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Surveillance

Nationwide surveillance of bacterial respiratory pathogens conducted by the surveillance committee of Japanese Society of Chemotherapy, the Japanese Association for Infectious Diseases, and the Japanese Society for clinical microbiology in 2014: General view of the pathogens' antibacterial susceptibility[☆]

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ABSTRACT

The nationwide surveillance on antimicrobial susceptibility of bacterial respiratory pathogens from the patients in Japan was conducted by Japanese Society of Chemotherapy, the Japanese Association for Infectious Diseases, and the Japanese Society for Clinical Microbiology in 2014.

The isolates were collected from clinical specimens obtained from well-diagnosed adult patients with respiratory tract infections during the period between January 2014 and April 2015 by three societies. Antimicrobial susceptibility testing was conducted at the central reference laboratory according to the method recommended by Clinical Laboratory Standards Institute.

Susceptibility testing was evaluated in 1534 strains (335 *Staphylococcus aureus*, 264 *Streptococcus* pneumoniae, 29 *Streptococcus pyogenes*, 281 *Haemophilus influenzae*, 164 *Moraxella catarrhalis*, 207 *Klebsiella pneumoniae*, and 254 *Pseudomonas aeruginosa*). Ratio of methicillin-resistant *S. aureus* was 43.6%, and those of penicillin-susceptible *S. pneumoniae* was 100%. Among *H. influenzae*, 8.2% of them were found to be β-lactamase-producing ampicillin-resistant strains, and 49.1% to be β-lactamase-non-producing ampicillin-resistant strains. Extended spectrum β-lactamase-producing *K. pneumoniae* and multi-drug resistant *P. aeruginosa* with metallo β-lactamase were 9.2% and 0.4%, respectively.

1. Introduction

Since the Japanese Society of Chemotherapy (JSC) established a nationwide surveillance network for bacterial respiratory pathogens in 2006 [1], the surveillance has provided the trend of antimicrobial susceptibilities of major pathogens in respiratory tract infections (RTIs). After 2009, this investigation is conducted as the joint surveillance by three societies; JSC, the Japanese Association for Infectious Diseases and the Japanese Society for Clinical Microbiology.

Because antimicrobial resistant pathogens are emerging for human health, the comprehensive data obtained from this surveillance can enrich the epidemiological knowledge about drug resistant bacteria as well as enhance the antimicrobial stewardship. Here, we report the seventh surveillance on antimicrobial susceptibilities of RTI pathogens.

2. Materials and methods

2.1. Collecting isolates and basic backgrounds

The bacteria isolated from the patients with RTI were collected between January 2014 and April 2015. The specimens were sputum or respiratory samples obtained by transtracheal aspiration or bronchoscopy. The subjects were *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. These isolates were judged as causative pathogens by physicians.

The isolates which were identified as the subjective bacteria in each clinical microbiology laboratory were suspended in Microbank tube (Asuka Junyaku Co.Ltd. Tokyo), stored in the freezer, and transferred to the central laboratory, Infection Control Research Center, Kitasato University (Tokyo, Japan).

The brief information about the patients including the settings, age, sex, respiratory diseases, the name of facility, and the name of the original specimens, were obtained. Ethics approval was the responsibility of each facility. The electronic uniform data sheets of each patient were also completed at each institution and sent to the reference center so that microbiological data obtained were able to be stratified under the settings and profiles of patients and under the diagnoses.

2.2. Antibacterial agents

The susceptibilities of the bacterial strains were tested for the following 46 antimicrobial agents; four penicillins such as benzylpenicillin (PCG), oxacillin (MPIPC), ampicillin (ABPC) and piperacillin (PIPC); three penicillins in combination with β-lactamase inhibitors such as clavulanic acid-amoxicillin (CVA/AMPC), sulbactam-ABPC (SBT/ABPC) and tazobactam-PIPC (TAZ/PIPC); four oral cephems such as cefaclor (CCL), cefdinir (CFDN), cefcapene (CFPN), and cefditoren (CDTR); eight parenteral cephems such as cefazolin (CEZ), cefoxitin (CFX), cefmetazole (CMZ), cefotiam (CTM), ceftazidime (CAZ), ceftriaxone (CTRX), cefepime (CFPM) and cefozopran (CZOP); one monobactam such as aztreonam (AZT); five carbapenems such as imipenem (IPM), panipenem (PAPM), meropenem (MEPM), biapenem (BIPM) and doripenem (DRPM); one penem such as faropenem (FRPM); four aminoglycosides such as gentamicin (GM), tobramycin (TOB), amikacin (AMK) and arbekacin (ABK); three macrolides such as erythromycin (EM), clarithromycin (CAM) and azithromycin (AZM); one lincosamide such as clindamycin (CLDM); a tetracycline minocycline (MINO); two glycopeptides such as vancomycin (VCM) and teicoplanin (TEIC); seven

Table 1
Antibacterial susceptibility of *Staphylococcus aureus*.

Antibacterial agent	All Strains, n = 335					
	MIC(μg/mL)			%		
	50%	90%	range	Susceptible	Intermediate	Resistant
PCG	4	16	≦0.06–64	25.1	–	74.9
MPIPC	0.5	≧256	0.125–≧256	56.4	–	43.6
ABPC	2	32	0.125–64	–	–	–
SBT/ABPC	2	16	0.125–32	–	–	–
CVA/AMPC	1	32	0.125–64	–	–	–
PIPC	4	128	0.5–≧256	–	–	–
TAZ/PIPC-1	4	128	0.5–≧256	–	–	–
TAZ/PIPC-2	2	128	0.25–≧256	–	–	–
CCL	2	128	0.5–≧256	–	–	–
CFDN	0.5	≧128	0.125–≧128	–	–	–
CFPN	1	≧256	0.5–≧256	–	–	–
CDTR	1	64	0.5–≧128	–	–	–
CEZ	0.5	≧256	0.25–≧256	–	–	–
CFX	4	≧128	1–≧128	56.1	–	43.9
CMZ	2	32	0.5–128	–	–	–
CTM	1	128	0.25–≧256	–	–	–
CAZ	16	≧128	4–≧128	–	–	–
CTRX	4	≧256	2–≧256	–	–	–
CFPM	4	128	1–≧256	–	–	–
CZOP	1	32	0.5–128	–	–	–
IPM	≦0.06	32	≦0.06–≧128	–	–	–
PAPM	≦0.06	16	≦0.06–128	–	–	–
MEPM	0.125	16	≦0.06–64	–	–	–
BIPM	0.125	16	≦0.06–64	–	–	–
DRPM	≦0.06	8	≦0.06–32	–	–	–
FRPM	0.25	≧256	≦0.06–≧256	–	–	–
GM	0.25	64	0.125–≧256	62.7	3.9	33.4
TOB	1	≧256	0.25–≧256	55.5	6	38.5
AMK	2	16	1–64	97	2.7	0.3
ABK	0.5	1	0.125–4	–	–	–
EM	≧256	≧256	0.25–≧256	45.1	1.5	53.4
CAM	≧128	≧128	0.125–≧128	46.6	0.3	53.1
AZM	≧256	≧256	0.125–≧256	45.7	0.6	53.7
CPFX	1	≧256	0.125–≧256	52.5	0.9	46.6
LVFX	0.5	≧256	≦0.06–≧256	53.7	2.1	44.2
TFLX	≦0.06	≧32	≦0.06–≧32	–	–	–
MFLX	0.125	32	≦0.06–128	54.9	5.1	40
PZFX	0.25	≧256	≦0.06–≧256	–	–	–
GRNX	≦0.06	32	≦0.06–≧256	–	–	–
STFX	≦0.06	4	≦0.06–32	–	–	–
MINO	0.125	16	≦0.06–32	75.5	4.5	20
CLDM	0.25	≧256	0.125–≧256	69.3	0.3	30.4
VCM	1	1	0.5–2	100	0	0
TEIC	0.5	1	0.25–8	100	0	0
LZD	2	2	1–4	100	–	0

The susceptibility of 45 antimicrobial agents against 335 strains of S.aureus was determined. PCG benzylpenicillin, MPIPC oxacillin, ABPC ampicillin, SBT/ABPC sulbactam - ABPC, CVA/AMPC clavulanic acid - amoxicillin, PIPC piperacillin, TAZ/PIPC-1 tazobactam – PIPC (tazobactam: PIPC = 1: 8), TAZ/PIPC-2 (tazobactam = 4 μg/mL), CCL cefaclor, CFDN cefdinir, CFPN cefcapene, CDTR cefditoren, CEZ cefazolin, CFX cefoxitin, CMZ cefmetazole, CTM cefotiam, CAZ ceftazidime, CTRX ceftriaxone, CFPM cefepime, CZOP cefozopran,IPM imipenem, PAPM panipenem, MEPM meropenem, BIPM biapenem, DRPM doripenem, FRPM faropenem, GM gentamicin, TOB tobramycin, AMK amikacin, ABK arbekacin, EM erythromycin, CAM clarithromycin, AZM azithromycin, CLDM clindamycin, MINO minocycline, VCM vancomycin, TEIC teicoplanin, CPFX ciprofloxacin, LVFX levofloxacin, TFLX tosufloxacin, MFLX moxifloxacin, PZFX pazufloxacin, GRNX garenoxacin, STFX sitafloxacin, LZD linezolid. -, not applicable.

fluoroquinolones such as ciprofloxacin (CPFX), levofloxacin (LVFX), tosufloxacin (TFLX), moxifloxacin (MFLX), pazufloxacin (PZFX), garenoxacin (GRNX), and sitafloxacin (STFX); one oxazolidinone such as linezolid (LZD) and one glycylcycline such as tigecycline (TGC). The stability of the antimicrobial agent-containing microplates was guaranteed by the manufacturer (Eiken Chemical Co., Ltd., Tokyo, Japan) for 9 months.

