DR); non-susceptible to ≥3 antimicrobial classes (multiple drug-resistant, MDR); susceptible to ≤2 antimicrobial classes (extensively drug-resistant, XDR); and non-susceptible to all antimicrobial classes tested (pandrug-resistant, PDR).

The testing panel of antimicrobial drugs was carefully selected to categorize pathogen-specific AMR. To ensure accurate isolations

and AST results, blind cross-checks between the analysis center and the quality control center had been carried out every month to validate the results, and feedback was given (Fig. 2). And also, all sentinel hospitals and the analysis center were certified by the External Quality Control program every three months.

4. Recovery of bacterial pathogens from blood cultures

During the one year of 2017, a total of 4129 (5.1%) isolates of target pathogens were recovered from the blood specimens of 81,176 patients (Fig. 3). *E. coli* (42.9%, 1772/4129) was the most common species, followed by *S. aureus* (17.1%, 708/4129) and *K. pneumoniae* (16.8%, 693/4129). *E. faecium* (7.0%, 288/4129) was the 4th most common species, with 1.6-fold more isolates than *E. faecalis* (4.2%, 175/4129). *Acinetobacter* spp. (5.7%, 235/4129) were
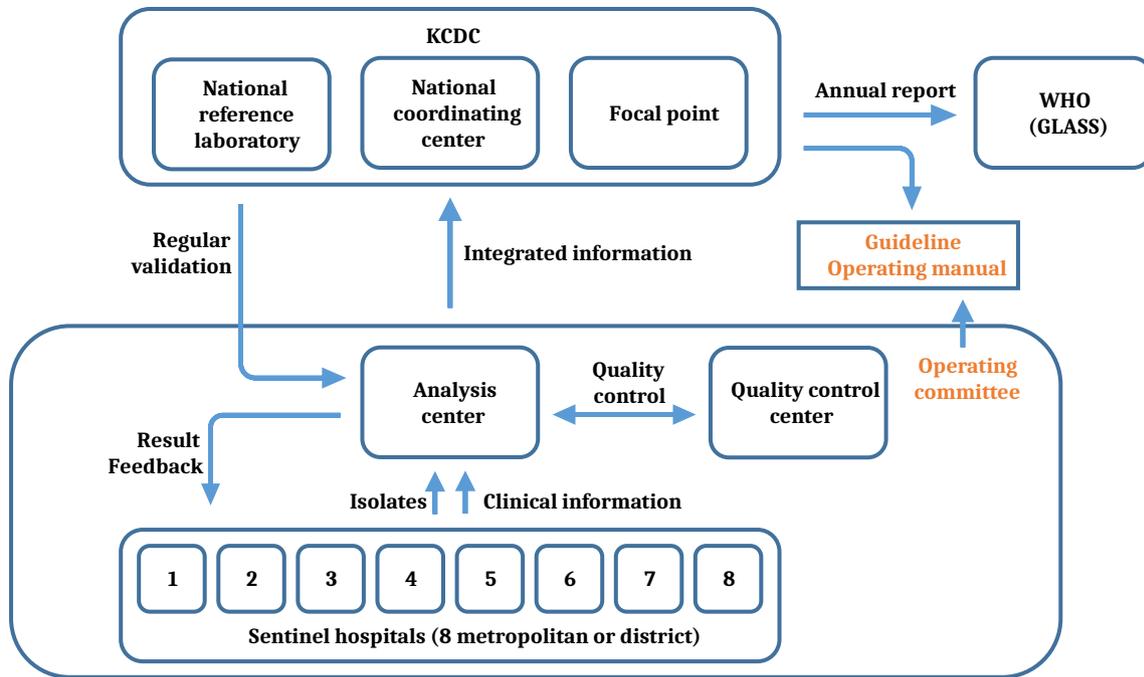
Fig. 2. Structure and governance of Kor-GLASS. Abbreviations: GLASS, Global Antimicrobial Resistance Surveillance System; KCDC, Korean Center for Disease Control and Prevention; WHO, World Health Organization.

the 5th most common, mostly consisting of *A. baumannii* (86.4%, 203/235). The non-*baumannii Acinetobacter* spp. (NBA, 32/235) included *A. nosocomialis* (16/32), *A. soli* (5/32), *A. pittii* (4/32), *A. bereziniae* (4/32), *A. seifertii* (2/32), and *A. grimontii* (1/32). *P. aeruginosa* was recovered from 149 (3.6%) patients, and *Salmonella* spp. (1.4%, 56/4129) and *S. pneumoniae* (1.3%, 53/4129) were occasionally recovered.

E. coli blood strains were recovered 1.4-fold more often from female patients than from male (male:female = 0.7:1) (Fig. 4), while the ratios were reversed for other species: 1.5:1 for *S. aureus*, 1.7:1 for *E. faecalis*, 1.6:1 for *K. pneumoniae*, 2.0:1 for *P. aeruginosa*, and 1.6:1 for *Acinetobacter* spp. *E. faecium* blood strains were equally recovered from both sexes. The majority of *Enterobacteriaceae* were recovered from infections of CO, 80.5% (1426/1772) of *E. coli* and 70.7% (490/693) of *K. pneumoniae*, while most of the *Acinetobacter* spp. (88.1%, 207/235) and *E. faecium* (80.6%, 232/288) were from recovered from infections of HO. The origins of *S. aureus* blood strains were nearly equal between CO and HO, at 358 and 350, respectively. The proportions of each species among nine target pathogens recovered from blood specimens differed by age group (AG) (Fig. 5). *S. aureus* blood strains peaked in the 5-<15 AG (45.5%) and decreased with age, and the lowest proportion was observed in the 75-<85 AG (15.2%). *E. coli* presented a different trend: its proportion was high in the <1 AG (32.5%), was markedly lower in the 1-<5 AG (26.5%) and 5-<15 AG (6.1%), increased with age to 34.8% in the 25-<35 AG, and peaked in the ≥85 AG (51.2%). The proportion of *K. pneumoniae* was the lowest in the <1 AG (2.5%), followed by gradual increase with age to 21.5% in the 45-<55 AG, and remaining at approximately 17% through the ≥85 AG.

The total patient-days of inpatients during the one year in the eight sentinel hospitals was 2,006,663 days, comprising 204,839 days in ICUs and 1,801,824 days in GWs. The mean rate of bacteremia occurrence per 10,000 patient-days for inpatients was the highest for *E. coli* at 4.9 (range: 1.1–9.1 by hospital), followed by 2.5 for *S. aureus* (1.3–5.0), 2.3 for *K. pneumoniae* (1.0–3.7), 1.3 for *E. faecium* (0.8–1.6), 0.9 for *A. baumannii* (0–1.6), 0.7 for *E. faecalis* (0.2–1.5), and 0.5 for *P. aeruginosa* (0.1–1.1) (Fig. 6). Bacteremia occurred more in ICU patients than in GW patients: the relative occurrence ICU:GW ratio was the highest for *A. baumannii* at 22.2 (6.6:0.3), followed by *E. faecalis* at 5.8 (2.8:0.5), *E. faecium* at 4.9 (4.6:0.9), *S. aureus* at 4.7 (8.6:1.8), *P. aeruginosa* at 3.9 (1.6:0.4), *K. pneumoniae* at 2.3 (4.7:2.0), and *E. coli* at 1.3 (6.2:4.8).

