J Infect Chemother 21 (2015) 410–420

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

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 2010: General view of the pathogens' antibacterial susceptibility

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http://dx.doi.org/10.1016/j.jiac.2015.02.008

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ARTICLE INFO

Article history:
Received 31 July 2014
Received in revised form
13 February 2015
Accepted 19 February 2015
Available online 28 February 2015

Keywords:
Surveillance
Susceptibility
Resistance
Respiratory tract infection

ABSTRACT

The nationwide surveillance on antimicrobial susceptibility of bacterial respiratory pathogens from patients in Japan, was conducted by Japanese Society of Chemotherapy, Japanese Association for Infectious Diseases and Japanese Society for Clinical Microbiology in 2010.

The isolates were collected from clinical specimens obtained from well-diagnosed adult patients with respiratory tract infections during the period from January and April 2010 by three societies. Antimicrobial susceptibility testing was conducted at the central reference laboratory according to the method recommended by Clinical and Laboratory Standard Institutes using maximum 45 antibacterial agents.

Susceptibility testing was evaluable with 954 strains (206 *Staphylococcus aureus*, 189 *Streptococcus pneumoniae*, 4 *Streptococcus pyogenes*, 182 *Haemophilus influenzae*, 74 *Moraxella catarrhalis*, 139 *Klebsiella pneumoniae* and 160 *Pseudomonas aeruginosa*). Ratio of methicillin-resistant *S. aureus* was as high as 50.5%, and those of penicillin-intermediate and -resistant *S. pneumoniae* were 1.1% and 0.0%, respectively. Among *H. influenzae*, 17.6% of them were found to be β-lactamase-non-producing ampicillin (ABPC)-intermediately resistant, 33.5% to be β-lactamase-non-producing ABPC-resistant and 11.0% to be β-lactamase-producing ABPC-resistant strains. Extended spectrum β-lactamase-producing *K. pneumoniae* and multi-drug resistant *P. aeruginosa* with metallo β-lactamase were 2.9% and 0.6%, respectively.

Continuous national surveillance of antimicrobial susceptibility of respiratory pathogens is crucial in order to monitor changing patterns of susceptibility and to be able to update treatment recommendations on a regular basis.

1. Introduction

In order to investigate comprehensively the antimicrobial susceptibility and resistance of bacterial respiratory pathogens, Japanese Society of Chemotherapy (JSC) established a nationwide surveillance network in 2006. The first survey was conducted in 2006 and we reported the trend of antimicrobial susceptibilities of bacterial species from patients with respiratory tract infections (RTI) [1]. Second and third surveys were continuously conducted in 2007 and in 2008, respectively. After third-year study, this survey was decided to be continued in association with JSC, the Japanese Association for Infectious Diseases and the Japanese Society for Clinical Microbiology. In 2009, the fourth year nationwide surveillance was conducted as the first survey conducted by three societies [2]. Here we report the study of fifth year nationwide surveillance which was the second survey conducted by three societies. These results obtained from this surveillance will be used as a set of controls for those conducted in future by three societies and by other organizations as well.

2. Materials and methods

2.1. Strains and quality control

The bacteria from the patients with RTI were isolated from sputum, specimens collected by trans-tracheal aspiration, or bronchoscopy between April and September in 2010. The subjects in the study were *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Microbiological laboratory test for respiratory pathogens were conducted by standard methods including Gram staining and quantitative culture of various respiratory samples at 34 medical institutions, as listed in Table 1. The isolated bacteria were identified as species

Table 1
List of participating institution contributing to our surveillance.

Asahikawa Medical University, Hokkaido, Japan
Iwate Prefectural Central Hospital, Iwate, Japan
Saiseikai Yamagata Saisei Hospital, Yamagata, Japan
Japanese Red Cross Sendai Hospital, Miyagi, Japan
Saka General Hospital, Miyagi, Japan
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Niigata City General Hospital, Niigata, Japan
Shinrakuen Hospital, Niigata, Japan
Kasugai Municipal Hospital, Aichi, Japan
Aichi Medical University Hospital, Aichi, Japan
Kinki University, Faculty of Medicine, Osaka, Japan
Osaka City General Hospital, Osaka, Japan
Center for Infectious Diseases, Nara Medical University, Nara, Japan
Kobe Red Cross Hospital, Hyogo, Japan
Osaka University Hospital, Osaka, Japan
Kawasaki Medical School, Okayama, Japan
Okayama University Hospital, Okayama, Japan
Hiroshima Prefectural Hospital, Hiroshima, Japan
Matsue Red Cross Hospital, Shimane, Japan
Kagawa University Hospital, Kagawa, Japan
Oita University Faculty of Medicine, Oita, Japan
Saga University, School of Medicine, Saga, Japan
Saiseikai Kumamoto Hospital, Kumamoto, Japan
Nagasaki University School of Medicine, Nagasaki, Japan
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level in each laboratory. The isolates were stored in the freezer and the causative bacteria judged by physicians were collected. When several strains were detected from the same patient, arbitrary 1 strain was selected. The isolates were suspended in Micro-bank tube (Asuka Junyaku Co.Ltd. Tokyo) and transferred to the central laboratory, the Research Center for Anti-infective Drugs of the Kitasato Institute. The electronic uniform data sheets of each patient from whom these strains isolated were also completed at each institution and sent to the Center so that microbiological data obtained were able to be stratified under the settings and profiles of patients and under the diagnoses.

A total of 1001 strains were received at the center and kept at −80 °C until the antimicrobial susceptibility testing conducted. Re-identification and cultivation of them gave evaluable 954 strains consisted of 206 *S. aureus,* 189 *S. pneumoniae*, 4 *S. pyogenes*, 182 *H. influenzae*, 74 *M. catarrhalis*, 139 *K. pneumoniae* and 160 *P. aeruginosa.*

Accuracy of determination for minimum inhibitory concentration (MIC) of antibacterial agents was controlled according to the recommendations of Clinical and Laboratory Standards Institute (CLSI) using the following control strains respectively: *S. aureus* ATCC29213 and *Escherichia coli* ATCC35218 for clinical isolates of *S. aureus* and *M. catarrhalis*; *S. pneumoniae* ATCC49619 for *S. pneumoniae*; *H. influenzae* ATCC49247 for *H. influenzae*; *E. coli* ATCC25922 for *K. pneumoniae* and *P. aeruginosa*; and *P. aeruginosa* ATCC27853 for *P. aeruginosa. E. coli* ATCC35218 was used as a control strain in case of MIC determination for β-lactam antibiotics combined with β -lactamase inhibitors.

2.2. Antibacterial agents

The susceptibilities of the bacterial strains were tested for the following 45 antimicrobial agents: four penicillins such as benzylpenicillin (PCG; Meiji Seika Kaisha Ltd.), oxacillin (MPIPC; Meiji), ampicillin (ABPC; Meiji) and piperacillin (PIPC; Toyama Chemical Co., Ltd.); three penicillins in combination with β-lactamase inhibitors such as clavulanic acid-amoxicillin (CVA/AMPC; Glaxo SmithKline K.K.), sulbactam-ABPC (SBT/ABPC; Pfizer Japan Inc.) and tazobactam-PIPC (TAZ/PIPC; Toyama); four oral cephems such as cefaclor (CCL; Shionogi & Co., Ltd.), cefdinir (CFDN; Astellas Pharma Inc.), cefcapene (CFPN; Shionogi), and cefditoren (CDTR; Meiji); eight parenteral cephems such as cefazolin (CEZ; Astellas), cefoxitin (CFX; Banyu Pharmaceutical Co., Ltd.), cefmetazole (CMZ; Daiichi-Sankyo Co., Ltd.), cefotiam (CTM; Takeda Pharmaceutical Co., Ltd.), ceftazidime (CAZ; Glaxo SmithKline), ceftriaxone (CTRX; Chugai Pharmaceutical Co., Ltd.), cefepime (CFPM; Meiji) and cefozopran (CZOP; Takeda); a monobactam aztreonam (AZT; Eisai Co., Ltd.); five carbapenems such as imipenem (IPM; Banyu), panipenem (PAPM; Daiichi-Sankyo), meropenem (MEPM; Dainippon Sumitomo Pharma Co., Ltd.), biapenem (BIPM; Meiji) and doripenem (DRPM; Shionogi); one penem such as faropenem (FRPM; Astellas); four aminoglycosides such as gentamicin (GM; Shionogi), tobramycin (TOB; J-dolph), amikacin (AMK; Banyu) and arbekacin (ABK; Meiji); three macrolides such as erythromycin (EM; Dainippon Sumitomo), clarithromycin (CAM; Toyama) and azithromycin (AZM; Pfizer); a lincosamide clindamycin (CLDM; Dainippon Sumitomo); a tetracycline minocycline (MINO; Wyeth K.K./Takeda); two glycopeptides such as vancomycin (VCM; Shionogi) and teicoplanin (TEIC; Astellas); seven fluoroquinolones such as ciprofloxacin (CPFX; BayerYakuhin Ltd.), levofloxacin (LVFX; Daiichi-Sankyo), tosufloxacin (TFLX; Toyama), moxifloxacin (MFLX; Shionogi), pazufloxacin (PZFX; Toyama), garenoxacin (GRNX; Astellas), and sitafloxacin (STFX; Daiichi Sankyo) and an oxazolidinone linezolide (LZD; Pfizer). These antimicrobial agents were serially diluted and placed under freeze-dried state in respective wells of microplates. The stability of the antimicrobial agent-containing microplates was guaranteed by the manufacturer (Eiken Kagaku) for 9 months.