2.3. Susceptibility testing and detection of β-lactamase

Susceptibility testing was performed with Eiken dry plates (Eiken Chemical Co., Ltd. Tokyo, Japan) [2]. Breakpoints were judged according to the CLSI document M100-S26 criteria [3]. Tested ranges were 0.06–256 μg/mL, except for CFDN, CDTR, CAM, and AZM (0.06–32 μg/mL), and TFLX (0.06–128 μg/mL).

To detect β-lactamase-producing *H. influenzae* strains, tests with Nitrocefin disks (BD BBL™, Tokyo) were conducted according to the manufacturer's manual. Extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae* strains were detected by using the Cica-Beta Test® (Kanto Chemical Co, Inc., Tokyo), or two-step process; screening by CAZ, AZT, CTX, CTRX, and CPDX (MIC of CPDX, ≥4 μg/mL or MIC of the others, ≥1 μg/mL) and confirmation by CVA inhibition. Metallo-β-lactamase (MBL) were detected by using Cica-Beta Test® and sodium mercaptoacetic acid (SMA) disk.

Table 2
Antibacterial susceptibility of *Staphylococcus aureus* (MRSA and MSSA).

Antibacterial agent	MRSA (MPIPC≧4 μg/mL or mecA-positive), n = 147						MSSA (MPIPC≦2 μg/mL), n = 188					
	MIC (μg/mL)			%			MIC (μg/mL)			%		
	50%	90%	range	Susceptible	Intermediate	Resistant	50%	90%	range	Susceptible	Intermediate	Resistant
PCG	16	32	0.5–64	0	–	100	0.25	8	≦0.06–16	44.7	–	55.3
MPIPC	128	≧256	2–≧256	0.7	–	99.3	0.25	0.5	0.125–2	100	–	0
ABPC	16	32	2–64	–	–	–	0.5	4	0.125–16	–	–	–
SBT/ABPC	16	32	2–32	–	–	–	0.25	2	0.125–2	–	–	–
CVA/AMPC	16	32	1–64	–	–	–	0.5	1	0.125–4	–	–	–
PIPC	64	≧256	4–≧256	–	–	–	1	8	0.5–32	–	–	–
TAZ/PIPC-1	64	128	4–≧256	–	–	–	1	4	0.5–8	–	–	–
TAZ/PIPC-2	64	128	2–≧256	–	–	–	1	2	0.25–2	–	–	–
CCL	64	128	2–≧256	–	–	–	1	2	0.5–2	–	–	–
CFDN	32	≧128	0.5–≧128	–	–	–	0.25	0.5	0.125–2	–	–	–
CFPN	≧256	≧256	1–≧256	–	–	–	1	1	0.5–2	–	–	–
CDTR	64	≧128	1–≧128	–	–	–	0.5	1	0.5–2	–	–	–
CEZ	128	≧256	0.5–≧256	–	–	–	0.5	0.5	0.25–1	–	–	–
CFX	64	≧128	8–≧128	0	–	100	2	4	1–4	100	–	0
CMZ	16	64	2–128	–	–	–	1	2	0.5–2	–	–	–
CTM	64	≧256	1–≧256	–	–	–	0.5	1	0.25–2	–	–	–
CAZ	≧128	≧128	8–≧128	–	–	–	8	16	4–32	–	–	–
CTRX	≧256	≧256	8–≧256	–	–	–	4	4	2–4	–	–	–
CFPM	128	≧256	4–≧256	–	–	–	2	4	1–4	–	–	–
CZOP	16	64	1–128	–	–	–	1	1	0.5–2	–	–	–
IPM	4	64	≦0.06–≧128	–	–	–	≦0.06	≦0.06	≦0.06–0.125	–	–	–
PAPM	4	64	≦0.06–128	–	–	–	≦0.06	≦0.06	≦0.06–0.25	–	–	–
MEPM	8	32	0.25–64	–	–	–	0.125	0.125	≦0.06–0.25	–	–	–
BIPM	8	32	0.125–64	–	–	–	≦0.06	0.125	≦0.06–0.125	–	–	–
DRPM	4	16	0.125–32	–	–	–	≦0.06	≦0.06	≦0.06–0.125	–	–	–
FRPM	8	≧256	0.125–≧256	–	–	–	0.125	0.25	≦0.06–0.25	–	–	–
GM	16	64	0.125–≧256	42.2	4.7	53.1	0.25	32	0.125–128	78.7	3.2	18.1
TOB	32	≧256	0.25–≧256	26.5	4.8	68.7	0.5	16	0.25–64	78.2	6.9	14.9
AMK	4	16	1–64	93.2	6.1	0.7	2	4	1–16	100	0	0
ABK	0.5	1	0.125–4	–	–	–	0.5	1	0.25–2	–	–	–
EM	≧256	≧256	0.5–≧256	8.8	0	91.2	0.5	≧256	0.25–≧256	73.4	2.7	23.9
CAM	≧128	≧128	0.125–≧128	8.8	0	91.2	0.25	≧128	0.125–≧128	76.1	0.5	23.4
AZM	≧256	≧256	0.5–≧256	8.8	0	91.2	1	≧256	0.125–≧256	74.5	1	24.5
CPFX	128	≧256	0.25–≧256	10.2	0	89.8	0.5	4	0.125–128	85.6	1.6	12.8
LVFX	16	≧256	0.125–≧256	10.2	2	87.8	0.25	4	≦0.06–≧256	87.8	2.1	10.1
TFLX	≧32	≧32	≦0.06–≧32	–	–	–	≦0.06	2	≦0.06–≧32	–	–	–
MFLX	4	32	≦0.06–128	11.6	8.1	80.3	≦0.06	1	≦0.06–64	88.8	2.7	8.5
PZFX	8	≧256	0.125–≧256	–	–	–	0.25	4	≦0.06–≧256	–	–	–
GRNX	4	64	≦0.06–≧256	–	–	–	≦0.06	0.5	≦0.06–32	–	–	–
STFX	1	8	≦0.06–32	–	–	–	≦0.06	0.125	≦0.06–8	–	–	–
MINO	8	16	≦0.06–32	45.6	10.2	44.2	0.125	0.125	≦0.06–16	98.9	0	1.1
CLDM	≧256	≧256	0.125–≧256	34	0.7	65.3	0.25	0.25	0.125–≧256	96.8	0	3.2
VCM	1	1	0.5–2	100	0	0	1	1	0.5–2	100	0	0
TEIC	0.5	1	0.25–2	100	0	0	0.5	1	0.25–8	100	0	0
LZD	2	2	1–4	100	–	0	2	2	1–4	100	–	0

The susceptibility of 45 antimicrobial agents against 147 strains of MRSA and 188 strains of MSSA was determined. PCG benzylpenicillin, MPIPC oxacillin, ABPC ampicillin, SBT/ABPC sulbactam - ABPC, CVA/AMPC clavulanic acid - amoxicillin, PIPC piperacillin, TAZ/PIPC-1 tazobactam – PIPC (tazobactam: PIPC = 1: 8), TAZ/PIPC-2 (tazobactam = 4 μg/mL), CCL cefaclor, CFDN cefdinir, CFPN cefcapene, CDTR cefditoren, CEZ cefazolin, CFX cefoxitin, CMZ cefmetazole, CTM cefotiam, CAZ ceftazidime, CTRX ceftriaxone, CFPM cefepime, CZOP cefozopran,IPM imipenem, PAPM panipenem, MEPM meropenem, BIPM biapenem, DRPM doripenem, FRPM faropenem, GM gentamicin, TOB tobramycin, AMK amikacin, ABK arbekacin, EM erythromycin, CAM clarithromycin, AZM azithromycin, CLDM clindamycin, MINO minocycline, VCM vancomycin, TEIC teicoplanin, CPFX ciprofloxacin, LVFX levofloxacin, TFLX tosufloxacin, MFLX moxifloxacin, PZFX pazufloxacin, GRNX garenoxacin, STFX sitafloxacin, LZD linezolid. -, not applicable.