The overall incidence of bacteremia caused by the top five pathogens (*E. coli*, *S. aureus*, *S. pneumoniae*, *E. faecalis*, and *E. faecium*) was increasingly reported in Europe between 2002 and 2008 based on the European Antimicrobial Resistance Surveillance System (EARSS) database [10]. In this study, both *E. coli* and *E. faecium* occupied more proportion among blood strains than *S. aureus* and *S. pneumoniae* (Fig. 3). The predominance of *E. coli* among bacteremia-causing pathogens corresponds to the worldwide trend, and the relative incidence of bacteremia caused by *S. aureus* vs. by *E. coli* in Kor-GLASS was 1:2.5, which was similar to the relative incidences of 1:2.4 in Taiwan [11] and 1:2.2 in the Netherlands [12]; lower than that of 1:3.1 in Norway [13]; and higher than those of 1:1.1 in Japan [14], 1:1.2 in Vietnam [15], 1:0 in Greece [16], and 1:1.3 in Malawi [17]. The relative incidences of bacteremia caused by *K. pneumoniae* vs. by *E. coli* in Kor-GLASS was similar, at 1:2.6, comparable to those in Japan (1:2.3) and Taiwan (1:3.0), lower than those in the Northern European countries (1:5.4 and 1:5.1 in the Netherlands and Norway, respectively), and higher than that in Vietnam (1:1.0). *S. pneumoniae* was frequently isolated from blood specimens in European countries (1:3.2 in the Netherlands, 1:3.0 in Norway), whereas it was rarely identified in
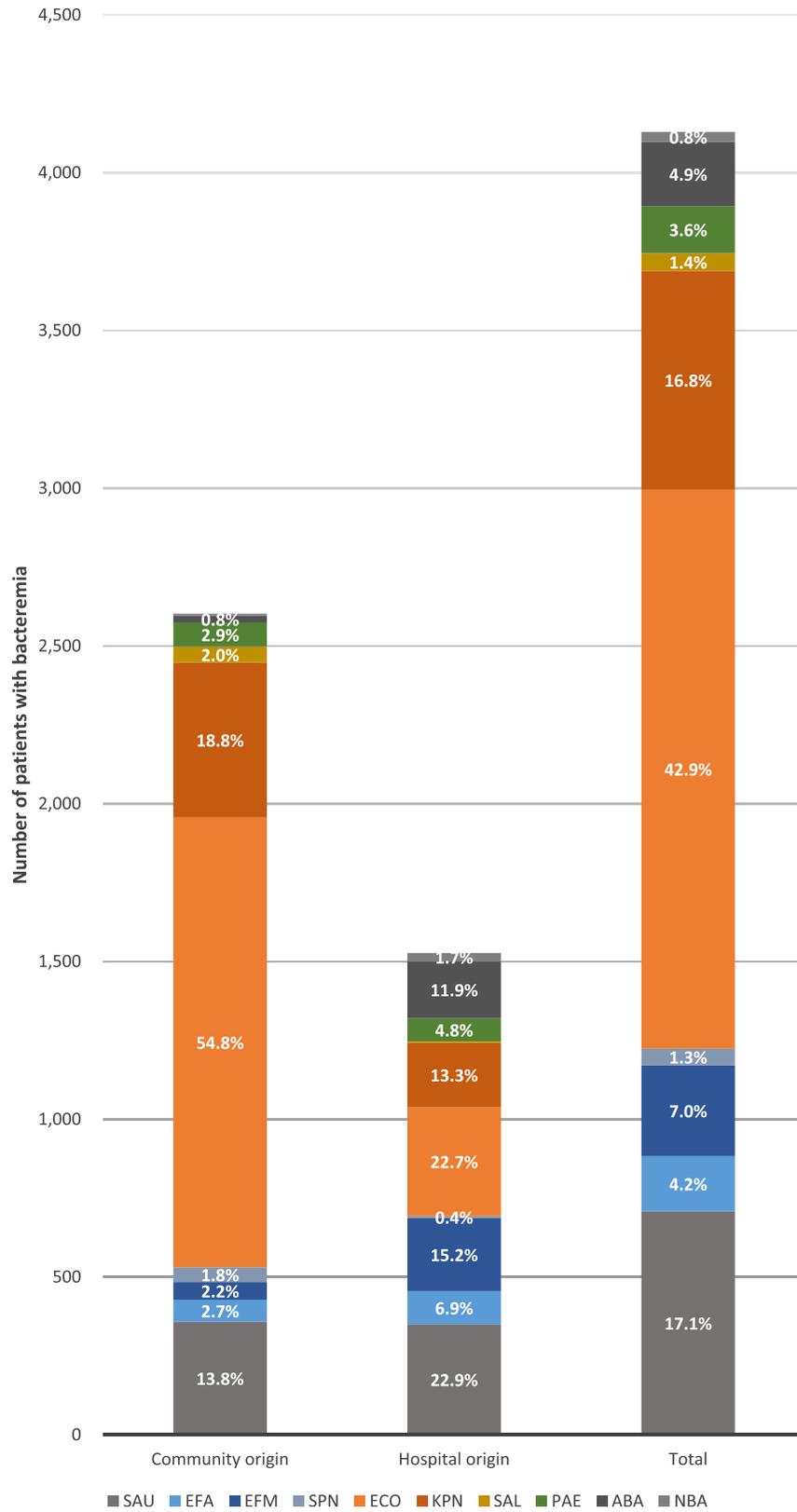
Fig. 3. Occurrence of bacteremia during the study period by infection origin. Abbreviations: ABA, *Acinetobacter baumannii*; ECO, *Escherichia coli*; EFA, *Enterococcus faecalis*; EFM, *Enterococcus faecium*; KPN, *Klebsiella pneumoniae*; NBA, Non-*baumannii Acinetobacter* species; SAL, *Salmonella* species; SAU, *Staphylococcus aureus*; SPN, *Streptococcus pneumoniae*.
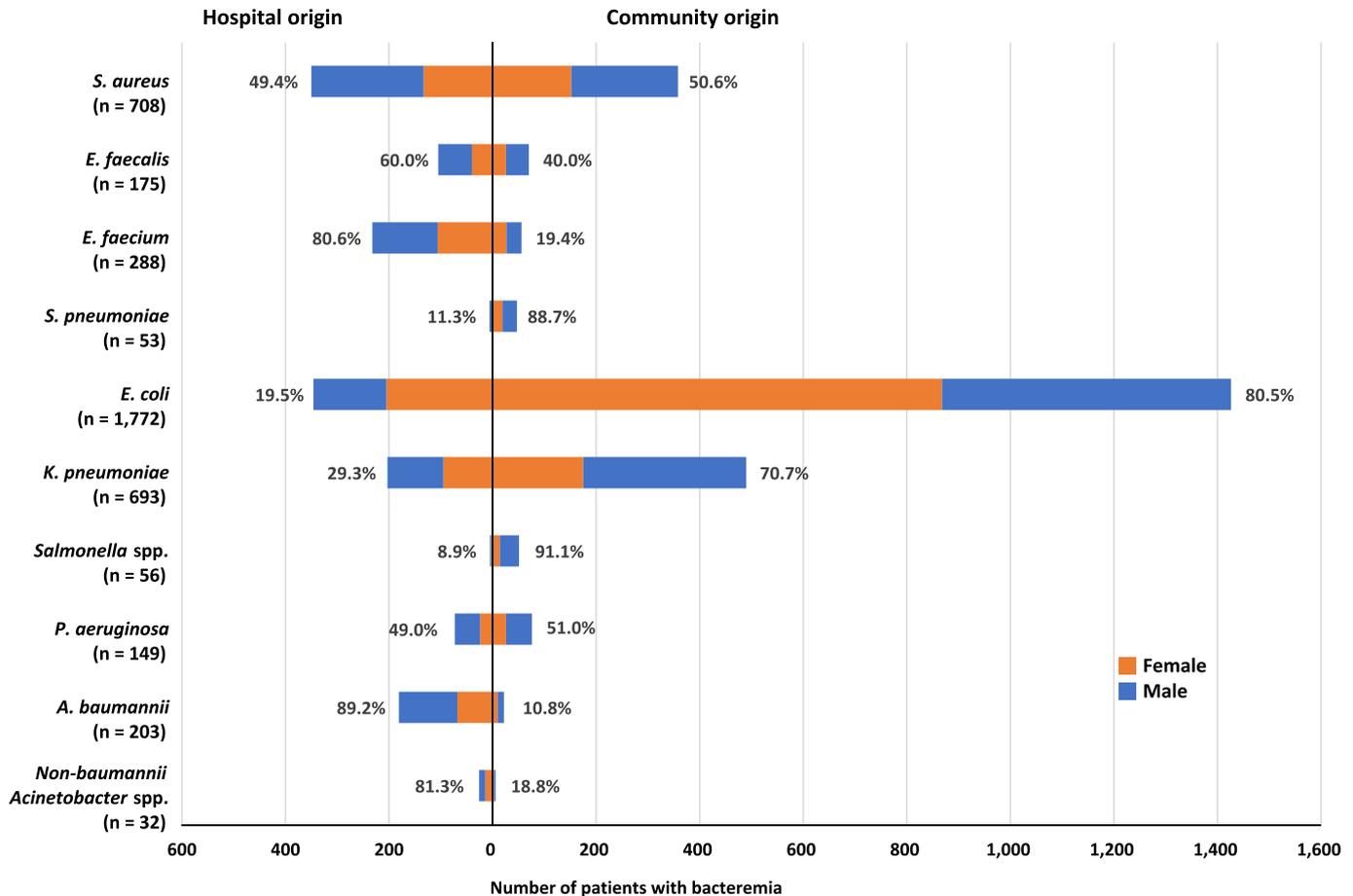
Fig. 4. The number of patients with bacteremia by infection origin and sex.

Kor-GLASS (1:33.4), similar to the ratios in Asian countries (1:18.3 in Vietnam and 1:31.8 in Taiwan). *Salmonella* spp. remain the major pathogens causing bacteremia in developing countries, such as Vietnam (1:2.8) and Malawi (1:0.9); however, in South Korea, the species were seldom identified (1:31.6), similar to the results in Taiwan (1:14.2).