2.3. Susceptibility testing and MIC determination

Susceptibility testing was performed according to CLSI standards M7-A8 for micro-broth dilution method [3,4]. In brief, cation-adjusted Mueller-Hinton broth (25 mg/L Ca^{++} and 12.5 mg/L Mg^{++}; CA–MH broth) was used to measure MIC against *S. aureus, M. catarrhalis, K. pneumoniae* and *P. aeruginosa*. For the determination of the MIC of oxacillin, NaCl was added at 2% to CA–MH broth. For measuring the MICs against *S. pneumoniae* and *H. influenzae*, 15 μg/mL nicotinamide, 5 mg/mL yeast-extract and horse blood at 5% were added to CA–MH broth.

A 0.005 mL portion of test organism solution, grown to turbidity of McFarland Number 0.5 and diluted tenfold with saline, was inoculated to CA–MH broth to make a final volume of 0.1 ± 0.02 mL. This was poured into a well on a microplate (Eiken Kagaku Co., Ltd., Tokyo, Japan) serially diluted freeze-dried test agent was placed, and the MIC was determined with the MIC2000 system (Eiken Kagaku Co., Ltd., Tokyo). Tested ranges were 0.06–128 μg/ml for CFDN, CDTR, CAM, and AZM, 0.06–32 μg/ml for TFLX, and 0.06–256 μg/ml for the other antimicrobials.

2.4. Detection of β-lactamases

To detect β-lactamases in *H. influenzae*, tests with Nitorocefin desks (Kanto Chemical Co, Inc., Tokyo) were conducted according to the reference manual supplied by the manufacturer.

A recently established rapid detection method, the Cica–Beta Test 1® (Kanto Chemical Co, Inc., Tokyo) being designed to detect

Table 2
Antibacterial susceptibility of *Staphylococcus aureus*.

Antibacterial agent	All strains, n = 206					
	MIC (μg/ml)			Susceptibility (%)		
	50%	90%	Range	S	I	R
PCG	8	32	≤0.06 to 64	25.7	–	74.3
MPIPC	8	≥256	0.125 to ≥256	49.5	–	50.5
ABPC	8	32	≤0.06 to 64	26.2		73.8
SBT/ABPC	4	32	≤0.06 to 64	59.7	27.2	13.1
CVA/AMPC	2	32	0.125 to64	53.4	–	46.6
PIPC	16	128	0.5 to ≥256	–	–	–
TAZ/PIPC	4	128	0.25 to ≥256	53.4	–	46.6
CCL	8	128	0.5 to ≥256	50.0	2.9	47.1
CFDN	1	≥128	0.125 to ≥128	50.5	2.9	46.6
CFPN	4	≥256	0.25 to ≥256	–	–	–
CDTR	4	≥128	0.25 to ≥128	–	–	–
CEZ	2	≥256	0.125 to≥256	54.4	0.5	45.1
CFX	8	≥256	2 to ≥256	49.0	–	51.0
CMZ	2	64	0.5 to 128	65.5	18.5	16.0
CTM	2	≥256	0.25 to ≥256	–	–	–
CAZ	16	≥128	4 to ≥128	48.5	3.9	47.6
CTRX	8	≥256	1 to ≥256	50.0	4.9	45.1
CFPM	4	≥256	1 to ≥256	53.9	1.0	45.1
CZOP	1	64	0.5 to 128	–	–	–
IPM	≤0.06	32	≤0.06 to ≥128	61.7	5.8	32.5
PAPM	0.125	16	≤0.06 to 64	–	–	–
MEPM	0.25	32	≤0.06 to 64	59.2	8.8	32.0
BIPM	0.25	32	≤0.06 to 128	–	–	–
DRPM	0.125	16	≤0.06 to 32	–	–	–
FRPM	0.25	≥256	≤0.06 to ≥256	–	–	–
GM	0.25	64	≤0.06 to ≥256	66.5	2.9	30.6
TOB	1	≥256	≤0.06 to ≥256	50.5	3.4	46.1
AMK	4	16	0.5 to 128	95.6	2.5	1.9
ABK	0.5	1	0.125 to 2	–	–	–
EM	≥256	≥256	0.125 to ≥256	36.4	1.0	62.6
CAM	≥128	≥128	0.125 to ≥128	36.9	1.0	62.1
AZM	≥128	≥128	0.25 to ≥128	36.4	0.5	63.1
CPFX	2	128	≤0.06 to ≥256	49.5	0.5	50.0
LVFX	1	≥256	≤0.06 to ≥256	50.0	0	50.0
TFLX	0.25	≥32	≤0.06 to ≥32	–	–	–
MFLX	0.125	32	≤0.06 to 64	50.0	7.8	42.2
PZFX	0.5	≥256	0.125 to ≥256	–	–	–
GRNX	0.125	32	≤0.06 to 64	–	–	–
STFX	0.125	8	≤0.06 to 16	–	–	–
MINO	0.125	16	≤0.06 to 32	69.9	6.8	23.3
CLDM	0.25	≥256	≤0.06 to ≥256	54.4	0	45.6
VCM	1	1	0.25 to 2	100	0	0
TEIC	1	2	≤0.06 to 8	100	0	0
LZD	2	2	1 to 2	100	–	0

The susceptibility of 44 antimicrobial agents against 206 strains of *S.aureus* was determined. PCG benzylpenicillin, MPIPC oxacillin, ABPC ampicillin, PIPC piperacillin, CVA/AMPC clavulanic acid - amoxicillin, SBT/ABPC sulbactam - ABPC, TAZ/PIPC tazobactam – PIPC (tazobactam: PIPC = 1: 8), CCL cefaclor, CFDN cefdinir, CFPN cefcapene, CDTR cefditoren, CEZ cefazolin, CFX cefoxitin, 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, VCM vancomycin, TEIC teicoplanin, CPFX ciprofloxacin, LVFX levofloxacin, TFLX tosufloxacin, MFLX moxifloxacin, PZFX pazufloxacin, GRNX garenoxacin, STFX sitafloxacin, LZD linezolid.

extended spectrum β-lactamase (ESBL) and metallo β-lactamase (MBL) directly in colonies of Gram-negative rods [5], was employed to identify *K. pneumoniae* and *P. aeruginosa* strains which produce such β-lactamases.

3. Results

3.1. Staphylococcus aureus

The *in vitro* antimicrobial susceptibilities, as MIC_{50} / MIC_{90} values, and the range of MICs for *S. aureus* isolates are shown in Table 2. Among the total 206 strains of *S. aureus*, 104 strains (50.5%) were found to be methicillin-resistant *S. aureus* (MRSA; MIC of MPIPC ≥ 4 μg/mL) [Table 3].

3.2. Susceptibility of methicillin-susceptible S. aureus (MSSA)

The MIC_{90}s of penicillins against 102 MSSA strains were 4.0–8.0 μg/mL; however, the MIC_{90} of penicillins in combinations with β-lactamase inhibitors (CVA/AMPC, SBT/ABPC and TAZ/PIPC) decreased to 1.0–4.0 μg/mL. The MIC_{90}s of CCL, CAZ, CTRX, CFPM and CFX ranged from 2.0 to 8.0 μg/mL and those of the other seven cephems from 0.25 to 1.0 μg/mL. Carbapenems showed the strongest activity, with MIC_{90}s of ≤0.125 μg/mL. As for aminoglycosides, GM, TOB, AMK and ABK showed MIC_{90} of 8.0, 8.0, 4.0 and 0.5 μg/mL, respectively. Among the macrolide-lincosamide antibiotics, CLDM showed relatively strong activity with MIC_{90} of 0.25 μg/mL, but the rest of macrolides showed weak activity with MIC_{90}s of ≥128 μg/mL. Relatively strong activities of MINO, VCM, TEIC and LZD were shown, with MIC_{90}s of 0.125–2.0 μg/mL. MIC_{90}s of the seven

Table 3
Antibacterial susceptibility of *Staphylococcus aureus* (MRSA and MSSA).