For the *S. aureus* strains with MIC of CFX ≥8 μg/mL, *mecA* gene was additionally screened by PCR [4] and the *mecA*-positive strains were considered as MRSA.

2.4. Quality control

All the collected isolates were re-cultured and reidentified in the central laboratory with matrix-assisted laser desorption ionization-time of flight mass spectrometry and phenotypic methods [5].

Accuracy of determination for minimum inhibitory concentration (MIC) of antibacterial agents was controlled according to the recommendations of CLSI using the following quality control strains: *S. aureus* ATCC29213 *S. pneumoniae* ATCC49619, *H. influenzae* ATCC49247, *H. influenzae* ATCC49766, *Escherichia coli* ATCC25922, and *P. aeruginosa* ATCC27853. For quality control of evaluation of β-lactamase inhibitors, *E. coli* ATCC 35218 was used. All results of the quality control were ensured throughout the study.

3. Results

3.1. The collected data of the surveillance

Forty-two medical institutions contributed to the surveillance. A total of 1619 isolates were received at the reference center and 1534 strains were successfully re-cultured and identified as the species which were objective pathogens in this surveillance. There were no error in quality control.

3.2. Staphylococcus aureus

Of the 335 *S. aureus* strains, 43.9% were methicillin-resistant *S. aureus* (MRSA; strain with MIC of MPIPC ≥4 μg/mL, or *mecA*-positive strain with MIC of CFX ≥8 μg/mL; Tables 1 and 2). Among the MRSA strains, the MIC_{90}s of ABK, VCM, TEIC, and LZD were 1, 1, 1, and 2 μg/mL, respectively. MRSA strains were partially susceptible

Table 3
Antibacterial susceptibility of *Streptococcus pneumoniae*.

Antibacterial agent	n = 264 [PSSP, n = 264 and PISP, n = 0]					
	MIC (μg/mL)			%		
	50%	90%	range	Susceptible	Intermediate	Resistant
PCG	≦0.06	1	≦0.06–2	100	0	0
ABPC	≦0.06	2	≦0.06–8	–	–	–
SBT/ABPC	≦0.06	2	≦0.06–8	–	–	–
CVA/AMPC	≦0.06	1	≦0.06–4	99.6	0.4	0
PIPC	≦0.06	2	≦0.06–4	–	–	–
TAZ/PIPC-1	≦0.06	2	≦0.06–4	–	–	–
TAZ/PIPC-2	≦0.06	2	≦0.06–4	–	–	–
CCL	1	32	0.125–128	56.1	7.2	36.7
CFDN	0.25	2	≦0.06–8	68.6	12.5	18.9
CFPN	0.25	0.5	≦0.06–2	–	–	–
CDTR	0.125	0.5	≦0.06–1	–	–	–
CEZ	0.125	2	≦0.06–8	–	–	–
CMZ	0.5	8	≦0.06–32	–	–	–
CTM	0.25	2	≦0.06–8	–	–	–
CAZ	4	8	≦0.06–32	–	–	–
CTRX	0.25	1	≦0.06–2	99.6	0.4	0
CFPM	0.5	1	≦0.06–2	97.7	2.3	0
CZOP	0.25	1	≦0.06–2	–	–	–
IPM	≦0.06	0.125	≦0.06–1	90.9	8.7	0.4
PAPM	≦0.06	≦0.06	≦0.06–0.5	–	–	–
MEPM	≦0.06	0.25	≦0.06–0.5	92.4	7.6	0
BIPM	≦0.06	0.25	≦0.06–1	–	–	–
DRPM	≦0.06	0.25	≦0.06–1	100	–	0
FRPM	≦0.06	0.25	≦0.06–1	–	–	–
GM	4	8	0.5–16	–	–	–
TOB	8	16	1–32	–	–	–
AMK	32	64	4–128	–	–	–
ABK	16	32	1–64	–	–	–
EM	≧256	≧256	≦0.06–≧256	7.6	1.9	90.5
CAM	≧128	≧128	≦0.06–≧128	9.1	4.5	86.4
AZM	≧256	≧256	≦0.06–≧256	9.8	6.9	83.3
CPFX	1	2	≦0.06–32	–	–	–
LVFX	1	1	0.5–16	97.7	0	2.3
TFLX	0.25	0.25	≦0.06–≧32	–	–	–
MFLX	0.25	0.5	0.125–4	98.1	0.4	1.5
PZFX	2	4	1–64	–	–	–
GRNX	≦0.06	≦0.06	≦0.06–1	–	–	–
STFX	≦0.06	≦0.06	≦0.06–0.5	–	–	–
MINO	8	16	≦0.06–32	–	–	–
CLDM	128	≧256	≦0.06–≧256	33.3	1.5	65.2
VCM	0.25	0.25	≦0.06–0.5	100	–	0
TEIC	0.125	0.125	≦0.06–0.25	–	–	–
LZD	0.5	1	≦0.06–2	100	–	0

The susceptibility of 43 antimicrobial agents against 264 strains of S. pneumoniae was determined. PCG benzylpenicillin, ABPC ampicillin, SBT/ABPC sulbactam - ABPC, CVA/AMPC clavulanic acid - amoxicillin, PIPC piperacillin, TAZ/PIPC-1 tazobactam – PIPC (tazobactam: PIPC = 1: 8), TAZ/PIPC-2 (tazobactam = 4 μg/mL), CCL cefaclor, CFDN cefdinir, CFPN cefcapene, CDTR cefditoren, CEZ cefazolin, CMZ cefmetazole, CTM cefotiam, CAZ ceftazidime, CTRX ceftriaxone, CFPM cefepime, CZOP cefozopran, IPM imipenem, PAPM panipenem, MEPM meropenem, BIPM biapenem, DRPM doripenem, FRPM faropenem, GM gentamicin, TOB tobramycin, AMK amikacin, ABK arbekacin, EM erythromycin, CAM clarithromycin, AZM azithromycin, CLDM clindamycin, MINO minocycline, VCM vancomycin, TEIC teicoplanin, CPFX ciprofloxacin, LVFX levofloxacin, TFLX tosufloxacin, MFLX moxifloxacin, PZFX pazufloxacin, GRNX garenoxacin, STFX sitafloxacin, LZD linezolid. -, not applicable.

to macrolides (8.8%), fluoroquinolones (10.2–11.6%), MINO (45.6%), CLDM (34%), and aminoglycosides except for ABK (26.5–93.2%).

Among the MSSA strains, for β-lactams, MICs to penicillins and cephems were ≤4 μg/mL, except for PCG, ABPC, PIPC, and CAZ. MICs to carbapenems were ≤0.125 μg/mL. The susceptibilities of aminoglycosides, macrolides and fluoroquinolones were 73.4–100% and those of MINO, CLDM, VCM, TEIC, and LZD were 96.8–100%.

3.3. *Streptococcus pneumoniae*

There were 264 *S. pneumoniae* strains (Table 3). All of strains were susceptible to PCG; therefore, penicillin-susceptible (PSSP), penicillin-intermediate (PISP), and penicillin-resistant strains (PRSP) were 100, 0, and 0%, respectively.

Among the β-lactams, MIC_{90}s of penicillins and cephems except for CCL, CMZ and CAZ revealed 0.5–2 μg/mL and those of carbapenems were ≤0.25 μg/mL. MIC_{90}s of fluoroquinolones were ≤0.06–4 μg/mL and MICs of GRNX and STFX against all the strains were ≤1 μg/mL. MIC_{90}s of VCM, TEIC and LZD were ≤0.25, ≤0.25 and ≤ 1 μg/mL, respectively. Aminoglycosides showed relatively high MIC_{90}s (8–64 μg/mL), and resistant strains against macrolides and CLDM were commonly observed (MIC_{90}s, ≥128 μg/mL).

3.4. *Streptococcus pyogenes*

About the 29 *S. pyogenes* strains (Table 4), MIC_{90}s of β-lactams were ≤0.5 μg/mL. MIC_{90}s of VCM, TEIC and LZD were 0.5, 0.125, and 2 μg/mL, respectively. Relatively high MIC_{90}s were observed in aminoglycosides (MIC_{90}s, 4–64 μg/mL) and macrolides (MIC_{90}s, ≥128 μg/mL). Among fluoroquinolones, various MIC_{90}s were observed; MIC_{90}s of MFLX, GRNX, and STFX were ≤0.5 μg/mL whereas those of CPFX and PZFX were 4 μg/mL.