5. Antimicrobial susceptibilities of major pathogens

5.1. S. aureus

Approximately one-half (53.2%, 377/708) of *S. aureus* blood strains exhibited resistance to cefoxitin, indicating methicillin-resistant *S. aureus* (MRSA) (Fig. 7a). Cefoxitin resistance was more frequently observed in infections of HO (66.3%, 232/377) than those in CO (40.5%, 145/377). The high prevalence of MRSA among blood strains in South Korea is likely decreasing according to the KARMS data, which revealed a decrease from 72% in 2013 to 66% in 2015 [18]. The 53.2% rate reported in 2017 by Kor-GLASS is, indeed, less than the prevalence of 66% reported in 2016 by KARMS.

Most of the *S. aureus* strains remained susceptible to recently developed anti-staphylococcal drugs, including tigecycline, linezolid, and quinupristin-dalfopristin, with a few exceptions: three (0.4%) were resistant to tigecycline, and five (0.7%) were resistant to quinupristin-dalfopristin. They were all susceptible to the traditional anti-MRSA drugs vancomycin and teicoplanin. The *S. aureus*

blood strains were categorized by their AMR phenotype: 38.4% (272/708) as DS, 8.3% (59/708) as DR, and 53.2% (377/708) as MDR (Fig. 8). No XDR or PDR strains were identified in this study. All the MDR strains were MRSA.

5.2. E. faecalis

Resistance to ampicillin in *E. faecalis* blood strains was rare (0.6%, 1/175), while the resistance rate to penicillin was 26.3% (46/175): 31.4% (33/105) among HO and 18.6% (13/70) among CO infections (Fig. 7b). None of the penicillin-resistant strains showed positive results in the Cefinase test for the identification of beta-lactamase production. The resistance phenotype has been identified in *E. faecalis* clinical strains in many countries, and it is associated with the overproduction of altered penicillin-binding protein 4 having a low affinity for beta-lactams [19,20]. Resistance to glycopeptides was also rare: 0.6% (1/175) for both vancomycin and teicoplanin. High-level resistance to gentamicin was observed in 26.9% (47/175) of strains, and that to streptomycin was observed in 6.3% (11/175) of strains. The *E. faecalis* blood strains mostly exhibited the DR (38.3%, 67/175) or MDR (25.1%, 44/175) phenotype (Fig. 8). Neither XDR nor PDR strains were identified. Most of the penicillin-resistant strains exhibited the MDR (80.4%, 37/46) phenotype, while penicillin-susceptible strains (5.4%, 7/129) rarely did.
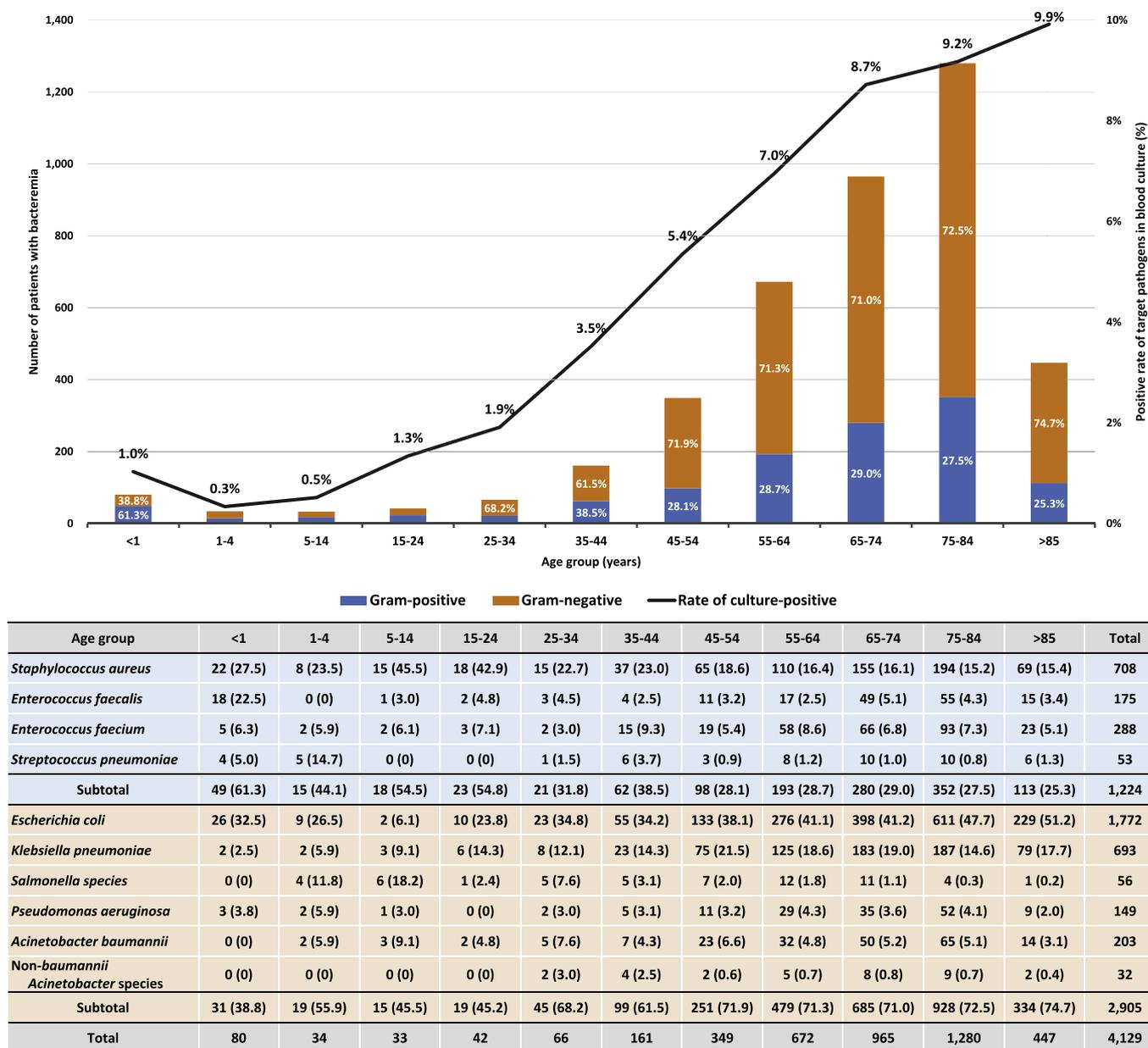
Fig. 5. Number of patients with bacteremia by target pathogen. The bar is the number of infected patients by Gram stain, and the black line is the percentage of patients positive for target pathogens. The table shows the number of patients with bloodstream infection by age group.

Age group	<1	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	>85	Total
Staphylococcus aureus	22 (27.5)	8 (23.5)	15 (45.5)	18 (42.9)	15 (22.7)	37 (23.0)	65 (18.6)	110 (16.4)	155 (16.1)	194 (15.2)	69 (15.4)	708
Enterococcus faecalis	18 (22.5)	0 (0)	1 (3.0)	2 (4.8)	3 (4.5)	4 (2.5)	11 (3.2)	17 (2.5)	49 (5.1)	55 (4.3)	15 (3.4)	175
Enterococcus faecium	5 (6.3)	2 (5.9)	2 (6.1)	3 (7.1)	2 (3.0)	15 (9.3)	19 (5.4)	58 (8.6)	66 (6.8)	93 (7.3)	23 (5.1)	288
Streptococcus pneumoniae	4 (5.0)	5 (14.7)	0 (0)	0 (0)	1 (1.5)	6 (3.7)	3 (0.9)	8 (1.2)	10 (1.0)	10 (0.8)	6 (1.3)	53
Subtotal	49 (61.3)	15 (44.1)	18 (54.5)	23 (54.8)	21 (31.8)	62 (38.5)	98 (28.1)	193 (28.7)	280 (29.0)	352 (27.5)	113 (25.3)	1,224
Escherichia coli	26 (32.5)	9 (26.5)	2 (6.1)	10 (23.8)	23 (34.8)	55 (34.2)	133 (38.1)	276 (41.1)	398 (41.2)	611 (47.7)	229 (51.2)	1,772
Klebsiella pneumoniae	2 (2.5)	2 (5.9)	3 (9.1)	6 (14.3)	8 (12.1)	23 (14.3)	75 (21.5)	125 (18.6)	183 (19.0)	187 (14.6)	79 (17.7)	693
Salmonella species	0 (0)	4 (11.8)	6 (18.2)	1 (2.4)	5 (7.6)	5 (3.1)	7 (2.0)	12 (1.8)	11 (1.1)	4 (0.3)	1 (0.2)	56
Pseudomonas aeruginosa	3 (3.8)	2 (5.9)	1 (3.0)	0 (0)	2 (3.0)	5 (3.1)	11 (3.2)	29 (4.3)	35 (3.6)	52 (4.1)	9 (2.0)	149
Acinetobacter baumannii	0 (0)	2 (5.9)	3 (9.1)	2 (4.8)	5 (7.6)	7 (4.3)	23 (6.6)	32 (4.8)	50 (5.2)	65 (5.1)	14 (3.1)	203
Non-*baumannii* *Acinetobacter* species	0 (0)	0 (0)	0 (0)	0 (0)	2 (3.0)	4 (2.5)	2 (0.6)	5 (0.7)	8 (0.8)	9 (0.7)	2 (0.4)	32
Subtotal	31 (38.8)	19 (55.9)	15 (45.5)	19 (45.2)	45 (68.2)	99 (61.5)	251 (71.9)	479 (71.3)	685 (71.0)	928 (72.5)	334 (74.7)	2,905
Total	80	34	33	42	66	161	349	672	965	1,280	447	4,129