Antibacterial agent	MRSA, n = 104						MSSA, n = 102					
	MIC (μg/ml)			Susceptibility (%)			MIC (μg/ml)			Susceptibility (%)		
	50%	90%	Range	S	I	R	50%	90%	Range	S	I	R
PCG	16	32	4 to 64	0	–	100	0.125	8	≤0.06 to 32	52.0	–	48.0
MPIPC	128	≥256	8 to ≥256	0	–	100	0.25	0.5	0.125 to 2	100	–	0
ABPC	32	32	8 to 64	0	–	100	0.25	4	≤0.06 to 16	52.9	–	47.1
SBT/ABPC	16	32	2 to 64	20.2	53.8	26.0	0.25	1	≤0.06 to 4	100	0	0
CVA/AMPC	16	32	2 to 64	7.7	–	92.3	0.25	1	0.125 to 2	100	–	0
PIPC	128	≥256	8 to ≥256	–	–	–	1	8	0.5 to 32	–	–	–
TAZ/PIPC	64	≥256	4 to ≥256	7.7	–	92.3	0.5	1	0.25 to 2	100	–	0
CCL	128	≥256	8 to ≥256	1.0	5.7	93.3	1	2	0.5 to 8	100	0	0
CFDN	≥128	≥128	1 to ≥128	1.9	5.8	92.2	0.25	0.5	0.125 to 0.5	100	0	0
CFPN	≥256	≥256	4 to ≥256	–	–	–	1	1	0.25 to 2	–	–	–
CDTR	64	≥128	4 to ≥128	–	–	–	0.5	1	0.25 to 2	–	–	–
CEZ	≥256	≥256	2 to ≥256	9.6	1.0	89.4	0.25	0.5	0.125 to 1	100	0	0
CFX	128	≥256	8 to ≥256	0	–	100	2	4	2 to 8	99.0	–	1.0
CMZ	32	128	2 to 128	31.7	36.6	31.7	1	1	0.5 to 1	100	0	0
CTM	128	≥256	2 to ≥256	–	–	–	0.5	1	0.25 to 1	–	–	–
CAZ	≥128	≥128	8 to ≥128	1.0	4.8	94.2	8	8	4 to 16	97.1	2.9	0
CTRX	≥256	≥256	8 to ≥256	1.0	9.6	89.4	4	4	1 to 8	100	0	0
CFPM	128	≥256	4 to ≥256	8.7	1.9	89.4	2	2	1 to 4	100	0	0
CZOP	32	64	1 to 128	–	–	–	1	1	0.5 to 1	–	–	–
IPM	16	64	≤0.06 to ≥128	24.0	11.6	64.4	≤0.06	≤0.06	≤0.06 to 0.125	100	0	0
PAPM	16	32	≤0.06 to 64	–	–	–	≤0.06	≤0.06	≤0.06 to 0.125	–	–	–
MEPM	16	32	0.25 to 64	19.2	17.3	63.5	≤0.06	0.125	≤0.06 to 0.125	100	0	0
BIPM	16	64	0.25 to 128	–	–	–	≤0.06	≤0.06	≤0.06 to 0.125	–	–	–
DRPM	8	16	0.125 to 32	–	–	–	≤0.06	≤0.06	≤0.06 to 0.125	–	–	–
FRPM	≥256	≥256	0.25 to ≥256	–	–	–	≤0.06	0.125	≤0.06 to 0.125	–	–	–
GM	16	64	≤0.06 to ≥256	44.2	2.9	52.9	0.25	8	0.125 to ≥256	89.2	3.0	7.8
TOB	128	≥256	0.25 to ≥256	12.5	3.8	83.7	0.5	8	≤0.06 to 64	89.2	3.0	7.8
AMK	8	16	0.5 to 128	91.3	4.9	3.8	2	4	0.5 to 8	100	0	0
ABK	0.5	1	0.125 to 2	–	–	–	0.5	0.5	0.125 to 2	–	–	–
EM	≥256	≥256	0.25 to ≥256	1.0	0	99.0	0.25	≥256	0.125 to ≥256	72.5	2.0	25.5
CAM	≥128	≥128	0.25 to ≥128	1.0	0	99.0	0.25	≥128	0.125 to ≥128	73.5	2.0	24.5
AZM	≥128	≥128	1 to ≥128	1.0	0	99.0	1	≥128	0.25 to ≥128	72.5	1.0	26.5
CPFX	128	≥256	0.125 to ≥256	6.7	0	93.3	0.5	1	≤0.06 to ≥256	93.1	1.0	5.9
LVFX	32	≥256	0.125 to ≥256	6.7	0	93.3	0.25	0.5	≤0.06 to ≥256	94.1	0	5.9
TFLX	≥32	≥32	≤0.06 to ≥32	–	–	–	≤0.06	0.125	≤0.06 to ≥32	–	–	–
MFLX	8	32	≤0.06 to 64	6.7	13.5	79.8	≤0.06	0.125	≤0.06 to 64	94.1	2.0	3.9
PZFX	16	≥256	0.125 to ≥256	–	–	–	0.25	0.25	0.125 to ≥256	–	–	–
GRNX	4	32	≤0.06 to 64	–	–	–	≤0.06	≤0.06	≤0.06 to 32	–	–	–
STFX	2	8	≤0.06 to 16	–	–	–	≤0.06	≤0.06	≤0.06 to 16	–	–	–
MINO	8	16	≤0.06 to 32	42.3	11.5	46.2	0.125	0.125	≤0.06 to 8	98.0	2.0	0
CLDM	≥256	≥256	0.125 to ≥256	12.5	0	87.5	0.125	0.25	≤0.06 to ≥256	97.1	0	2.9
VCM	1	1	0.25 to 2	100	0	0	1	1	0.25 to 2	100	0	0
TEIC	1	2	0.25 to 8	100	0	0	0.5	1	≤0.06 to 4	100	0	0
LZD	2	2	1 to 2	100	–	0	2	2	1 to 2	100	–	0

The susceptibility of 44 antimicrobial agents against 104 strains of MRSA and 102 strains of MSSA was determined. Ratio of MRSA was 50.5%.

fluoroquinolones were within the range of ≤0.06–1.0 μg/mL. GRNX and STFX showed the strongest activities among the fluoroquinolones.

3.3. Susceptibility of MRSA

Only four agents, ABK, VCM, TEIC and LZD, showed strong activity against MRSA with MIC_{90} of ≤2.0 μg/mL. MINO showed weak activity with MIC_{90}s of 16 μg/mL. Other agents showed almost no activity, with MIC_{90}s of ≥32 μg/mL.

3.4. Streptococcus pneumoniae

The susceptibilities of the 189 strains of *S. pneumoniae* to PCG revealed that 187 strains (98.9%), 2 strains (1.1%), and 0 strains (0.0%) were identified as penicillin-susceptible (PSSP), penicillin-intermediate (PISP), and penicillin-resistant strains (PRSP), respectively, with the breakpoint for PCG defined by the CLSI standards [Table 4].

Among the β-lactams, CCL, CAZ and CMZ showed high MIC_{90}s (64, 8 and 16 μg/mL, respectively) while many of the other β-lactams, except for the carbapenems, showed potent activities, with MIC_{90}s of 1.0–4.0 μg/mL. All five carbapenems showed strong activities (MIC_{90}: ≤0.25 μg/mL) against all *S. pneumoniae* strains, regardless of their different susceptibilities to PCG. Fluoroquinolones also showed potent activities against the strains with MIC_{90}s of ≤0.06–2 μg/mL. STFX was the strongest fluoroquinolone and the MIC against all strains was ≤0.5 μg/mL. The glycopeptides (VCM and TEIC) showed strong activities (MIC_{90}: ≤0.5 μg/mL). Aminoglycosides were substantially less active, with MIC_{90}s of 8.0–64.0 μg/mL. High frequencies of resistance against the macrolide antibiotics, EM, CAM, and AZM, were shown, with MIC_{90}s of ≥128 μg/mL.

3.5. Streptococcus pyogenes

The susceptibilities of the 4 *S. pyogenes* strains are summarized in Table 5. All β-lactams showed strong activities (MIC_{90}: ≤0.5 μg/mL). Aminoglycosides and macrolides were less active, with MIC_{90}s of 8.0–≥256 μg/mL. Among fluoroquinolones, MFLX, GRNX and STFX showed potent activities (MIC_{90}: ≤0.25 μg/mL), while the MIC_{90} of PZFX was 4.0 μg/mL.