Table 4
Antibacterial susceptibility of Streptococcus pyogenes.

Antibacterial agent	n = 29					
	MIC (μg/mL)			%		
	50%	90%	range	Susceptible	Intermediate	Resistant
PCG	≦0.06	≦0.06	≦0.06	100	–	0
ABPC	≦0.06	≦0.06	≦0.06–0.125	100	–	0
SBT/ABPC	≦0.06	≦0.06	≦0.06	–	–	–
CVA/AMPC	≦0.06	≦0.06	≦0.06	–	–	–
PIPC	≦0.06	≦0.06	≦0.06	–	–	–
TAZ/PIPC-1	≦0.06	≦0.06	≦0.06	–	–	–
TAZ/PIPC-2	≦0.06	≦0.06	≦0.06	–	–	–
CCL	≦0.06	0.125	≦0.06–0.125	–	–	–
CFDN	≦0.06	≦0.06	≦0.06	–	–	–
CFPN	≦0.06	≦0.06	≦0.06	–	–	–
CDTR	≦0.06	≦0.06	≦0.06	–	–	–
CEZ	0.125	0.125	≦0.06–0.125	–	–	–
CMZ	0.5	0.5	0.125–1	–	–	–
CTM	≦0.06	≦0.06	≦0.06	–	–	–
CAZ	≦0.06	0.125	≦0.06–0.125	–	–	–
CTRX	≦0.06	≦0.06	≦0.06	100	–	0
CFPM	≦0.06	≦0.06	≦0.06–0.125	100	–	0
CZOP	≦0.06	≦0.06	≦0.06	–	–	–
IPM	≦0.06	≦0.06	≦0.06	–	–	–
PAPM	≦0.06	≦0.06	≦0.06	–	–	–
MEPM	≦0.06	≦0.06	≦0.06	100	–	0
BIPM	≦0.06	≦0.06	≦0.06	–	–	–
DRPM	≦0.06	≦0.06	≦0.06	100	–	0
FRPM	≦0.06	≦0.06	≦0.06	–	–	–
GM	4	4	1–8	–	–	–
ToB	8	16	2–16	–	–	–
AMK	32	64	16–64	–	–	–
ABK	8	16	0.5–16	–	–	–
EM	0.125	≧256	≦0.06–≧256	58.6	0	41.4
CAM	≦0.06	≧128	≦0.06–≧128	58.6	0	41.4
AZM	0.125	≧256	≦0.06–≧256	58.6	0	41.4
CPFX	1	4	≦0.06–16	–	–	–
LVFX	1	2	≦0.06–8	96.6	0	3.4
TFLX	0.25	1	≦0.06–4	–	–	–
MFLX	0.25	0.5	≦0.06–2	–	–	–
PZFX	2	4	1–8	–	–	–
GRNX	0.125	0.25	≦0.06–0.5	–	–	–
STFX	≦0.06	≦0.06	≦0.06–0.125	–	–	–
MINO	0.125	8	≦0.06–8	–	–	–
CLDM	0.125	≧256	≦0.06–≧256	79.3	0	20.7
VCM	0.25	0.5	0.125–0.5	100	–	0
TEIC	0.125	0.125	≦0.06–0.125	–	–	–
LZD	1	2	0.25–2	100	–	0

The susceptibility of 43 antimicrobial agents against 29 strains of S. pyogenes was determined. PCG benzylpenicillin, ABPC ampicillin, SBT/ABPC sulbactam - ABPC, CVA/AMPC clavulanic acid - amoxicillin, PIPC piperacillin, TAZ/PIPC-1 tazobactam – PIPC (tazobactam: PIPC = 1: 8), TAZ/PIPC-2 (tazobactam = 4 μg/mL), CCL cefaclor, CFDN cefdinir, CFPN cefcapene, CDTR cefditoren, CEZ cefazolin, CMZ cefmetazole, CTM cefotiam, CAZ ceftazidime, CTRX ceftriaxone, CFPM cefepime, CZOP cefozopran, IPM imipenem, PAPM panipenem, MEPM meropenem, BIPM biapenem, DRPM doripenem, FRPM faropenem, GM gentamicin, TOB tobramycin, AMK amikacin, ABK arbekacin, EM erythromycin, CAM clarithromycin, AZM azithromycin, CLDM clindamycin, MINO minocycline, VCM vancomycin, TEIC teicoplanin, CPFX ciprofloxacin, LVFX levofloxacin, TFLX tosufloxacin, MFLX moxifloxacin, PZFX pazufloxacin, GRNX garenoxacin, STFX sitafloxacin, LZD linezolid. -, not applicable.

3.5. *Haemophilus influenzae*

Of the 281 *H. influenzae* strains (Table 5), β-lactamase-producing ampicillin-resistant (BLPAR) strains were 8.2%. While MIC_{90}s of ABPC and PIPC were ≥256 μg/mL, those of SBT/ABPC, CVA/ABPC, and TAZ/PIPC-1 (tazobactam: PIPC = 1: 8) against BLPAR were 8, 8, and 1 μg/mL, respectively. MIC_{90}s of fluoroquinolones against BLPAR were ≤0.25 μg/mL. Among the BLPAR strains, 30.4% were β-lactamase-producing clavulanic acid/ampicillin-resistant (BLPACR).

Among the *H. influenzae* strains, β-lactamase-non-producing ampicillin-resistant ABPC-susceptible (BLNAS), -intermediate (BLNAI), and -resistant (BLNAR) strains were 33.8, 17.1, and 49.1%, respectively (Table 6). MIC_{90}s of PIPC, CAZ and CTRX were ≤1 μg/mL. Among carbapenems, MEPM showed the lowest MIC_{90}s against all types of *H. influenzae*. Among aminoglycosides, macrolides and fluoroquinolones, no significant differences were observed in MIC_{90}s between BLNAS, BLNAI, and BLNAR. MIC_{90}s of fluoroquinolones against BLNAR were ≤0.125 μg/mL.

3.6. *Moraxella catarrhalis*

About the 164 *M. catarrhalis* strains (Table 7), MIC_{90}s of β-lactam/β-lactamase inhibitor combinations (BLBLI) were ≤0.25 μg/mL. While MIC_{90}s of cephems ranged from 0.25 to 16 μg/mL, those of carbapenems, aminoglycosides, fluoroquinolones, and minocycline were ≤0.125, ≤0.5, ≤0.125, and 0.25 μg/mL, respectively. No CLDM-susceptible strain was observed (MIC_{90}s, 8 μg/mL).

3.7. *Klebsiella pneumoniae*

Among the 207 *K. pneumoniae* strains (Table 8), 19 (9.2%) were extended-spectrum β-lactamase producers. MIC_{90}s of BLBLI, cephems and monobactam were ≤16 μg/mL and the susceptibilities of these β-lactams were ≥80.7%. MIC_{90}s of carbapenems were ≤0.5 μg/mL and the susceptibilities were ≥99.5%. MIC_{90}s of aminoglycosides, fluoroquinolones, AZM, MINO, and TGC were ≤2, ≤1, 16, 8, and 2 μg/mL, respectively.

Table 5
Antibacterial susceptibility of *Haemophilus influenzae* (all strains and β-lactamase-producing strains).