5.3. E. faecium

Most (89.6%, 258/288) of the *E. faecium* blood strains were resistant to ampicillin, and resistance to vancomycin (34.0%, 98/288) and teicoplanin (18.8%, 54/288) was more frequently observed in *E. faecium* strains than in *E. faecalis* strains (Fig. 7c). For the three drugs, the resistance rates in HO infections were much higher than those in CO infections: 92.7% vs. 76.8% for ampicillin, 37.9% vs. 17.9% for vancomycin, and 21.1% vs. 8.9% for teicoplanin. Notably, the 54/98 vancomycin-resistant *E. faecium* blood strains were also resistant to teicoplanin, while 25 and 19 were intermediate and susceptible to the drug, though they were all *vanA*-positive. These

findings may be due to the dissemination of clones with *vanA* genotype-VanD phenotypes as a result of the impairment of *vanY* and *vanZ* in the *vanA* operon by the rearrangement of Tn*1546* [21,22]. High-level resistance to gentamicin was observed in 18.1% (52//288) of strains, and that to streptomycin was observed in 1.0% (3/288) of strains. Regarding the recently developed antimicrobial drugs for Gram-positive strains, 8.3%/3.1% and 1.4%/0% of strains were intermediate/resistant to quinupristin-dalfopristin and linezolid, respectively, and 0.3% (1/288) was resistant to tigecycline. More than one-half of *E. faecium* blood strains were MDR (55.9%, 161/288), one-third were DR (40.3%, 116/288), and the remaining were DS (3.8%, 11/288) (Fig. 8). All the vancomycin-resistant
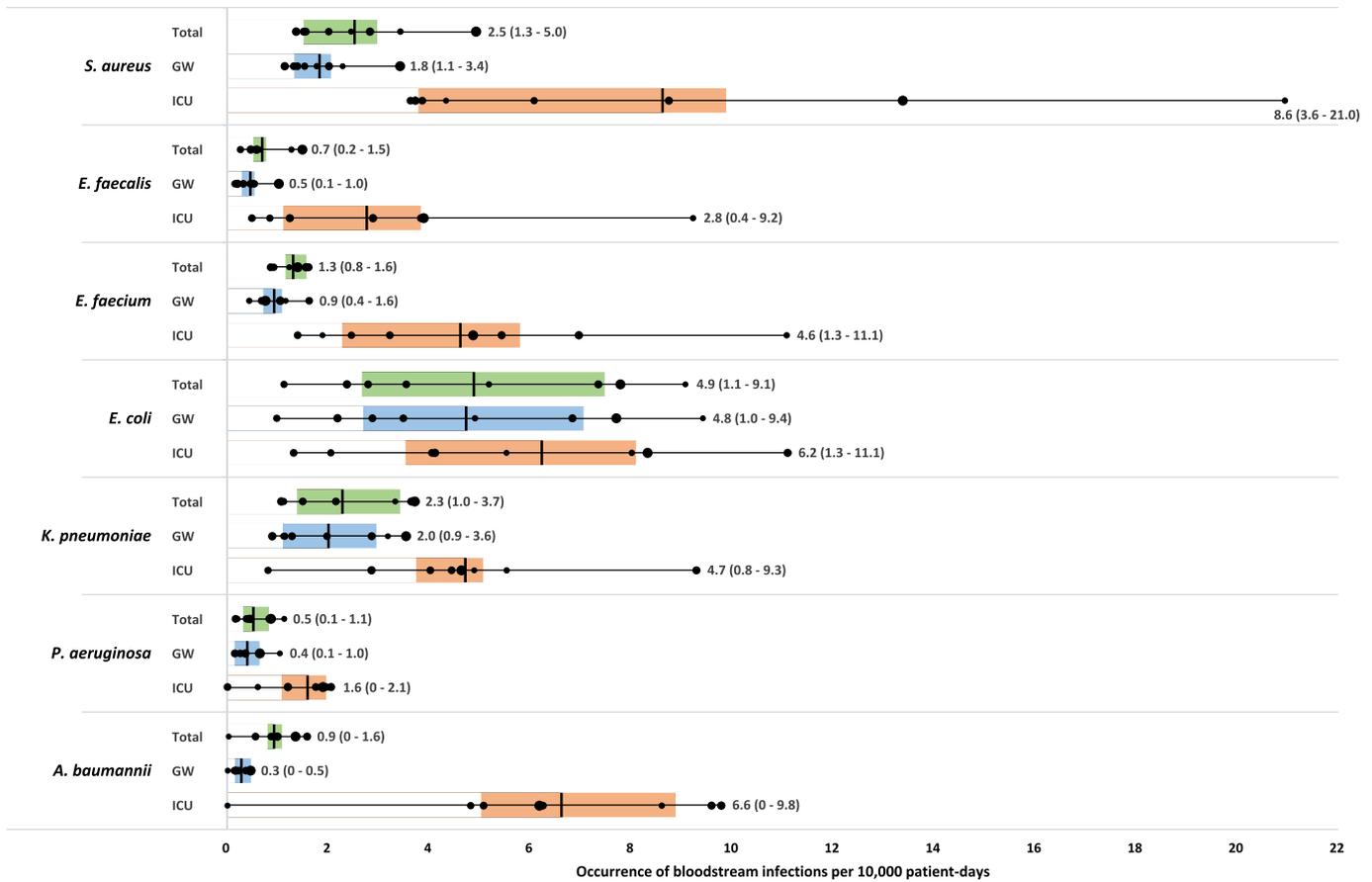
Fig. 6. Occurrence of bacteremia per 10,000 patient-days by target pathogen (total patient days = 2,006,663). Abbreviations: GW, general ward; ICU, intensive care unit. The figure shows the mean occurrence across all eight hospitals, with the lowest and highest indicated by error bars. The color box for each line represents the first to the third quartile, and the size of the dot depends on the number of beds in each sentinel hospital.

E. faecium strains exhibited MDR phenotypes compared to only 33.2% (63/190) of vancomycin-susceptible *E. faecium* strains.

5.4. S. pneumoniae

Most of the *S. pneumoniae* blood strains remained susceptible to penicillin and ceftriaxone with some exceptions: five (9.4%) were resistant and 14 (26.4%) were intermediate to penicillin, and one (1.9%) was resistant and five (9.4%) were intermediate to ceftriaxone (Fig. 7d). Of note, the 19 penicillin-resistant or penicillin-intermediate strains were frequently non-susceptible to other drugs, including amoxicillin-clavulanic acid (intermediate in three and resistant in 10), cefuroxime (resistant in 18), ceftriaxone (intermediate in four and resistant in one), erythromycin (resistant in 19), and trimethoprim-sulfamethoxazole (intermediate in three and resistant in 13). Two strains were resistant to levofloxacin (MIC ≥4 μg/mL). A relatively high rate of erythromycin resistance (77.4%, 41/53) was observed in the strains.