Table 4
Antibacterial susceptibility of *Streptococcus pneumoniae*.

Antibacterial agent	All strains, n = 189						PSSP, n = 187						PISP, n = 2	
	MIC(μg/ml)			Susceptibility (%)			MIC(μg/ml)			Susceptibility (%)			MIC(μg/ml)	
	50%	90%	Range	S	I	R	50%	90%	Range	S	I	R	50%	90%
PCG	0.25	2	≤0.06 to 4	42.9	41.8	15.3	0.25	2	≤0.06 to 2	100	0	0	4	4
ABPC	0.25	2	≤0.06 to 8	–	–	–	0.25	2	≤0.06 to 4	–	–	–	8	8
SBT/ABPC	0.25	2	≤0.06 to 8	–	–	–	0.25	2	≤0.06 to 4	–	–	–	8	8
CVA/AMPC	0.125	1	≤0.06 to 4	99.5	0.5	0	0.125	1	≤0.06 to 2	100	0	0	1	4
PIPC	0.25	2	≤0.06 to 8	–	–	–	0.25	2	≤0.06 to 4	–	–	–	4	8
TAZ/PIPC	0.25	2	≤0.06 to 4	–	–	–	0.25	2	≤0.06 to 4	–	–	–	4	4
CCL	4	64	0.25 to 128	41.8	6.3	51.9	4	64	0.25 to 128	42.2	6.5	51.3	128	128
CFDN	0.5	4	≤0.06 to 32	50.8	10.6	38.6	0.5	4	≤0.06 to 32	51.3	10.7	38.0	8	16
CFPN	0.25	1	≤0.06 to 16	–	–	–	0.25	1	≤0.06 to 16	–	–	–	1	4
CDTR	0.125	0.5	≤0.06 to 4	–	–	–	0.125	0.5	≤0.06 to 4	–	–	–	1	2
CEZ	0.5	2	≤0.06 to 32	–	–	–	0.5	2	≤0.06 to 32	–	–	–	4	32
CMZ	1	16	≤0.06 to 64	–	–	–	1	16	≤0.06 to 32	–	–	–	32	64
CTM	0.5	4	≤0.06 to 32	–	–	–	0.5	4	≤0.06 to 16	–	–	–	4	32
CAZ	4	8	≤0.06 to 64	–	–	–	4	8	≤0.06 to 64	–	–	–	16	16
CTRX	0.5	1	≤0.06 to 4	96.8	1.1	2.1	0.5	1	≤0.06 to 4	97.9	0.5	1.6	2	4
CFPM	0.5	1	≤0.06 to 8	95.8	3.2	1.1	0.5	1	≤0.06 to 8	96.3	2.6	1.1	1	2
CZOP	0.5	1	≤0.06 to 4	–	–	–	0.5	1	≤0.06 to 4	–	–	–	2	4
IPM	≤0.06	0.25	≤0.06 to 1	77.2	21.2	1.6	≤0.06	0.25	≤0.06 to 1	78.1	20.8	1.1	0.5	1
PAPM	≤0.06	0.125	≤0.06 to 0.25	–	–	–	≤0.06	0.125	≤0.06 to 0.25	–	–	–	0.125	0.25
MEPM	≤0.06	0.25	≤0.06 to 1	92.6	6.3	1.1	≤0.06	0.25	≤0.06 to 1	93.6	5.9	0.5	0.5	1
BIPM	≤0.06	0.25	≤0.06 to 1	–	–	–	≤0.06	0.25	≤0.06 to 0.5	–	–	–	0.5	1
DRPM	≤0.06	0.25	≤0.06 to 1	–	–	–	≤0.06	0.25	≤0.06 to 0.5	–	–	–	0.5	1
FRPM	≤0.06	0.25	≤0.06 to 2	–	–	–	≤0.06	0.25	≤0.06 to 1	–	–	–	0.5	2
GM	8	8	1 to 16	–	–	–	8	8	1 to 16	–	–	–	4	8
TOB	16	32	4 to 32	–	–	–	16	32	4 to 32	–	–	–	8	16
AMK	64	64	8 to 128	–	–	–	64	64	8 to 128	–	–	–	32	64
ABK	16	32	4 to 64	–	–	–	16	32	4 to 64	–	–	–	16	32
EM	≥256	≥256	≤0.06 to 256	11.1	0	88.9	≥256	≥256	≤0.06 to ≥256	11.2	0	88.8	≥256	≥256
CAM	≥128	≥128	≤0.06 to ≥128	11.6	0.6	87.8	≥128	≥128	≤0.06 to ≥128	11.8	0.5	87.7	≥128	≥128
AZM	≥128	≥128	≤0.06 to ≥128	11.1	1.1	87.8	≥128	≥128	≤0.06 to ≥128	11.2	1.1	87.7	≥128	≥128
CPFX	1	2	≤0.06 to 64	–	–	–	1	2	≤0.06 to 64	–	–	–	1	64
LVFX	1	2	0.5 to 64	97.9	0.5	1.6	1	2	0.5 to 64	98.4	0.5	1.1	1	16
TFLX	0.25	0.25	≤0.06 to ≥32	–	–	–	0.25	0.25	≤0.06 to 16	–	–	–	0.25	≥32
MFLX	0.25	0.25	0.125 to 4	98.4	0.5	1.1	0.25	0.25	0.125 to 4	98.9	0.6	0.5	0.25	4
PZFX	2	4	1 to 64	–	–	–	2	4	1 to 64	–	–	–	2	32
GRNX	≤0.06	≤0.06	≤0.06 to 1	–	–	–	≤0.06	≤0.06	≤0.06 to 0.5	–	–	–	≤0.06	1
STFX	≤0.06	≤0.06	≤0.06 to 0.5	–	–	–	≤0.06	≤0.06	≤0.06 to 0.5	–	–	–	≤0.06	0.5
MINO	16	32	≤0.06 to 64	–	–	–	16	32	≤0.06 to 64	–	–	–	8	8
CLDM	128	≥256	≤0.06 to ≥256	40.2	0	59.8	128	≥256	≤0.06 to ≥256	40.6	0	59.4	128	128
VCM	0.25	0.5	≤0.06 to 0.5	100	–	0	0.25	0.5	≤0.06 to 0.5	100	–	0	0.25	0.5
TEIC	0.125	0.125	≤0.06 to 0.25	–	–	–	0.125	0.125	≤0.06 to 0.25	–	–	–	≤0.06	0.125
LZD	1	1	≤0.06 to 2	100	–	0	1	1	≤0.06 to 2	100	–	0	0.5	0.5

The susceptibility of 42 antimicrobial agents against 189 strains of *S.pneumoniae* was determined. Ratio of peniciliin-susceptible, penicillin-intermediate and penicillin resistant *S. pneumoniae* (PSSP, PISP and PRSP) was 98.9%, 1.1% and 0%, respectively.

3.6. *Haemophilus influenzae*

The susceptibilities of the 182 *H. influenzae* strains are summarized in Table 6 and Table 7. According to the CLSI breakpoint for ABPC, 69 (37.9%) were found to be ABPC-susceptible, 32 (17.6%) to be ABPC-intermediate and 61 (33.5%) to be ABPC-resistant. With the use of the Nitrocephin disks, all ABPC-intermediate and ABPC-resistant strains were found to be β-lactamase-non-producing, and they were defined as BLNAI and BLNAR, respectively. The other 20 (11.0%) ABPC-resistant strains were found to be β-lactamase-producing strains, designated as BLPAR. The MIC_{50} and MIC_{90} values of PCG and ABPC for BLPAR isolates were at least threefold higher than those for BLNAR isolates. However, there were no differences in the MIC_{50} and MIC_{90} values of SBT/ABPC and CVA/AMPC among BLNAR isolates and BLPAR isolates. Regardless of susceptibility to ABPC, all of the *H. influenzae* strains were extremely susceptible to all seven fluoroquinolones (MIC_{50}s: ≤0.06 μg/mL). STFX showed a potent activity and the maximum MIC value was 0.25 μg/mL, whereas those of the other fluoroquinolones were 4.0-≥32 μg/mL. BLPAR strains showed high levels of resistance against PIPC, with MIC_{90} values of ≥256 μg/mL, whereas TAZ/PIPC showed strong activities, with MIC_{90}s of 1.0 μg/mL. Among the cephems, CDTR, CAZ and CTRX showed the most potent activities, with MIC_{90}s of ≤0.06 μg/mL. Of the five carbapenem agents, MEPM showed the most potent activity against all types of *H. influenzae* strains. Among macrolide, AZM showed the most potent activity, with MIC_{90}s of 2.0 μg/mL.