Antibacterial agent	All strains, n = 281						β-lactamase-producing strains, n = 23					
	MIC (μg/mL)			%			MIC (μg/mL)			%		
	50%	90%	range	Susceptible	Intermediate	Resistant	50%	90%	range	Susceptible	Intermediate	Resistant
PCG	4	16	≦0.06–≧256	–	–	–	128	≧256	32–≧256	–	–	–
ABPC	2	8	≦0.06–≧256	33.8	17.1	49.1	64	≧256	16–≧256	0	0	100
SBT/ABPC	2	8	≦0.06–32	58	–	42	2	8	0.5–8	56.5	–	43.5
CVA/AMPC	4	8	≦0.06–64	64.8	–	35.2	2	8	0.5–8	69.6	–	30.4
PIPC	≦0.06	0.25	≦0.06–≧256	–	–	–	32	≧256	4–≧256	–	–	–
TAZ/PIPC-1	≦0.06	0.25	≦0.06–1	–	–	–	0.25	1	0.125–1	–	–	–
TAZ/PIPC-2	≦0.06	0.125	≦0.06–0.5	100	–	0	≦0.06	0.125	≦0.06–0.25	100	–	0
CCL	8	64	0.5–≧256	53.4	8.9	37.7	4	32	2–64	69.6	8.7	21.7
CFDN	2	8	≦0.06–16	46.6	–	53.4	0.25	4	0.125–4	65.2	–	34.8
CFPN	0.5	2	≦0.06–8	–	–	–	≦0.06	1	≦0.06–2	–	–	–
CDTR	0.125	0.25	≦0.06–1	–	–	–	≦0.06	0.25	≦0.06–0.5	–	–	–
CEZ	4	128	0.5–≧256	–	–	–	8	64	2–128	–	–	–
CMZ	8	16	0.5–64	–	–	–	4	16	2–16	–	–	–
CTM	4	64	≦0.06–128	–	–	–	1	32	0.5–32	–	–	–
CAZ	0.25	0.5	≦0.06–2	100	–	0	0.125	0.5	≦0.06–0.5	100	–	0
CTRX	0.125	0.25	≦0.06–0.5	100	–	0	≦0.06	0.25	≦0.06–0.25	100	–	0
CFPM	1	2	≦0.06–4	93.6	–	6.4	0.125	2	≦0.06–2	100	–	0
CZOP	8	16	≦0.06–128	–	–	–	0.25	16	≦0.06–16	–	–	–
IPM	1	2	≦0.06–8	97.2	–	2.8	1	2	0.25–8	95.7	–	4.3
PAPM	1	2	≦0.06–4	–	–	–	1	2	0.125–4	–	–	–
MEPM	0.25	0.5	≦0.06–2	94	–	6	0.125	0.5	≦0.06–0.5	100	–	0
BIPM	2	8	≦0.06–16	–	–	–	2	4	0.25–8	–	–	–
DRPM	0.5	2	≦0.06–8	84	–	16	0.25	1	≦0.06–2	95.7	–	4.3
FRPM	2	4	≦0.06–8	–	–	–	1	2	0.25–2	–	–	–
AZT	1	2	≦0.06–≧256	90.4	–	9.6	≦0.06	1	≦0.06–2	100	–	0
GM	1	2	0.25–4	–	–	–	1	2	0.5–2	–	–	–
TOB	2	4	0.5–4	–	–	–	2	4	2–4	–	–	–
AMK	4	8	0.5–16	–	–	–	4	8	2–8	–	–	–
ABK	4	4	0.5–8	–	–	–	4	4	2–8	–	–	–
EM	4	8	0.125–≧256	–	–	–	4	8	1–≧256	–	–	–
CAM	4	16	0.125–≧128	89.3	8.9	1.8	4	16	2–≧128	82.6	8.7	8.7
AZM	1	2	≦0.06–64	99.3	–	0.7	0.5	2	≦0.06–64	95.7	–	4.3
CPFX	≦0.06	≦0.06	≦0.06–32	98.6	–	1.4	≦0.06	0.125	≦0.06–0.25	100	–	0
LVFX	≦0.06	≦0.06	≦0.06–16	98.6	–	1.4	≦0.06	≦0.06	≦0.06–0.25	100	–	0
TFLX	≦0.06	≦0.06	≦0.06–≧32	–	–	–	≦0.06	≦0.06	≦0.06–0.125	–	–	–
MFLX	≦0.06	0.125	≦0.06–16	98.6	–	1.4	≦0.06	0.25	≦0.06–0.25	100	–	0
PZFX	≦0.06	≦0.06	≦0.06–32	–	–	–	≦0.06	≦0.06	≦0.06–0.25	–	–	–
GRNX	≦0.06	≦0.06	≦0.06–16	–	–	–	≦0.06	≦0.06	≦0.06–0.125	–	–	–
STFX	≦0.06	≦0.06	≦0.06–1	–	–	–	≦0.06	≦0.06	≦0.06	–	–	–
MINO	0.5	0.5	≦0.06–1	–	–	–	0.5	1	≦0.06–1	–	–	–
CLDM	8	16	0.5–64	–	–	–	8	16	2–32	–	–	–

The susceptibility of 41 antimicrobial agents against 281 strains of H. influenzae including 23 strains of β-lactamase-producer was determined. PCG benzylpenicillin, ABPC ampicillin, SBT/ABPC sulbactam - ABPC, CVA/AMPC clavulanic acid - amoxicillin, PIPC piperacillin, TAZ/PIPC-1 tazobactam – PIPC (tazobactam: PIPC = 1: 8), TAZ/PIPC-2 (tazobactam = 4 μg/mL), CCL cefaclor, CFDN cefdinir, CFPN cefcapene, CDTR cefditoren, CEZ cefazolin, CMZ cefmetazole, CTM cefotiam, CAZ ceftazidime, CTRX ceftriaxone, CFPM cefepime, CZOP cefozopran, AZT aztreonam, IPM imipenem, PAPM panipenem, MEPM meropenem, BIPM biapenem, DRPM doripenem, FRPM faropenem, GM gentamicin, TOB tobramycin, AMK amikacin, ABK arbekacin, EM erythromycin, CAM clarithromycin, AZM azithromycin, CLDM clindamycin, MINO minocycline, CPFX ciprofloxacin, LVFX levofloxacin, TFLX tosufloxacin, MFLX moxifloxacin, PZFX pazufloxacin, GRNX garenoxacin, STFX sitafloxacin. -, not applicable.

Table 6
Antibacterial susceptibility of β-lactamase-non-producing *Haemophilus influenzae*.