5.5. E. coli

Resistance to ampicillin was frequently observed in *E. coli* blood strains (65.3%, 1157/1772), and the rate decreased to 28.9% (512/1772) with supplementation with the enzyme inhibitor sulbactam (Fig. 7e). The resistance rates to the expanded-spectrum cephalosporins were as follows: 32.4% (574/1772) to cefotaxime, 11.8% (209/1772) to ceftazidime, and 20.3% (360/1772) to cefepime. The difference between the AMR rate to cefotaxime and that to ceftazidime may be the result of the dissemination of CTX-M type extended-spectrum beta-lactamases (ESBLs). With some exceptions such as CTX-M-15, CTX-M-55, and CTX-M-27, CTX-M type ESBLs usually confer resistance to cefotaxime but not to ceftazidime to the bacterial hosts [23]. Resistance to cefoxitin was rarely identified (3.9%, 69/1772). Non-susceptibility to carbapenems was rarely observed: three were resistant to imipenem, three were resistant to meropenem, and two were intermediate and three were resistant to ertapenem. Of these, a strain was identified as a *K. pneumoniae* carbapenemase (KPC) producer that is currently disseminating in South Korea [24,25]. The resistance rate to ciprofloxacin was 35.8% (635/1772), and that to amikacin was low, at 0.8% (14/1772), whereas that to gentamicin was higher at 26.6% (471/1772). Resistance to colistin was rare and was detected only in three strains. HO strains had comparably higher AMR rates to most of the antimicrobials tested than CO strains. More than one-half of the *E. coli* blood strains (58.0%, 1027/1772) exhibited MDR phenotypes, and 17.7% (314/1772) of them exhibited DR phenotypes
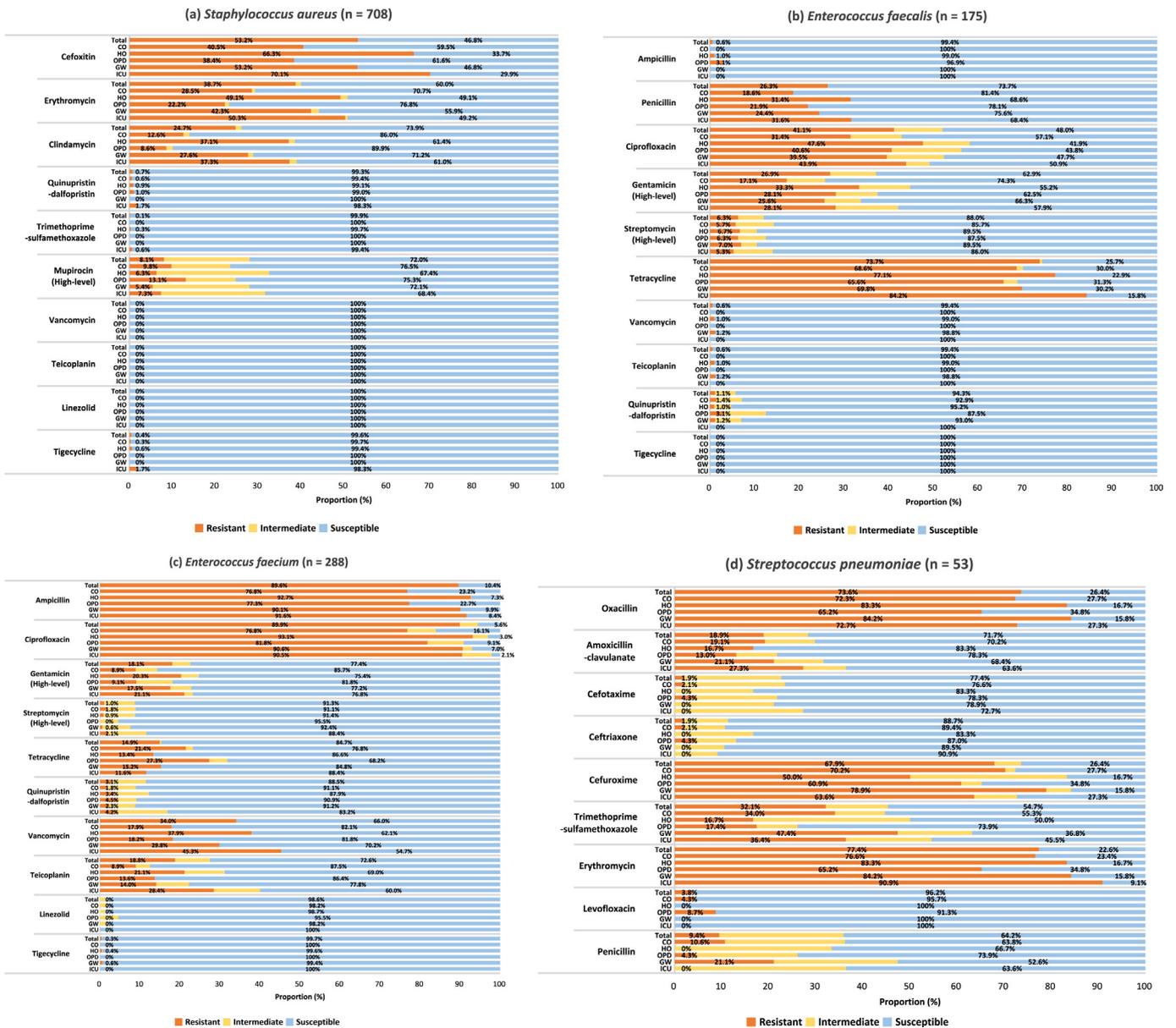
Fig. 7. Percentage of resistance to major antimicrobials of blood isolates by infection origin and by patient admission type. Abbreviations: CO, community origin; GW, general ward; HO, hospital origin; ICU, intensive care unit; OPD, outpatient department.

(Fig. 8). All (100%, 593/593) of the cefotaxime-non-susceptible strains showed MDR phenotypes compared to only 36.8% (434/1179) of the cefotaxime-susceptible strains. No XDR or PDR strains were identified in this study.

5.6. K. pneumoniae

One-third (28.9%, 200/693) of *K. pneumoniae* blood strains were resistant to piperacillin, penicillinase-resistant penicillin, and a quarter (27.0%, 187/693) of the strains were resistant to ampicillin-

sulbactam (Fig. 7f). For the expanded-spectrum cephalosporins, 26.1% (181/693) of strains were resistant to cefotaxime, 21.2% (147/693) to ceftazidime, and 20.6% (143/693) to cefepime. Cefoxitin resistance was observed in 6.3% (44/693) of the strains. Resistance to carbapenems was identified more frequently in *K. pneumoniae* blood strains than in *E. coli* strains: 0.7% (5/693) to imipenem, 0.9% (6/693) to meropenem, and 1.0% (7/693) to ertapenem. Of them, five strains were identified as KPC producers. The resistance rate to ciprofloxacin was 18.9% (131/693), and the rates to amikacin and gentamicin were 2.6% (18/693) and 12.0% (83/693), respectively.
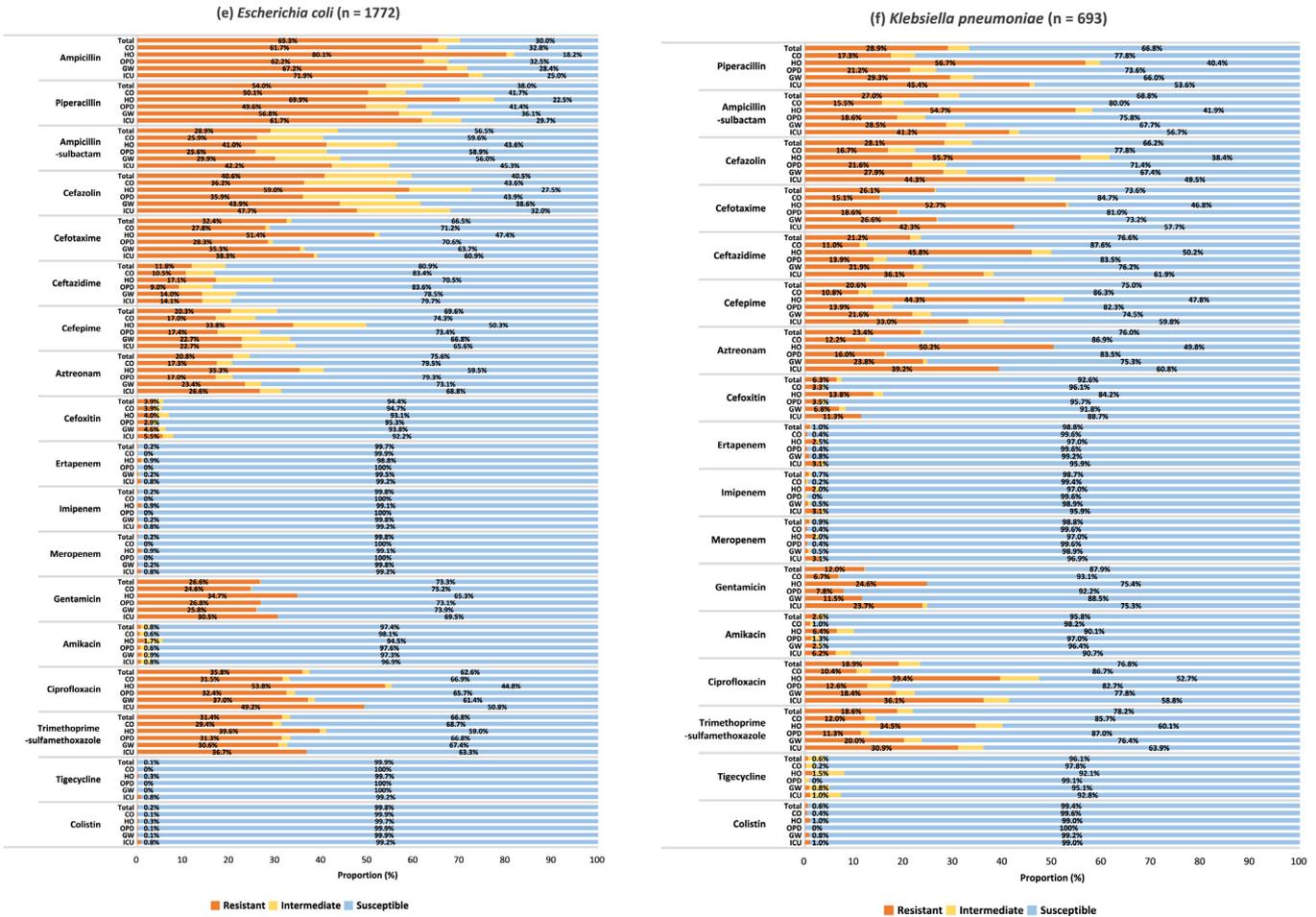
Fig. 7. (continued).