3.7. *Moraxella catarrhalis*

The susceptibilities of 74 *M. catarrhalis* strains are shown in Table 8. For the penicillins, β-lactamase inhibitors restored the activities of penicillins; e.g., SBT decreased the MIC_{90} of ABPC from 16 to 0.25 μg/mL and TAZ decrease the MIC_{90} of PIPC from 8.0 to 0.125 μg/mL. Carbapenems showed strong activities, with MIC_{90}s of ≤0.06 μg/mL. Fluoroquinolones also showed strong activities, with MIC_{90}s of ≤0.06 μg/mL (CPFX, TFLX, PZFX, GRNX and STFX). Several cephems (CFDN, CFPN, CDTR, CAZ and CMZ), four aminoglycosides (GM, TOB, AMK and ABK), and three macrolides (EM, CAM, and

Table 5
Antibacterial susceptibility of *Streptococcus pyogenes*.

Antibacterial agent	All strains, n = 4	
	MIC(μg/ml)	
	50%	90%
PCG	≤0.06	≤0.06
ABPC	≤0.06	≤0.06
SBT/ABPC	≤0.06	≤0.06
CVA/AMPC	≤0.06	≤0.06
PIPC	≤0.06	≤0.06
TAZ/PIPC	≤0.06	≤0.06
CCL	≤0.06	≤0.06
CFDN	≤0.06	≤0.06
CFPN	≤0.06	≤0.06
CDTR	≤0.06	≤0.06
CEZ	≤0.06	0.125
CMZ	0.25	0.5
CTM	≤0.06	≤0.06
CAZ	0.125	0.125
CTRX	≤0.06	≤0.06
CFPM	≤0.06	≤0.06
CZOP	≤0.06	≤0.06
IPM	≤0.06	≤0.06
PAPM	≤0.06	≤0.06
MEPM	≤0.06	≤0.06
BIPM	≤0.06	≤0.06
DRPM	≤0.06	≤0.06
FRPM	≤0.06	≤0.06
GM	4	8
TOB	8	16
AMK	32	64
ABK	8	16
EM	1	≥256
CAM	0.5	≥128
AZM	0.25	≥128
CPFX	0.5	2
LVFX	0.5	1
TFLX	0.125	0.5
MFLX	0.125	0.25
PZFX	1	4
GRNX	≤0.06	0.25
STFX	≤0.06	≤0.06
MINO	0.125	8
CLDM	≤0.06	128
VCM	0.25	0.5
TEIC	≤0.06	0.125
LZD	1	1

The susceptibility of 42 antimicrobial agents against 4 strains of *S. pyogenes* was determined.

AZM) also showed potent activities, with the MIC_{90}s of 0.125–1.0 μg/mL.

3.8. *Klebsiella pneumoniae*

The susceptibilities of 139 *K. pneumoniae* strains are shown in Table 9. Carbapenems showed strong activities, with MIC_{90}s of ≤0.5 μg/mL; in particular, MEPM showed the most potent activities, with MIC_{90}s ≤ 0.06 μg/mL. Of the cephems and the monobactam, CFPM showed the most potent activity, with MIC_{90}s ≤ 0.06 μg/mL, and CFDN, CTM, CAZ, CTRX, CZOP and AZT also showed strong activities, with MIC_{90}s of 0.125–0.25 μg/mL. All fluoroquinolones we tested and three aminoglycosides (GM, TOB and ABK) showed potent activities, with MIC_{90}s of 0.5–2.0 μg/mL β-lactamase inhibitors apparently restored the activities of penicillins; e.g., SBT decreased the MIC_{90} of ABPC from 128 to 8 μg/mL and TAZ decreased the MIC_{90} of PIPC from 16 to 8.0 μg/mL. Proportions of susceptible/intermediate/resistant for CEZ, CAZ, CTRX and AZT were 96.4/0.0/3.6, 98.6/0.7/0.7, 97.8/0.0/2.2 and 97.8/1.4/0.7, respectively. Four of 139 strains (2.9%) were found to be ESBL-producing strains.

3.9. *Pseudomonas aeruginosa*

A total 160 *P. aeruginosa* strains were tested for antimicrobial susceptibility [Table 10]. Among the β-lactams, three carbapenems (MEPM, BIPM and DRPM) showed potent activities, with MIC_{50}s of 0.5 μg/mL; however, these agents showed relatively higher MIC_{90} levels, of 8.0–16 μg/mL. Among the fluoroquinolones, STFX showed the most potent activity, with MIC_{50}s and MIC_{90}s of 0.25 and 4.0 μg/mL, respectively. Other fluoroquinolones also showed strong activities with MIC_{50}s of 0.25–2.0 μg/mL, whereas MIC_{90} levels (8.0 to ≥32 μg/mL) suggested partial resistance. Both PIPC and TAZ/PIPC showed potent activities, with MIC_{50}s of 8.0 μg/mL, but higher levels of MIC_{90}s (128 μg/mL) of these agents were also observed. The MIC_{50}s of the four aminoglycosides (GM, TOB, AMK and ABK), three cephems (CAZ, CFPM and CZOP), and the monobactam (AZT) were within the range of 1.0–8.0 μg/mL. Among the 160 *P. aeruginosa* isolates, we found 1 multidrug-resistant isolate (0.6%) and the isolate was confirmed to produce metallo-β-lactamase.

According to the CLSI breakpoint M100-S20, susceptible and resistant rates for PIPC were 87.5% and 12.5%, respectively. Proportions of susceptible/intermediate/resistant for carbapenems were 71.9/11.9/16.3 for IPM and 81.9/4.4/13.8 for MEPM.

4. Discussion

The Japanese Society of Chemotherapy (JSC) established a nationwide surveillance network in 2006 to establish the resource of information about antimicrobial susceptibility of bacterial pathogens in Japan. Our research focuses on major seven major bacterial respiratory pathogens, such as *S. aureus*, *S. pneumoniae*, *S. pyogenes*, *H. influenzae*, *M. catarrhalis*, *K. pneumoniae* and *P. aeruginosa*. It is desirable that analysis of antimicrobial susceptibility is done with the use of bacterial strains that actually cause the infections. To analyze the actual pathogens causing infections, we collected clinical isolates only from well-diagnosed adult patients with respiratory tract infections (RTIs).

Our surveillance was conducted for four consecutive years from 2006. The total number of strains at surveillance conducted in 2006, 2007, 2008, 2009 and 2010 were 887, 1108, 987, 635 and 955, respectively. To reflect the trend of pathogens of respiratory infections in Japan, we think we should increase the scope of the survey by reflecting results with a greater numbers of pathogens.

The ratio of MRSA was as high as 50.5% that was decreased from 58.5% in RTI 2009 [2]. These MRSA strains are susceptible to ABK, VCM, TEIC and LZD except that a few strains somewhat less susceptible (MIC 8.0 μg/mL) to TEIC. Although the emergence of resistant MRSA against VCM, TEIC or LZD has already been reported in Japan, such a resistant strain was not detected in this surveillance. The MRSA with a MIC of 2.0 μg/mL to VCM was 5.8% of MRSA. MRSA isolates with VCM MIC at 2.0 μg/mL are categorized in susceptible strains, however, the isolates can be associated with treatment failures, mainly in bloodstream infection [6]. Therefore, this population should be observed continuously in the next surveillance.

Since the surveillance in 2009 [2], the susceptibility of *S. pneumoniae* to PCG was categorized with the new criteria of breakpoint MICs, and the proportion of PSSP/PISP/PRSP was found to be 99:1:0. These findings were similar to those in RTI 2009 (94:6:0) and suggest that penicillin is still effective against community-acquired pneumonia caused by *S. pneumoniae* but penicillin-intermediate strains are partly present.

Table 6
Antibacterial susceptibility of *Haemophilus influenzae* (all strains and β-lactamase-producing strains).