	BLNAS (ABPC ≦ 1.0 μg/mL, β-lactamase-non-producer), n = 95						BLNAI (ABPC = 2.0 μg/mL, β-lactamase-non-producer), n = 48						BLNAR (ABPC ≧ 4.0 μg/mL, β-lactamase-non-producer), n = 115					
	MIC (μg/mL)			%			MIC (μg/mL)			%			MIC (μg/mL)			%		
	50%	90%	range	Susceptible	Intermediate	Resistant	50%	90%	range	Susceptible	Intermediate	Resistant	50%	90%	range	Susceptible	Intermediate	Resistant
PCG	0.5	2	≦0.06–8	–	–	–	2	4	2–16	–	–	–	4	8	2–32	–	–	–
ABPC	0.25	1	≦0.06–1	100	0	0	2	2	2	0	100	0	4	8	4–32	0	0	100
SBT/ABPC	0.25	1	≦0.06–1	100	–	0	2	2	1–4	97.9	–	2.1	4	8	2–32	7	–	93
CVA/AMPC	0.5	4	≦0.06–4	100	–	0	4	8	2–8	83.3	–	16.7	8	16	1–64	27	–	73
PIPC	≦0.06	≦0.06	≦0.06–0.25	–	–	–	≦0.06	0.125	≦0.06–0.25	–	–	–	≦0.06	0.25	≦0.06–0.5	–	–	–
TAZ/PIPC-1	≦0.06	≦0.06	≦0.06–0.25	–	–	–	≦0.06	0.125	≦0.06–0.25	–	–	–	≦0.06	0.125	≦0.06–0.5	–	–	–
TAZ/PIPC-2	≦0.06	≦0.06	≦0.06–0.25	100	–	0	≦0.06	0.125	≦0.06–0.25	100	–	0	≦0.06	0.25	≦0.06–0.5	100	–	0
CCL	2	16	0.5–32	89.5	6.3	4.2	8	64	4–64	52.1	14.6	33.3	32	64	4–≧256	20.9	8.7	70.4
CFDN	0.25	1	≦0.06–16	90.5	–	9.5	2	8	0.5–8	35.4	–	64.6	4	8	1–16	11.3	–	88.7
CFPN	≦0.06	0.5	≦0.06–1	–	–	–	0.5	2	≦0.06–4	–	–	–	1	4	≦0.06–8	–	–	–
CDTR	≦0.06	≦0.06	≦0.06–0.5	–	–	–	0.125	0.25	≦0.06–0.5	–	–	–	0.25	0.5	≦0.06–1	–	–	–
CEZ	2	8	0.5–64	–	–	–	4	64	1–128	–	–	–	16	≧256	1–≧256	–	–	–
CMZ	2	8	0.5–16	–	–	–	8	16	4–32	–	–	–	8	32	4–64	–	–	–
CTM	1	4	≦0.06–64	–	–	–	8	32	0.125–64	–	–	–	32	64	2–128	–	–	–
CAZ	0.125	0.5	≦0.06–1	100	–	0	0.25	0.5	≦0.06–1	100	–	0	0.5	1	0.125–2	100	–	0
CTRX	≦0.06	0.125	≦0.06–0.25	100	–	0	0.125	0.25	≦0.06–0.5	100	–	0	0.25	0.5	≦0.06–0.5	100	–	0
CFPM	0.125	1	≦0.06–2	100	–	0	1	2	0.125–4	93.8	–	6.2	2	4	0.5–4	87	–	13
CZOP	0.125	4	≦0.06–16	–	–	–	8	8	0.25–32	–	–	–	8	32	4–128	–	–	–
IPM	0.5	1	≦0.06–4	100	–	0	1	2	0.25–8	97.9	–	2.1	1	4	0.25–8	94.8	–	5.2
PAPM	0.5	1	≦0.06–2	–	–	–	1	2	0.25–4	–	–	–	1	4	0.25–4	–	–	–
MEPM	≦0.06	0.125	≦0.06–0.5	100	–	0	0.25	0.5	≦0.06–0.5	100	–	0	0.25	1	≦0.06–2	85.2	–	14.8
BIPM	1	4	≦0.06–8	–	–	–	2	8	1–8	–	–	–	4	8	0.5–16	–	–	–
DRPM	0.125	0.5	≦0.06–2	98.9	–	1.1	0.5	1	0.25–2	97.9	–	2.1	1	2	0.125–8	63.5	–	36.5
FRPM	0.5	2	≦0.06–4	–	–	–	2	4	0.125–4	–	–	–	2	4	0.5–8	–	–	–
AZT	≦0.06	0.5	≦0.06–2	100	–	0	1	2	≦0.06–128	93.8	–	6.2	1	4	0.25–≧256	79.1	–	20.9
GM	1	2	0.25–4	–	–	–	1	2	0.5–2	–	–	–	1	2	0.5–2	–	–	–
TOB	2	4	0.5–4	–	–	–	2	4	1–4	–	–	–	2	4	0.5–4	–	–	–
AMK	4	8	0.5–16	–	–	–	4	8	2–8	–	–	–	4	8	1–16	–	–	–
ABK	2	4	0.5–8	–	–	–	4	4	2–8	–	–	–	4	4	1–8	–	–	–
EM	4	4	0.125–128	–	–	–	4	8	0.5–8	–	–	–	4	8	1–8	–	–	–
CAM	4	8	0.125–≧128	91.6	5.2	3.2	8	16	0.5–16	89.6	10.4	0	8	16	0.25–16	88.7	11.3	0
AZM	0.5	2	≦0.06–8	98.9	–	1.1	1	2	0.125–2	100	–	0	1	1	0.25–2	100	–	0
CPFX	≦0.06	≦0.06	≦0.06–16	98.9	–	1.1	≦0.06	≦0.06	≦0.06–32	97.9	–	2.1	≦0.06	≦0.06	≦0.06–16	98.3	–	1.7
LVFX	≦0.06	≦0.06	≦0.06–8	98.9	–	1.1	≦0.06	≦0.06	≦0.06–16	97.9	–	2.1	≦0.06	≦0.06	≦0.06–16	98.3	–	1.7
TFLX	≦0.06	≦0.06	≦0.06–≧32	–	–	–	≦0.06	≦0.06	≦0.06–≧32	–	–	–	≦0.06	≦0.06	≦0.06–≧32	–	–	–
MFLX	≦0.06	≦0.06	≦0.06–8	98.9	–	1.1	≦0.06	≦0.06	≦0.06–8	97.9	–	2.1	≦0.06	0.125	≦0.06–16	98.3	–	1.7
PZFX	≦0.06	≦0.06	≦0.06–4	–	–	–	≦0.06	≦0.06	≦0.06–32	–	–	–	≦0.06	0.125	≦0.06–32	–	–	–
GRNX	≦0.06	≦0.06	≦0.06–8	–	–	–	≦0.06	≦0.06	≦0.06–2	–	–	–	≦0.06	≦0.06	≦0.06–16	–	–	–
STFX	≦0.06	≦0.06	≦0.06–0.25	–	–	–	≦0.06	≦0.06	≦0.06–0.5	–	–	–	≦0.06	≦0.06	≦0.06–1	–	–	–
MINO	0.25	0.5	≦0.06–1	–	–	–	0.25	0.5	≦0.06–0.5	–	–	–	0.5	0.5	≦0.06–1	–	–	–
CLDM	8	16	0.5–64	–	–	–	8	16	1–32	–	–	–	8	16	2to64	–	–	–

The susceptibility of 41 antimicrobial agents against 258 strains of β-lactamase-non-producing H. influenzae was determined. PCG benzylpenicillin, ABPC ampicillin, SBT/ABPC sulbactam - ABPC, CVA/AMPC clavulanic acid - amoxicillin, PIPC piperacillin, TAZ/PIPC-1 tazobactam – PIPC (tazobactam: PIPC = 1: 8), TAZ/PIPC-2 (tazobactam = 4 μg/mL), CCL cefaclor, CFDN cefdinir, CFPN cefcapene, CDTR cefditoren, CEZ cefazolin, CMZ cefmetazole, CTM cefotiam, CAZ ceftazidime, CTRX ceftriaxone, CFPM cefepime, CZOP cefozopran, AZT aztreonam, IPM imipenem, PAPM panipenem, MEPM meropenem, BIPM biapenem, DRPM doripenem, FRPM faropenem, GM gentamicin, TOB tobramycin, AMK amikacin, ABK arbekacin, EM erythromycin, CAM clarithromycin, AZM azithromycin, CLDM clindamycin, MINO minocycline, CPFX ciprofloxacin, LVFX levofloxacin, TFLX tosufloxacin, MFLX moxifloxacin, PZFX pazufloxacin, GRNX garenoxacin, STFX sitafloxacin. -, not applicable.

Table 7
Antibacterial susceptibility of *Moraxella catarrhalis*.

Antibacterial agent	n = 164					
	MIC (μg/mL)			%		
	50%	90%	range	Susceptible	Intermediate	Resistant
PCG	16	32	≦0.06–64	–	–	–
ABPC	8	16	≦0.06–32	–	–	–
SBT/ABPC	0.125	0.25	≦0.06–0.25	–	–	–
CVA/AMPC	0.25	0.25	≦0.06–1	100	–	0
PIPC	4	16	≦0.06–32	–	–	–
TAZ/PIPC-1	≦0.06	0.125	≦0.06–0.25	–	–	–
TAZ/PIPC-2	≦0.06	≦0.06	≦0.06	–	–	–
CCL	1	4	≦0.06–32	–	–	–
CFDN	0.25	0.5	≦0.06–2	–	–	–
CFPN	0.5	1	≦0.06–1	–	–	–
CDTR	0.5	1	≦0.06–4	–	–	–
CEZ	4	16	0.5–64	–	–	–
CMZ	0.5	1	≦0.06–2	–	–	–
CTM	1	2	0.25–8	–	–	–
CAZ	0.125	0.25	≦0.06–1	100	–	0
CTRX	1	2	≦0.06–8	98.2	–	1.8
CFPM	1	4	≦0.06–8	–	–	–
CZOP	2	4	0.125–16	–	–	–
IPM	≦0.06	0.125	≦0.06–0.25	–	–	–
PAPM	≦0.06	≦0.06	≦0.06–0.25	–	–	–
MEPM	≦0.06	≦0.06	≦0.06–0.125	–	–	–
BIPM	≦0.06	≦0.06	≦0.06–0.125	–	–	–
DRPM	≦0.06	≦0.06	≦0.06	–	–	–
FRPM	0.5	0.5	≦0.06–1	–	–	–
AZT	2	4	0.25–8	–	–	–
GM	0.125	0.125	≦0.06–0.5	–	–	–
TOB	0.25	0.25	≦0.06–0.5	–	–	–
AMK	0.5	0.5	0.25–1	–	–	–
ABK	0.25	0.25	≦0.06–0.5	–	–	–
EM	0.25	0.25	≦0.06–≧256	99.4	–	0.6
CAM	0.125	0.125	≦0.06–≧128	99.4	–	0.6
AZM	≦0.06	≦0.06	≦0.06–≧256	99.4	–	0.6
CPFX	≦0.06	≦0.06	≦0.06–1	100	–	0
LVFX	≦0.06	0.125	≦0.06–2	100	–	0
TFLX	≦0.06	≦0.06	≦0.06–0.125	–	–	–
MFLX	0.125	0.125	≦0.06–1	–	–	–
PZFX	≦0.06	≦0.06	≦0.06–2	–	–	–
GRNX	≦0.06	≦0.06	≦0.06–0.25	–	–	–
STFX	≦0.06	≦0.06	≦0.06–0.125	–	–	–
MINO	0.125	0.25	≦0.06–0.25	–	–	–
CLDM	4	8	1–≧256	0	20.1	79.9

The susceptibility of 41 antimicrobial agents against 164 strains of M. catarrhalis was determined. PCG benzylpenicillin, ABPC ampicillin, SBT/ABPC sulbactam - ABPC, CVA/AMPC clavulanic acid - amoxicillin, PIPC piperacillin, TAZ/PIPC-1 tazobactam – PIPC (tazobactam: PIPC = 1: 8), TAZ/PIPC-2 (tazobactam = 4 μg/mL), CCL cefaclor, CFDN cefdinir, CFPN cefcapene, CDTR cefditoren, CEZ cefazolin, CMZ cefmetazole, CTM cefotiam, CAZ ceftazidime, CTRX ceftriaxone, CFPM cefepime, CZOP cefozopran, AZT aztreonam, IPM imipenem, PAPM panipenem, MEPM meropenem, BIPM biapenem, DRPM doripenem, FRPM faropenem, GM gentamicin, TOB tobramycin, AMK amikacin, ABK arbekacin, EM erythromycin, CAM clarithromycin, AZM azithromycin, CLDM clindamycin, MINO minocycline, CPFX ciprofloxacin, LVFX levofloxacin, TFLX tosufloxacin, MFLX moxifloxacin, PZFX pazufloxacin, GRNX garenoxacin, STFX sitafloxacin. -, not applicable.