The AMR rates in *K. pneumoniae* of HO were higher than in those of CO. More than one-half of the *K. pneumoniae* strains were classified as DS (60.6%, 420/693), which were all susceptible to cefotaxime (Fig. 8). Cefotaxime-non-susceptible strains belonged to either MDR (94.5%, 173/183) or XDR (3.8%, 7/183) with a few exceptions of DR (1.6%, 3/183).

5.7. Salmonella spp.

Among 56 *Salmonella* blood strains, two (3.6%) were resistant to cefotaxime, and all of them were intermediate or resistant to ceftazidime (Fig. 7g). All the strains remained susceptible to imipenem. Two strains were resistant to ciprofloxacin, and 17.9% (10/56) of strains were intermediate to the drug.

5.8. P. aeruginosa

Non-susceptibility to piperacillin in *P. aeruginosa* blood strains was observed in 30/149 (20.1%) strains [nine (6.0%) intermediate and 21 (14.1%) resistant] (Fig. 7h). The resistance rates to

ceftazidime and cefepime were 14.1% (21/149) and 10.7% (16/149), respectively. The rates of carbapenem resistance were higher than those to expanded-spectrum cephalosporins: 19.5% (29/149) to imipenem and 18.1% (27/149) to meropenem. Additionally, 5.4% (8/149) of strains were resistant to amikacin, 8.7% (13/149) to gentamicin, 6.0% (9/149) to tobramycin, and 15.4% (23/149) to ciprofloxacin. An approximately two-fold higher rate of resistance was observed in strains of HO compared to those of CO. The amikacin-non-susceptible *P. aeruginosa* blood strains mostly belonged to XDR (90.9%, 10/11) with one exception belonging to DR (Fig. 8), while among the imipenem-non-susceptible strains, 42.1% (16/38) were XDR, 13.2% (5/38) were MDR, and 44.7% (17/38) were DR, indicating that amikacin non-susceptibility is the better indicator of XDR *P. aeruginosa* than imipenem-non-susceptibility.

5.9. Acinetobacter spp.

AMR rates in *A. baumannii* blood strains to all the drugs tested were over 70% (Fig. 7i): 93.1% (189/203) to piperacillin, 81.3% (165/203) to ampicillin-sulbactam, 87.7% (178/203) to
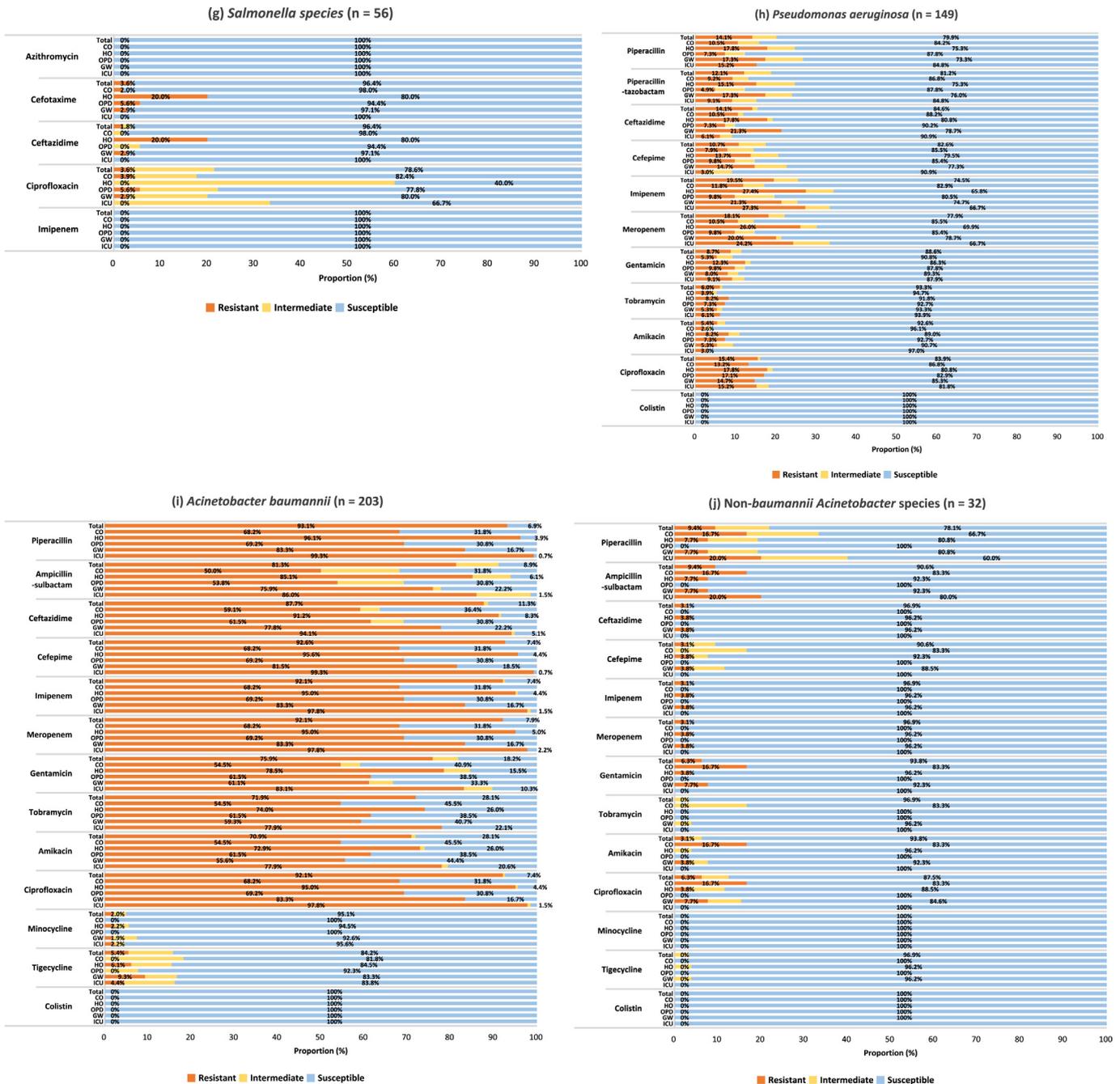
(g) Salmonella species (n = 56)

(h) Pseudomonas aeruginosa (n = 149)

(i) Acinetobacter baumannii (n = 203)

(j) Non-baumannii Acinetobacter species (n = 32)

Fig. 7. (continued).

ceftazidime, 92.6% (188/203) to cefepime, 92.1% (187/203) to both imipenem and meropenem, 75.9% (154/203) to gentamicin, 71.9% (146/203) to tobramycin, 70.9% (144/203) to amikacin, and 92.1% (187/203) to ciprofloxacin. For those drugs, the AMR rates in the strains of HO were approximately two times higher than in those of CO. Two exceptional anti-Acinetobacter drugs, minocycline and tigecycline, were still active in 95.1% (193/203) and 84.2% (171/203) strains, respectively. NBA blood strains exhibited markedly lower rates of AMR than A. baumannii blood