Antimicrobial agent	All strains, n = 182						β-lactamase (+), n = 20					
	MIC (μg/ml)			Susceptibility (%)			MIC (μg/ml)			Susceptibility (%)		
	50%	90%	Range	S	I	R	50%	90%	Range	S	I	R
PCG	4	32	0.125 to ≥256	–	–	–	≥256	≥256	4 to ≥256	–	–	–
ABPC	2	32	0.125 to ≥256	37.9	17.6	44.5	128	≥256	4 to ≥256	0	0	100
SBT/ABPC	2	8	≤0.06 to 16	59.3	–	40.7	8	8	1 to 8	30.0	–	70.0
CVA/AMPC	4	8	≤0.06 to 16	78.0	–	22.0	4	8	0.5 to 16	65.0	–	35.0
PIPC	≤0.06	1	≤0.06 to ≥256	–	–	–	64	≥256	0.25 to ≥256	–	–	–
TAZ/PIPC	≤0.06	0.125	≤0.06 to 0.5	100	–	0	≤0.06	0.125	≤0.06 to 0.125	100	–	0
CCL	16	64	≤0.06 to ≥256	46.7	8.2	45.1	32	64	4 to 128	35.0	10.0	55.0
CFDN	2	8	≤0.06 to 16	44.5	–	55.5	2	4	0.25 to 8	30.0	–	70.0
CFPN	1	2	≤0.06 to 8	–	–	–	1	2	≤0.06 to 2	–	–	–
CDTR	0.125	0.25	≤0.06 to 1	–	–	–	0.125	0.25	≤0.06 to 0.5	–	–	–
CEZ	8	128	0.5 to ≥256	–	–	–	32	128	2 to 128	–	–	–
CMZ	8	32	0.5 to 64	–	–	–	8	16	2 to 16	–	–	–
CTM	8	64	0.125 to 128	–	–	–	16	64	1 to 64	–	–	–
CAZ	0.25	0.5	≤0.06 to 4	99.5	–	0.5	0.25	0.5	≤0.06 to 0.5	100	–	0
CTRX	0.125	0.25	≤0.06 to 1	100	–	0	0.125	0.25	≤0.06 to 0.5	100	–	0
CFPM	1	2	≤0.06 to 4	97.8	–	2.2	1	2	0.125 to 2	100	–	0
CZOP	4	16	≤0.06 to 32	–	–	–	8	16	0.125 to 16	–	–	–
IPM	1	2	≤0.06 to 8	99.5	–	0.5	1	2	0.25 to 4	100	–	0
PAPM	0.5	2	≤0.06 to 4	–	–	–	0.5	1	0.125 to 4	–	–	–
MEPM	0.125	0.25	≤0.06 to 1	97.8	–	2.2	0.125	0.25	≤0.06 to 0.5	100	–	0
BIPM	2	4	≤0.06 to8	–	–	–	2	4	0.25 to 4	–	–	–
DRPM	0.25	1	≤0.06 to 4	–	–	–	0.25	1	≤0.06 to 1	–	–	–
FRPM	1	2	≤0.06 to 8	–	–	–	2	2	0.25 to 4	–	–	–
AZT	0.5	2	≤0.06 to 8	96.7	–	3.3	0.5	1	≤0.06 to 1	100	–	0
GM	1	2	0.25 to 2	–	–	–	2	2	0.5 to 2	–	–	–
TOB	2	4	0.25 to 4	–	–	–	2	4	0.5 to 4	–	–	–
AMK	4	8	0.5 to 16	–	–	–	8	8	2 to 8	–	–	–
ABK	4	4	1 to 8	–	–	–	4	4	2 to 8	–	–	–
EM	4	8	0.125 to 16	–	–	–	4	8	2 to 8	–	–	–
CAM	4	8	0.125 to 32	91.8	7.1	1.1	4	8	2 to 16	90.0	10.0	0
AZM	1	2	≤0.06 to 4	100	–	0	1	2	0.5 to 4	100	–	0
CPFX	≤0.06	≤0.06	≤0.06 to 16	99.5	–	0.5	≤0.06	≤0.06	≤0.06	100	–	0
LVFX	≤0.06	≤0.06	≤0.06 to 8	99.5	–	0.5	≤0.06	≤0.06	≤0.06	100	–	0
TFLX	≤0.06	≤0.06	≤0.06 to ≥32	–	–	–	≤0.06	≤0.06	≤0.06	–	–	–
MFLX	≤0.06	≤0.06	≤0.06 to 4	98.9	–	1.1	≤0.06	≤0.06	≤0.06	100	–	0
PZFX	≤0.06	≤0.06	≤0.06 to 8	–	–	–	≤0.06	≤0.06	≤0.06	–	–	–
GRNX	≤0.06	≤0.06	≤0.06 to 4	–	–	–	≤0.06	≤0.06	≤0.06	–	–	–
STFX	≤0.06	≤0.06	≤0.06 to 0.25	–	–	–	≤0.06	≤0.06	≤0.06	–	–	–
MINO	0.25	0.5	0.125 to 2	–	–	–	0.5	0.5	0.25 to 0.5	–	–	–
CLDM	8	16	0.5 to 64	–	–	–	8	16	2 to 16	–	–	–

The susceptibility of 40 antimicrobial agents against 182 strains of *H. influenzae* was determined.

To understand the trend of the susceptibility of *S. pneumoniae* to PCG, we also compared the ratio of the *S. pneumoniae* isolation in each year with the previous criteria, which was determined by reference to the susceptibility breakpoint for meningitis (0.06 μg/mL). Although the proportion of PSSP/PISP/PRSP of 2006 and 2007 were similar level (61:35:4 and 65:30:5, respectively), the susceptibility of *S. pneumoniae* to PCG continuously decreased and the prevalence in 2010 was 43:42:15. Because it is difficult to detect these alarming trends by the new criteria of breakpoint MICs, careful watching using the previous criteria should be continuously needed.

Concerning *H. influenzae*, half of the strains in the present survey showed decreased susceptibility to ABPC without production of β-lactamase; BLNAI (17.6%) and BLNAR (33.5%). The ratio of BLNAI and BLNAR in adults is thought to be lower than in children [7]. The β-lactamase-producing clavulanic acid/ampicillin-resistant strains (BLPACR) have been also increasing and reached 4.8% of clinical isolates in children [7]. In this surveillance, we observed 7 (3.8%) BLPACR strains and the prevalence was similar to children, suggesting that BLPACR may be increasing in both children and adults. BLPACR can be included in the β-lactamase positive population. All seven fluoroquinolones demonstrated extremely strong activity ($MIC_{90} \leq 0.06$ μg/mL) against *H. influenzae* strains, regardless of their ABPC susceptibility. Among the rest of agents, PIPC, TAZ/PIPC, CDTR, CTRX, and MEPM showed strong activities (MIC_{90}s of 0.125–1.0 μg/mL) against BLNAS, BLNAI and BLNAR strains. TAZ markedly restored the activity of PIPC against BLPAR (MIC_{90} decreased from ≥256 μg/mL to 1.0 μg/mL).

The susceptibilities of *M. catarrhalis* in the present survey showed that β-lactamase inhibitors restored the activities of penicillins against these strains: SBT decreased the MIC_{90} of ABPC from 16 to 0.25 μg/mL. The data suggest that most of the strains were resistant to penicillins because of β-lactamase production. For the treatment of *M. catarrhalis* infections, carbapenems, macrolides, and fluoroquinolones may be recommended because these drugs showed strong activities, with MIC_{90}s of ≤0.06–0.25 μg/mL.

The prevalence of ESBL strains has become a concern in recent years. In 1990s, the ratio of ESBL among *K. pneumoniae* and *E. coli* was 0.3% and <0.1%, respectively [8]. The prevalence of this study (2.9%) was elevated when compared with the RTI 2009 (1.3%). The increasing tendency was also observed in previous reports [9,10]. The improvement of susceptibilities of β-lactams due to β-lactamase inhibitors might suggest that β-lactamase-producers including ESBL-producing strains.

In M100-S20 breakpoint criteria for *K. pneumoniae* [3], no carbapenem-resistant isolate was observed. However, when based

Table 7
Antibacterial susceptibility of β-lactamase-non-producing *Haemophilus influenzae*