3.8. *Pseudomonas aeruginosa*

There were 254 *P. aeruginosa* strains including 1 (0.4%) metallo-β-lactamase producer (Table 9). Cephalosporins except for CTRX and monobactam showed relatively low MIC levels (MIC_{50}s, 2–4 μg/mL; MIC_{90}s, 16–32 μg/mL), compared with PIPC and TAZ/PIPC (MIC50s, ≤8 μg/mL; MIC90s, 128 μg/mL). The susceptibilities of PIPC, TAZ/PIPC, cephalosporins except for CTRX, and monobactam were 79.9, 81.9, 85–86.6 and 78%, respectively. Among the carbapenems, MEPM, BIPM, and DRPM showed the lowest MIC levels (MIC_{50}s, ≤0.5 μg/mL; MIC_{90}s, 8 μg/mL) compared with IPM (MIC_{50}s, 1 μg/mL; MIC_{90}s, 16 μg/mL) and PAPM (MIC_{50}s, 8 μg/mL; MIC_{90}s, 32 μg/mL). The susceptibilities of IPM, MEPM, and DRPM were 76.4, 83.1, and 85.8%, respectively.

Among the aminoglycosides, TOB showed the lowest MIC levels (MIC_{50}s, 1 μg/mL; MIC_{90}s, 2 μg/mL) and the susceptibilities of aminoglycosides were 96.9–99.6%. Among the fluoroquinolones, STFX showed the lowest MIC levels (MIC_{50}s, 0.125 μg/mL; MIC_{90}s, 2 μg/mL) and the susceptibilities of CPFX and LVFX were 84.3 and 81.1%, respectively.

4. Discussion

In the present surveillance, the prevalence of MRSA in *S. aureus* was smaller than the previous surveillances (43.6%, vs. 58.5% in 2009, 50.5% in 2010, and 51.3% in 2012) [6–8]. In MSSA, the percentages of susceptibility in macrolides, fluoroquinolones, and CLDM were similar levels to the previous surveillances [6,7]. In MRSA, the susceptibilities of macrolides, fluoroquinolones and CLDM in the present study were 8.8%, 10.2–11.6%, and 34%, respectively, while those in a surveillance in 2010 were 1%, 6.7%, and 12.5%, respectively [7]. These findings could imply the increase

Table 8
Antibacterial susceptibility of *Klebsiella pneumoniae*.

Antibacterial agent	n = 207					
	MIC (μg/mL)			%		
	50%	90%	range	Susceptible	Intermediate	Resistant
ABPC	64	≧256	1–≧256	2.9	9.2	87.9
SBT/ABPC	4	16	1–≧256	80.7	10.1	9.2
CVA/AMPC	4	16	1–64	88.9	7.2	3.9
PIPC	8	≧256	1–≧256	84.1	3.8	12.1
TAZ/PIPC-1	4	16	1–≧256	–	–	–
TAZ/PIPC-2	2	8	1–≧256	96.6	1	2.4
CCL	0.5	4	0.25–≧256	90.8	0	9.2
CFDN	0.125	1	≦0.06–≧128	90.8	1	8.2
CFPN	0.5	4	≦0.06–128	–	–	–
CDTR	0.25	2	≦0.06–≧128	–	–	–
CEZ	1	16	0.5–≧256	86	3.4	10.6
CMZ	1	2	0.5–16	100	0	0
CTM	0.125	2	≦0.06–≧256	–	–	–
CAZ	0.125	1	≦0.06–64	96.6	0.5	2.9
CTRX	≦0.06	0.25	≦0.06–≧256	91.8	0	8.2
CFPM	≦0.06	0.5	≦0.06–≧256	92.8	–	7.2
CZOP	≦0.06	0.125	≦0.06–≧256	–	–	–
IPM	0.25	0.5	0.125–2	99.5	0.5	0
PAPM	0.125	0.25	≦0.06–1	–	–	–
MEPM	≦0.06	≦0.06	≦0.06–0.125	100	0	0
BIPM	0.125	0.5	≦0.06–2	–	–	–
DRPM	≦0.06	≦0.06	≦0.06–0.25	100	0	0
FRPM	0.5	1	≦0.06–4	–	–	–
AZT	≦0.06	0.25	≦0.06–128	96.1	0	3.9
GM	0.25	0.5	0.125–≧256	96.6	0	3.4
TOB	0.5	1	0.125–16	96.1	2.5	1.4
AMK	1	2	0.25–8	100	0	0
ABK	0.5	0.5	0.25–2	–	–	–
AZM	8	16	4–≧256	–	–	–
CPFX	≦0.06	0.5	≦0.06–≧256	94.2	1.5	4.3
LVFX	≦0.06	0.5	≦0.06–128	95.7	1.4	2.9
TFLX	≦0.06	0.5	≦0.06–≧32	–	–	–
MFLX	0.125	1	≦0.06–128	–	–	–
PZFX	≦0.06	0.25	≦0.06–64	–	–	–
GRNX	0.125	1	≦0.06–128	–	–	–
STFX	≦0.06	0.25	≦0.06–8	–	–	–
MINO	2	8	1–≧128	86.5	3.8	9.7
TGC	0.5	2	0.25–8	–	–	–

The susceptibility of 38 antimicrobial agents against 207 strains of *K. pneumoniae* was determined. ABPC ampicillin, SBT/ABPC sulbactam - ABPC, CVA/AMPC clavulanic acid - amoxicillin, PIPC piperacillin, TAZ/PIPC-1 tazobactam – PIPC (tazobactam: PIPC = 1: 8), TAZ/PIPC-2 (tazobactam = 4 μg/mL), CCL cefaclor, CFDN cefdinir, CFPN cefcapene, CDTR cefditoren, CEZ cefazolin, CMZ cefmetazole, CTM cefotiam, CAZ ceftazidime, CTRX ceftriaxone, CFPM cefepime, CZOP cefozopran, AZT aztreonam, IPM imipenem, PAPM panipenem, MEPM meropenem, BIPM biapenem, DRPM doripenem, FRPM faropenem, GM gentamicin, TOB tobramycin, AMK amikacin, ABK arbekacin, AZM azithromycin, MINO minocycline, CPFX ciprofloxacin, LVFX levofloxacin, TFLX tosufloxacin, MFLX moxifloxacin, PZFX pazufloxacin, GRNX garenoxacin, STFX sitafloxacin, TGC tigercycline. -, not applicable.

in community-acquired MRSA and/or the clonal shifting among MRSA strains because these strains reportedly show good susceptibilities against these agents [9–11].

Most β-lactams were active against *S. pneumoniae* and *S. pyogenes*. A several years has passed since new fluoroquinolones such as STFX, GRNX, and MFLX became available; however, these agents still showed potent activities [12,13]. These data suggest that β-lactams and fluoroquinolones are effective against community-acquired pneumonia caused by *S. pneumoniae*; however, proper use of these agents and continuous surveillance are still necessary to notify the emergence of quinolone resistant *S. pneumoniae*.

Concerning *H. influenzae* strains, BLNAR was continuously increasing (49.1%, vs. 33.6% in 2010 and 37.2% in 2014). Japan has been known to have a high prevalence of BLNAR [14,15] whereas the global prevalence is <5% [16]. Our surveillance indicates that TAZ/PIPC and fluoroquinolones still have activities against these drug-resistant strains.

The β-lactamase inhibitors restored the activities of penicillins against *M. catarrhalis*, supporting that most of the strains produce penicillinase. Other β-lactams, aminoglycosides, macrolides, and fluoroquinolones also showed activities against *M. catarrhalis*.