strains (Fig. 7j): 9.4% (3/32) to piperacillin, 9.4% (3/32) to ampicillin-sulbactam, 3.1% (1/32) to ceftazidime, 3.1% (1/32) to cefepime, 3.1% (1/32) to both imipenem and meropenem, 6.3% (2/32) to gentamicin, 3.1% (1/32) to amikacin, and 6.3% (2/32) to ciprofloxacin. None of the strains were resistant to tobramycin, minocycline, tigecycline, or colistin. Among the A. baumannii blood strains, 80.8% (164/203) and 12.3% (25/203) belonged to XDR and MDR, respectively, and all of those, except one MDR strain, were imipenem-non-susceptible (Fig. 8).
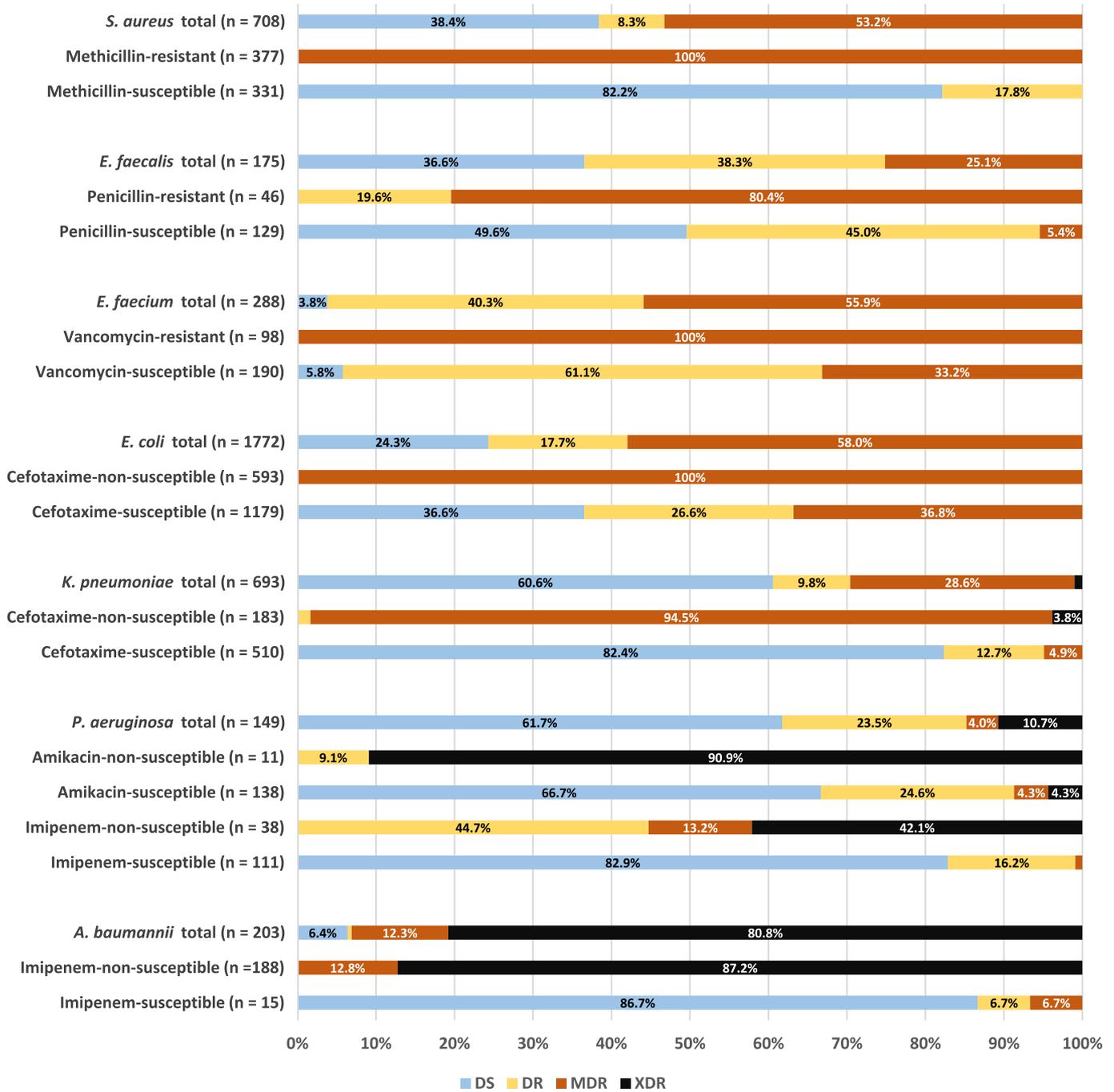
Fig. 8. Categorization of resistance phenotypes by bacterial pathogens. Abbreviations: DS, susceptible to all tested drugs; DR, non-susceptible to one or two antimicrobial classes; MDR, non-susceptible to ≥3 antimicrobial classes; and XDR, susceptible to ≤2 antimicrobial classes.

6. The occurrence of bacteremia caused by major AMR pathogens stratified by patient admission type

The AMR rates of major pathogens stratified by patient admission type were assessed (Fig. 9a). In general, the AMR rates of blood strains from ICU patients were the highest followed by those from GW patients, and those from outpatients were the lowest: MRSA, 70.1% vs. 53.2% vs. 38.4%; penicillin-resistant *E. faecalis*, 31.6% vs. 24.4% vs. 21.9%; vancomycin-resistant *E. faecium*, 45.3% vs. 29.8% vs. 18.2%; cefotaxime-resistant *E. coli*, 38.3% vs. 35.3% vs. 28.3%; cefotaxime-resistant *K. pneumoniae*, 42.3% vs 26.6% vs. 18.6%; meropenem-resistant *P. aeruginosa*, 24.2% vs. 20.0% vs. 9.8%; and meropenem-resistant *A. baumannii*, 97.1% vs. 83.3% vs. 69.2%. The AMR rates of major pathogens were much higher in infections of HO than in infections of CO (Fig. 9b).

a

b
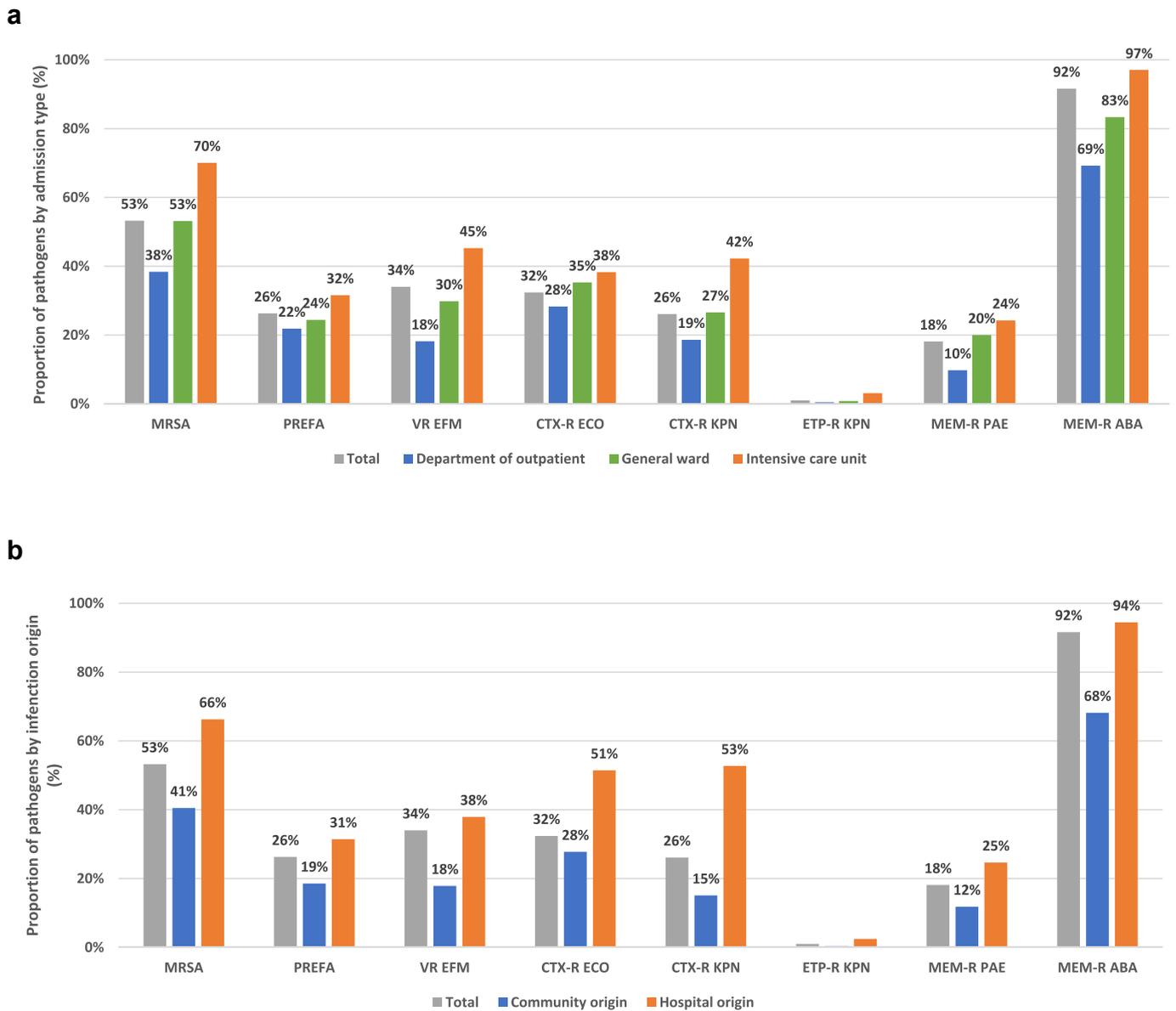
Fig. 9. (a). The prevalence of major AMR pathogens recovered from blood specimens by admission type. Admission types are grouped into outpatients (OPD), inpatients hospitalized in general wards (GW), and those hospitalized in intensive care units (ICU). (b). The prevalence of major AMR pathogens recovered from blood specimens by infection origin. Infection origins are grouped into community origin and hospital origin. Abbreviations: CTX-R ECO, cefotaxime-resistance *Escherichia coli*; CTX-R KPN, cefotaxime-resistant *Klebsiella pneumoniae*; ETP-R KPN, ertapenem-resistance *Klebsiella pneumoniae*; GW, general ward; ICU, intensive care unit; MEM-R ABA, meropenem-resistant *Acinetobacter baumannii*; MEM-R PAE, meropenem-resistant *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*; PREFA, penicillin-resistant *Enterococcus faecalis*; VR EFM, vancomycin-resistant *Enterococcus faecium*.