Antimicrobial agent	BLNAS [ABPC ≤ 1, β-lactamase (−)], n = 69						BLNAI [ABPC = 2, β-lactamase (−)], n = 32						BLNAR [ABPC ≥ 4, β-lactamase (−)],n = 61					
	MIC (μg/ml)			Susceptibility (%)			MIC (μg/ml)			Susceptibility (%)			MIC (μg/ml)			Susceptibility (%)		
	50%	90%	Range	S	I	R	50%	90%	Range	S	I	R	50%	90%	Range	S	I	R
PCG	0.5	2	0.125 to 8	–	–	–	4	4	1 to 8	–	–	–	8	8	2 to 16	–	–	–
ABPC	0.25	1	0.125 to 1	100	0	0	2	2	2	0	100	0	4	8	4 to 16	0	0	100
SBT/ABPC	0.25	1	≤0.06 to 2	100	–	0	2	2	2 to 4	96.9	–	3.1	4	8	2 to 16	3.3	–	96.7
CVA/AMPC	0.5	2	≤0.06 to 4	100	–	0	4	4	2 to 8	90.6	–	9.4	4	8	2 to 16	50.8	–	49.2
PIPC	≤0.06	0.125	≤0.06 to 0.125	–	–	–	≤0.06	0.125	≤0.06 to 0.25	–	–	–	0.125	0.125	≤0.06 to 0.25	–	–	–
TAZ/PIPC	≤0.06	≤0.06	≤0.06 to 0.25	100	–	0	≤0.06	0.125	≤0.06 to 0.25	100	–	0	≤0.06	0.125	≤0.06 to 0.5	100	–	0
CCL	4	16	≤0.06 to 64	79.7	11.6	8.7	16	64	2 to 128	46.9	15.6	37.5	32	64	4 to ≥256	13.1	0	86.9
CFDN	0.25	4	≤0.06 to 8	79.7	–	20.3	2	8	0.5 to 16	46.9	–	53.1	8	8	1 to 16	8.2	–	91.8
CFPN	≤0.06	1	≤0.06 to 2	–	–	–	1	2	≤0.06 to 4	–	–	–	2	4	0.5 to 8	–	–	–
CDTR	≤0.06	0.25	≤0.06 to 0.5	–	–	–	0.125	0.25	≤0.06 to 0.5	–	–	–	0.25	0.25	0.125 to 1	–	–	–
CEZ	2	16	0.5 to 64	–	–	–	2	64	1 to ≥256	–	–	–	32	128	1 to ≥256	–	–	–
CMZ	2	8	0.5 to 32	–	–	–	8	32	2 to 64	–	–	–	8	64	2 to 64	–	–	–
CTM	2	32	0.125 to 64	–	–	–	8	64	1 to 64	–	–	–	32	64	1 to 128	–	–	–
CAZ	0.125	0.5	≤0.06 to 1	100	–	0	0.25	0.5	≤0.06 to 2	100	–	0	0.25	1	≤0.06 to 4	98.4	–	1.6
CTRX	≤0.06	0.25	≤0.06 to 0.25	100	–	0	0.25	0.25	≤0.06 to 0.5	100	–	0	0.25	0.5	≤0.06 to 1	100	–	0
CFPM	0.125	2	≤0.06 to 2	100	–	0	1	2	0.25 to 4	96.9	–	3.1	2	2	0.5 to 4	95.1	–	4.9
CZOP	0.25	8	≤0.06 to 8	–	–	–	8	16	0.5 to 32	–	–	–	8	16	4 to 32	–	–	–
IPM	0.5	2	≤0.06 to 2	100	–	0	1	2	0.125 to 4	100	–	0	1	2	0.25 to 8	98.4	–	1.6
PAPM	0.5	1	≤0.06 to 2	–	–	–	0.5	2	≤0.06 to 2	–	–	–	1	2	0.125 to 4	–	–	–
MEPM	≤0.06	0.125	≤0.06 to 0.25	100	–	0	0.125	0.25	≤0.06 to 0.5	100	–	0	0.25	0.5	≤0.06 to 1	93.4	–	6.6
BIPM	0.5	4	≤0.06 to 8	–	–	–	2	4	≤0.06 to 4	–	–	–	4	8	0.5 to 8	–	–	–
DRPM	0.125	0.5	≤0.06 to 1	–	–	–	0.5	1	≤0.06 to 1	–	–	–	0.5	2	≤0.06 to 4	–	–	–
FRPM	0.5	2	≤0.06 to 2	–	–	–	2	2	0.5 to 4	–	–	–	2	4	0.5 to 8	–	–	–
AZT	≤0.06	1	≤0.06 to 8	98.6	–	1.4	0.5	1	≤0.06 to 4	96.9	–	3.1	1	2	0.25 to 4	93.4	–	6.6
GM	1	2	0.25 to 2	–	–	–	1	2	0.5 to 2	–	–	–	1	2	0.5 to 2	–	–	–
TOB	2	4	0.5 to 4	–	–	–	2	4	0.5 to 4	–	–	–	2	4	0.25 to 4	–	–	–
AMK	4	8	0.5 to 8	–	–	–	4	8	2 to 8	–	–	–	4	8	2 to 16	–	–	–
ABK	4	4	1 to 8	–	–	–	2	4	2 to 4	–	–	–	4	4	2 to 8	–	–	–
EM	2	4	0.125 to 8	–	–	–	4	4	0.25 to 16	–	–	–	4	8	1 to16	–	–	–
CAM	4	8	0.125 to 16	95.7	4.3	0	4	8	0.25 to 32	90.6	6.3	3.1	8	16	2 to 32	88.5	9.9	1.6
AZM	1	2	≤0.06 to 2	100	–	0	1	2	0.125 to 2	100	–	0	1	2	0.25 to 4	100	–	0
CPFX	≤0.06	≤0.06	≤0.06 to 16	98.6	–	1.4	≤0.06	≤0.06	≤0.06 to 1	100	–	0	≤0.06	≤0.06	≤0.06 to0.125	100	–	0
LVFX	≤0.06	≤0.06	≤0.06 to 8	98.6	–	1.4	≤0.06	≤0.06	≤0.06 to 1	100	–	0	≤0.06	≤0.06	≤0.06	100	–	0
TFLX	≤0.06	≤0.06	≤0.06 to ≥32	–	–	–	≤0.06	≤0.06	≤0.06 to 1	–	–	–	≤0.06	≤0.06	≤0.06	–	–	–
MFLX	≤0.06	0.125	≤0.06 to 4	98.6	–	1.4	≤0.06	≤0.06	≤0.06 to 2	96.9	–	3.1	≤0.06	≤0.06	≤0.06 to 0.125	100	–	0
PZFX	≤0.06	≤0.06	≤0.06 to 8	–	–	–	≤0.06	≤0.06	≤0.06 to 1	–	–	–	≤0.06	≤0.06	≤0.06 to 0.25	–	–	–
GRNX	≤0.06	≤0.06	≤0.06 to 4	–	–	–	≤0.06	≤0.06	≤0.06 to 2	–	–	–	≤0.06	≤0.06	≤0.06 to 0.125	–	–	–
STFX	≤0.06	≤0.06	≤0.06 to 0.25	–	–	–	≤0.06	≤0.06	≤0.06	–	–	–	≤0.06	≤0.06	≤0.06	–	–	–
MINO	0.25	0.5	0.125 to 2	–	–	–	0.25	0.5	0.125 to 1	–	–	–	0.5	0.5	0.125 to 1	–	–	–
CLDM	8	16	0.5 to 32	–	–	–	4	16	1 to 64	–	–	–	8	16	2 to 64	–	–	–

The susceptibility of 40 antimicrobial agents against 162 strains of β-lactamase-non-producing *H. influenzae* was determined.

Table 8
Antibacterial susceptibility of *Moraxella catarrhalis*.

Antibacterial agent	MIC (μg/ml)			Susceptibility (%)		
	50%	90%	Range	S	I	R
PCG	16	32	≤0.06 to 64	–	–	–
ABPC	4	16	≤0.06 to 16	–	–	–
SBT/ABPC	0.125	0.25	≤0.06 to 0.25	–	–	–
CVA/AMPC	0.125	0.25	≤0.06 to 0.5	100	–	0
PIPC	4	8	≤0.06 to 16	–	–	–
TAZ/PIPC	≤0.06	≤0.06	≤0.06	–	–	–
CCL	1	4	0.25 to 32	94.6	4.0	1.4
CFDN	0.25	0.5	≤0.06 to 1	–	–	–
CFPN	0.5	1	≤0.06 to 2	–	–	–
CDTR	0.5	1	≤0.06 to 4	–	–	–
CEZ	8	16	0.5 to 32	–	–	–
CMZ	0.5	1	≤0.06 to 1	–	–	–
CTM	1	2	0.25 to 4	–	–	–
CAZ	0.125	0.5	≤0.06 to 0.5	100	–	0
CTRX	1	2	≤0.06 to 8	97.3	–	2.7
CFPM	1	4	0.125 to 8	–	–	–
CZOP	2	4	0.25 to 8	–	–	–
IPM	≤0.06	0.125	≤0.06 to 0.25	–	–	–
PAPM	≤0.06	≤0.06	≤0.06	–	–	–
MEPM	≤0.06	≤0.06	≤0.06	–	–	–
BIPM	≤0.06	≤0.06	≤0.06	–	–	–
DRPM	≤0.06	≤0.06	≤0.06	–	–	–
FRPM	0.25	0.5	≤0.06 to 1	–	–	–
AZT	2	2	0.25 to 4	–	–	–
GM	0.125	0.125	≤0.06 to 0.25	–	–	–
TOB	0.25	0.25	≤0.06 to 0.5	–	–	–
AMK	0.5	1	0.25 to 2	–	–	–
ABK	0.25	0.25	≤0.06 to 0.5	–	–	–
EM	0.25	0.5	≤0.06 to 1	97.3	2.7	0
CAM	0.125	0.25	≤0.06 to 0.5	100	0	0
AZM	≤0.06	≤0.06	≤0.06 to 0.125	100	0	0
CPFX	≤0.06	≤0.06	≤0.06 to 1	100	–	0
LVFX	≤0.06	0.125	≤0.06 to 2	100	–	0
TFLX	≤0.06	≤0.06	≤0.06 to 0.125	–	–	–
MFLX	≤0.06	0.125	≤0.06 to 1	–	–	–
PZFX	≤0.06	≤0.06	≤0.06 to 1	–	–	–
GRNX	≤0.06	≤0.06	≤0.06 to 0.25	–	–	–
STFX	≤0.06	≤0.06	≤0.06 to 0.125	–	–	–
MINO	0.125	0.125	≤0.06 to 0.25	–	–	–
CLDM	4	8	2 to 8	0	20.3	79.7

The susceptibility of 40 antimicrobial agents against 74 strains of *M. catarrhalis* was determined.

on the updated criteria in M100-S21 [11], one strain was considered to be intermediate for imipenem and resistant for meropenem.