The percentage of ESBL-producing *K. pneumoniae* was elevated compared with previous surveillances (9.2%, vs. 2.9% in 2010 and 4.2% in 2012) [6,7]. The susceptibility to CFPM might be gradually decreasing (% susceptibility; 92.8%, vs. 97.6% in 2012 and 98.6% in 2010) while CMZ showed stable activity [6,7]. ESBL-producers are often accompanied by fluoroquinolone-resistance; however, the prevalence of fluoroquinolone-resistant strains was not increased compared with the previous surveillances [6,7]. Although carbapenem-resistant strains were not isolated in the present surveillance, strains with elevated MIC against TGC were observed. Susceptibilities against TGC should be continuously followed in the next surveillance because European Committee on Antimicrobial Susceptibility Testing specifies that MIC >2 μg/mL against TGC is resistant [17]. Although the mechanism of TGC resistance is complex, it has been reported that increased expression of efflux pumps can strongly affect the susceptibility [18].

In *P. aeruginosa* strains, the susceptibilities of carbapenems may be improving since 2010 (the susceptibility of IPM, 76.4%, vs. 67.5% in 2010; the susceptibility of MEPM, 83.1%, vs. 76.9% in 2010) as well as those of fluoroquinolones (the susceptibility of CPFX, 84.3%, vs. 75.6% in 2010) [7]. The gradual improvement in the susceptibilities

Table 9
Antibacterial susceptibility of *Pseudomonas aeruginosa*.

Antibacterial agent	n = 254					
	MIC (μg/mL)			%		
	50%	90%	range	Susceptible	Intermediate	Resistant
PIPC	8	128	0.125–≧256	79.9	7.1	13
TAZ/PIPC-1	8	128	0.125–≧256	–	–	–
TAZ/PIPC-2	4	128	≦0.06–≧256	81.9	7.5	10.6
CAZ	2	32	0.125–≧128	85	2.8	12.2
CTRX	64	≧256	0.5–≧256	–	–	–
CFPM	4	16	0.125–≧256	86.6	8.3	5.1
CZOP	2	16	0.125–≧256	–	–	–
IPM	1	16	≦0.06–≧128	76.4	6.7	16.9
PAPM	8	32	0.125–128	–	–	–
MEPM	0.5	8	≦0.06–≧256	83.1	2.7	14.2
BIPM	0.5	8	≦0.06–64	–	–	–
DRPM	0.25	8	≦0.06–≧128	85.8	4	10.2
AZT	4	32	≦0.06–≧256	78	9.4	12.6
GM	2	4	0.125–≧256	96.9	1.1	2
TOB	1	2	0.125–≧256	98.8	0	1.2
AMK	4	8	0.25–32	99.6	0.4	0
ABK	1	4	0.25–16	–	–	–
CPFX	0.25	4	≦0.06–128	84.3	4.3	11.4
LVFX	1	8	≦0.06–≧256	81.1	7.5	11.4
TFLX	0.25	16	≦0.06–≧32	–	–	–
MFLX	2	16	≦0.06–≧256	–	–	–
PZFX	0.5	4	≦0.06–128	–	–	–
GRNX	1	16	≦0.06–≧256	–	–	–
STFX	0.125	2	≦0.06–16	–	–	–
MINO	16	64	1–≧256	–	–	–

The susceptibility of 25 antimicrobial agents against 254 strains of *P. aeruginosa* was determined. PIPC piperacillin, TAZ/PIPC-1 tazobactam – PIPC (tazobactam: PIPC = 1: 8), TAZ/PIPC-2 (tazobactam = 4 μg/mL), CAZ ceftazidime, CTRX ceftriaxone, CFPM cefepime, CZOP cefozopran, AZT aztreonam, IPM imipenem, PAPM panipenem, MEPM meropenem, BIPM biapenem, DRPM doripenem,GM gentamicin, TOB tobramycin, AMK amikacin, ABK arbekacin, MINO minocycline, CPFX ciprofloxacin, LVFX levofloxacin, TFLX tosufloxacin, MFLX moxifloxacin, PZFX pazufloxacin, GRNX garenoxacin, STFX sitafloxacin. -, not applicable.

of these agents might be affected by the decreased number of patients with chronic colonization by *P. aeruginosa* and the optimized use of antibiotics.

The antimicrobial resistant is a global emergent problem. Because the microbiological data provide the evidence to enhance the appropriate use of antimicrobial agents, our surveillance data will be a useful reference for the treatment of respiratory infections in our country. Thus, the surveillance should be continuously performed to update the knowledge about antimicrobial resistant bacteria in major respiratory pathogens.

Conflicts of interest

Katsunori Yanagihara received speaker honoraria from Taisho Toyama Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd., Pfizer Japan Inc., MSD K.K., Astellas Pharma Inc., Daiichi Sankyo Co., Ltd., Nippon Becton Dickinson Company, Ltd., and bioMerieux Japan Ltd., and received scholarship donations from Toyama Chemical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Daiichi Sankyo Co., Ltd., Pfizer Japan Inc., MSD K.K., Biofermin Seiyaku Co.,Ltd., and Roche Diagnostics K.K.. Tetsuya Matsumoto received speaker honoraria from Taisho Toyama Pharmaceutical Co., Ltd., MSD K.K., and Pfizer Japan Inc., Nobuki Aoki received speaker honoraria from Kyorin Pharmaceutical Co., Ltd., Hiroshi Kiyota received scholarship donations from Taisho Toyama Pharmaceutical Co., Toyama Chemical Co.,Ltd., Daiichi Sankyo Co., Ltd., Astellas Pharma Inc.,TAIHO Pharmaceutical Co., Ltd., and Sanofi K.K., Kazuhiro Tateda received scholarship donations from Toyama Chemical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Daiichi Sankyo Co., Taisho Toyama Pharmaceutical Co., Asahi Kasei Pharma Corporation, and Shionogi & Co., received research fund from Spero OpCo, Inc., Makoto Miki received speaker honoraria from Kyorin Pharmaceutical Co., Ltd., Satoshi Iwata received speaker honoraria from Meiji Seika Pharma Co., Ltd., and MSD K.K., Atsushi Nakamura received speaker honoraria from Pfizer Japan Inc., Taisho Toyama Pharmaceutical Co., Ltd., and MSD K.K., Hiroshige Mikamo received speaker honoraria from Astellas Pharma Inc., MSD K.K., Shionogi & Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Pfizer Japan Inc., Toyama Chemical Co., Ltd., Asahi Kasei Pharma Corporation, Miyarisan Pharmaceutical Co., Ltd., and Meiji Seika Pharma Co., Ltd. and received scholarship donations from MSD K.K., Taisho Toyama Pharmaceutical Co., Ltd., Astellas Pharma Inc., Daiichi Sankyo Co., Ltd., Toyama Chemical Co.,Ltd., Asahi Kasei Pharma Corporation, Miyarisan Pharmaceutical Co., Ltd., Meiji Seika Pharma Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., FUJIFILM Pharma Co., Ltd., and Pfizer Japan Inc., Hiroshi Kakeya received speaker honoraria from MSD K.K., Sumitomo Dainippon Pharma Co., Ltd., Pfizer Japan Inc., Astellas Pharma Inc., and Daiichi Sankyo Co., Ltd., Junichi Kadota received speaker honoraria from Daiichi Sankyo Co., Ltd., Kyorin Pharmaceutical Co., Ltd., MSD K.K., Shionogi & Co., Ltd., Pfizer Japan Inc., Taisho Toyama Pharmaceutical Co.,Ltd., Mylan EPD., Sawai Pharmaceutical CO., Ltd., Nippon Boehringer Ingelheim Co., Ltd., and The Japan Respiratory Society., received scholarship donations from Daiichi Sankyo Co., Ltd., Chugai Pharmaceutical Co.,Ltd., MSD K.K., Astellas Pharma Inc., Sumitomo Dainippon Pharma Co., Ltd., Meiji Seika Pharma Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., and Pfizer Japan Inc., and received research fund from Kyorin Pharmaceutical Co., Ltd., MSD K.K., Toyama Chemical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd. and Taisho Toyama Pharmaceutical Co., Ltd., and payments for manuscript drafting and editing from Nankodo Co., Ltd., Yosuke Aoki received speaker honoraria from MSD K.K., and received scholarship donations from Shionogi & Co., Ltd., Hiroshi Mukae received speaker honoraria from Daiichi Sankyo Co., Ltd., Kyorin Pharmaceutical Co., Taisho Toyama Pharmaceutical Co.,Led., Shionogi & Co., Ltd., Astellas Pharma Inc., MSD K.K., Sumitomo Dainippon Pharma Co., Ltd., Nippon Boehringer

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