7. The occurrence of bacteremia caused by major AMR pathogens in inpatients

The occurrence of bacteremia caused by major AMR pathogens in inpatients per 10,000 patient-days was estimated (Fig. 10). The mean value of bacteremia occurrence caused by cefotaxime-resistant *E. coli* was the highest at 1.7 (n = 351, ranged from 0.4 to 3.7 by hospital), followed by 1.5 for MRSA (n = 301, 0.8–2.8), 0.9 for imipenem-resistant *A. baumannii*

(n = 177, 0–1.5), 0.7 for cefotaxime-resistant *K. pneumoniae* (n = 138, 0.4–1.1), 0.5 for vancomycin-resistant *E. faecium* (n = 94, 0.2–0.8), 0.2 for penicillin-resistant *E. faecalis* (n = 39, 0.1–0.3), and 0.1 for meropenem-resistant *P. aeruginosa* (n = 23, 0–0.4). The ratio of bacteremia occurrence in ICU patients to that in GW patients was the highest at 7.5 (0.9 vs. 0.1) for penicillin-resistant *E. faecalis*, followed by 7.4 (2.1 vs. 0.3) for vancomycin-resistant *E. faecium*, 6.2 (6.1 vs. 1.0) for MRSA, 4.7 (0.4 vs. 0.1) for meropenem-resistant *P. aeruginosa*, 3.7 (2.0 vs.
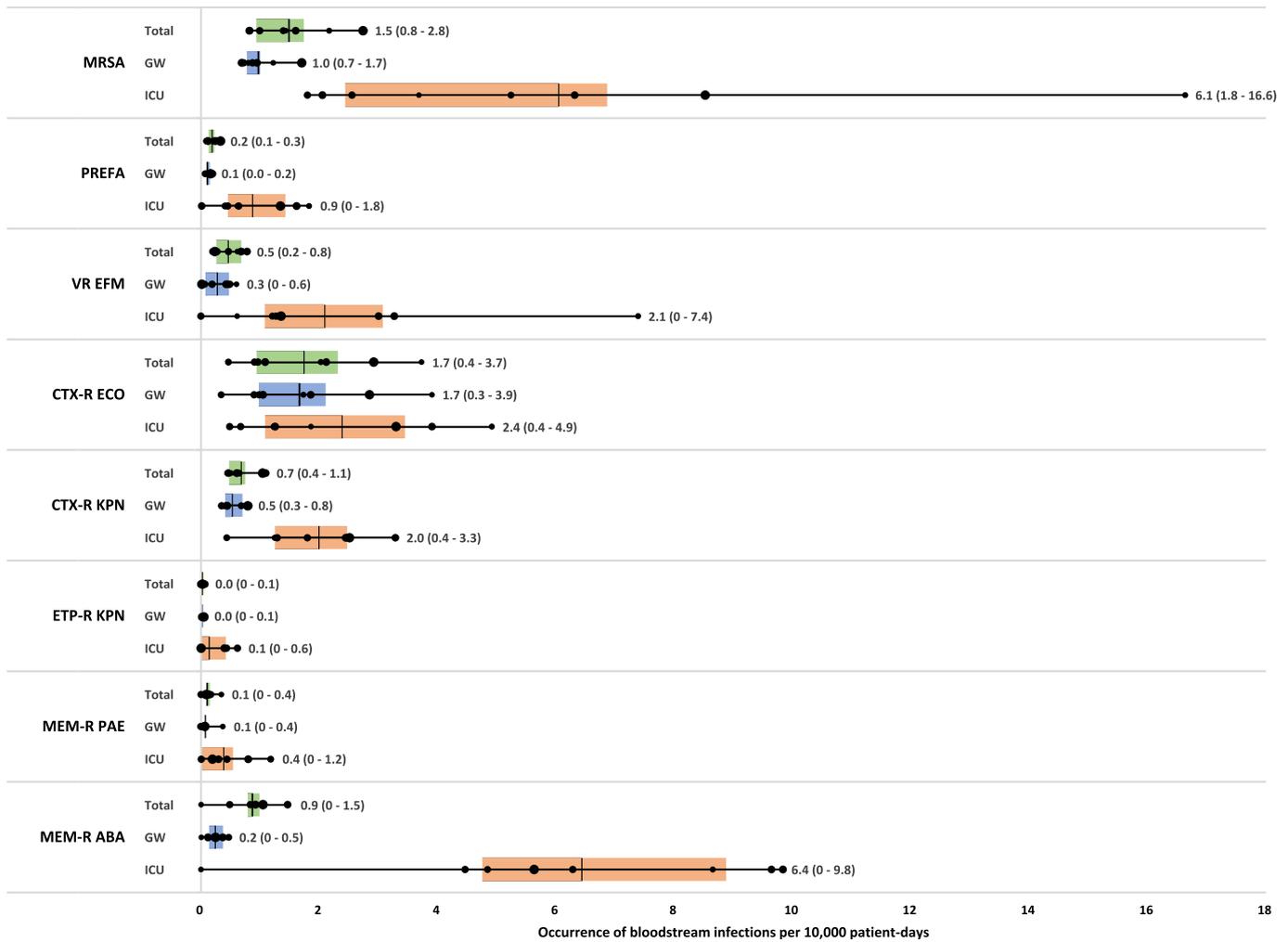
Fig. 10. Occurrence of bacteremia per 10,000 patient-days caused by major antimicrobial-resistant pathogens (total patient days = 2,006,663). Abbreviations: CTX-R ECO, cefotaxime-resistance *Escherichia coli*; CTX-R KPN, cefotaxime-resistant *Klebsiella pneumoniae*; ETP-R KPN, ertapenem-resistance *Klebsiella pneumoniae*; GW, general ward; ICU, intensive care unit; MEM-R ABA, meropenem-resistant *Acinetobacter baumannii*; MEM-R PAE, meropenem-resistant *Pseudomonas aeruginosa*; MRSA, methicillin-resistant *Staphylococcus aureus*; PREFA, penicillin-resistant *Enterococcus faecalis*; VR EFM, vancomycin-resistant *Enterococcus faecium*. The figure shows the mean occurrence across all eight hospitals, with the lowest and highest values indicated by error bars. The color box for each line represents the first to the third quartile, and the size of the dot depends on the number of beds in each sentinel hospital.

0.5) for cefotaxime-resistant *K. pneumoniae*, and the lowest, 1.4 (2.4 vs. 1.7), for cefotaxime-resistant *E. coli*.

8. Conclusion

Through the pilot phase of Kor-GLASS, we established a reliable system of AMR surveillance, which includes i) the entire process of AMR surveillance from collecting the isolates to reporting the results, ii) a web-based data-managing system for registering the clinical data by the sentinel hospitals, filing of laboratory data by the analysis center, and recording of the quality control assessment results by the quality control center, and iii) secure quality control of the AST results in charge of the quality control center. Setting the phase as the starting point, we were able to assess the first year of phase I of the Kor-GLASS study, and our data indicated an actual AMR status in South Korea. Former KARMS data of overestimated AMR due to the duplicate isolation of drug-resistant pathogens were all corrected, and comparing the error-free AMR data with those of other countries were made. The higher incidence of bacteremia caused by major AMR pathogens among inpatients specifically hospitalized in ICUs distressed the importance of infection control in hospitals and the needs of amelioration of the crowded hospitalization system in South Korea. The isolation rate of the *Salmonella* spp. is decreasing, reflecting the current socio-economic status of South Korea. The proportions of bacterial species in the blood isolates were similar to those in other Asian countries with similar lifestyles.

Ethical statement

The research, which did not involve human subjects but did use clinical isolates, qualified as an exempt category not needing approval from the Ethics Committee on Human Research of the Health Ministry in South Korea, and the study design was not reviewed by the committee.

Funding

Conflicts of interest

None.

Authors' contributions

SHJ: conceived the surveillance project; EJY, DK, and SHJ: operated the surveillance system; CL, EJY, DK, and SHJ: analyzed the data; CL, E-JY, and SHJ: wrote the manuscript; JHS, SHK, JHS, KSS, YAK, YU, HSK, and YRK: were responsible for collecting the bacterial strains and clinical data.

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