In the present survey, only one (0.6%) isolate of the 160 *P. aeruginosa* isolate was metallo-β-lactamase (MBL)-producing multidrug-resistant. The proportion of MBL-producing *P. aeruginosa* was at a similar level to a previous report in which MBL-producing *P. aeruginosa* was detected at 1.6% [10].

CLSI changed the break points of penicillins and carbapenems against *P. aeruginosa* in 2012 [12]. We also evaluated the resistant isolates according to the M100-S22 breakpoint criteria. Among penicillins, the intermediate range was newly categorized (32–64 μg/mL) and the susceptible strains for PIPC and TAZ/PIPC were shifted from 87.5% in M100-S20 to 79.4% and 80.0%, respectively. According to the M100-S22, proportions of susceptible/intermediate/resistant among *P. aeruginosa* were 67.5/4.4/28.1 for IPM and 76.9/5.0/18.1 for MEPM. Because the change of breakpoint criteria affects the proportions, the continuous evaluation will be also required in the next surveillance.

STFX was newly added in the present study. STFX showed stable activities to all species except for MRSA. However, we should keep appropriate use of antibiotics to prevent the emergence of resistant strain.

We think our surveillance data will be a useful reference for the treatment of respiratory infections in our country. There is

Table 9
Antibacterial susceptibility of *Klebsiella pneumoniae*.

Antibacterial agent	MIC (μg/ml)			Susceptibility (%)		
	50%	90%	Range	S	I	R
ABPC	32	128	4 to ≥256	3.6	15.8	80.6
SBT/ABPC	4	8	1 to 64	93.5	3.6	2.9
CVA/AMPC	2	4	0.5 to 64	97.1	2.2	0.7
PIPC	4	16	0.25 to ≥256	90.6	5.1	4.3
TAZ/PIPC	2	4	≤0.06 to ≥256	97.8	1.5	0.7
CCL	0.5	1	0.125 to ≥256	96.4	0	3.6
CFDN	≤0.06	0.25	≤0.06 to ≥128	96.4	0.7	2.9
CFPN	0.25	1	≤0.06 to 128	–	–	–
CDTR	0.125	0.5	≤0.06 to ≥128	–	–	–
CEZ	1	2	0.5 to ≥256	79.1	13	7.9
CMZ	0.5	2	0.125 to 128	99.3	0	0.7
CTM	0.125	0.25	≤0.06 to ≥256	–	–	–
CAZ	0.125	0.25	≤0.06 to ≥128	98.6	0	1.4
CTRX	≤0.06	0.125	≤0.06 to ≥256	97.1	0	2.9
CFPM	≤0.06	≤0.06	≤0.06 to 32	98.6	0.7	0.7
CZOP	≤0.06	0.125	≤0.06 to ≥256	–	–	–
IPM	0.25	0.5	≤0.06 to 2	100	0	0
PAPM	0.125	0.25	≤0.06 to 1	–	–	–
MEPM	≤0.06	≤0.06	≤0.06 to 4	100	0	0
BIPM	0.125	0.5	≤0.06 to 1	–	–	–
DRPM	≤0.06	0.125	≤0.06 to 2	–	–	–
FRPM	0.25	0.5	≤0.06 to 16	–	–	–
AZT	≤0.06	0.125	≤0.06 to ≥256	97.8	0	2.2
GM	0.25	0.5	0.125 to 1	100	0	0
TOB	0.5	1	0.25 to 4	100	0	0
AMK	1	2	0.125 to 4	100	0	0
ABK	0.5	0.5	0.25 to 2	–	–	–
AZM	8	16	1 to ≥128	–	–	–
CPFX	≤0.06	0.25	≤0.06 to 128	95.7	0.7	3.6
LVFX	≤0.06	0.25	≤0.06 to 64	96.4	0.7	2.9
TFLX	≤0.06	0.125	≤0.06 to ≥32	–	–	–
MFLX	0.125	0.5	≤0.06 to 64	–	–	–
PZFX	≤0.06	0.25	≤0.06 to 32	–	–	–
GRNX	0.125	0.5	≤0.06 to 128	–	–	–
STFX	≤0.06	0.125	≤0.06 to 4	–	–	–
MINO	2	4	≤0.06 to 128	95.0	3.6	1.4

The susceptibility of 36 antimicrobial agents against 139 strains of *K. pneumoniae* was determined.

Table 10
Antibacterial susuceptibility of *Pseudomonas aeruginosa*.

Anitibacterial agent	MIC (μg/ml)			Susceptibility (%)		
	50%	90%	Range	S	I	R
PIPC	8	128	0.25 to ≥256	87.5	–	12.5
TAZ/PIPC	8	128	0.125 to ≥256	87.5	–	12.5
CAZ	2	32	0.25 to ≥128	84.4	4.4	11.2
CTRX	64	≥256	0.5 to ≥256	15.6	23.1	61.3
CFPM	4	16	0.25 to ≥256	81.9	13.7	4.4
CZOP	2	16	0.125 to ≥256	–	–	–
IPM	2	16	≤0.06 to 32	71.9	11.9	16.3
PAPM	4	16	≤0.06 to 64	–	–	–
MEPM	0.5	16	≤0.06 to 64	81.9	4.4	13.8
BIPM	0.5	16	≤0.06 to 64	–	–	–
DRPM	0.5	8	≤0.06 to 64	–	–	–
AZT	8	32	≤0.06 to ≥256	65.6	13.2	21.2
GM	2	4	≤0.06 to ≥256	95.0	3.8	1.2
TOB	1	2	≤0.06 to ≥256	98.1	0	1.9
AMK	4	8	0.25 to ≥256	98.1	0	1.9
ABK	2	4	≤0.06 to ≥256	–	–	–
CPFX	0.25	8	≤0.06 to 64	75.6	5.0	19.4
LVFX	1	16	≤0.06 to ≥256	67.5	12.5	20.0
TFLX	0.25	≥32	≤0.06 to ≥32	–	–	–
MFLX	2	16	≤0.06 to ≥256	–	–	–
PZFX	0.5	8	≤0.06 to ≥256	–	–	–
GRNX	2	32	≤0.06 to ≥256	–	–	–
STFX	0.25	4	≤0.06 to 8	–	–	–
MINO	16	128	0.5 to ≥256	–	–	–

The susceptibility of 35 antimicrobial agents against 160 strains of *P. aeruginosa* was determined.

substantial evidence that the overuse of antibiotics is a major cause for the emergence of resistance in respiratory pathogens. To prevent the further spread of antimicrobial resistance in respiratory pathogens, proper antibiotic use is needed. We should also continue the surveillance to determine the actual situation of the resistance shown by bacterial respiratory pathogens to antimicrobial agents.

Conflict of interest

Katsunori Yanagihara has received speaker's honorarium from Daiichi Sankyo Co., Ltd., Pfizer Japan Inc., Taisho Toyama Pharmaceutical Co.,Ltd., Astellas Pharma Inc. and MSD K.K., donation from Daiichi Sankyo Co., Ltd., Pfizer Japan Inc., Taisho Toyama Pharmaceutical Co.,Ltd. and MSD K.K. and supported, in part, by a fund from Pfizer Japan Inc. and Taisho Toyama Pharmaceutical Co.,Ltd. Junichi Kadota has received speaker's honorarium from Taisho Toyama Pharmaceutical Co.,Ltd., Pfizer Japan Inc., MSD K.K., Kyorin Pharmaceutical Co.,Ltd., Daiichi Sankyo Co., Ltd., Glaxo SmithKline K.K., payments for a manuscript drafting and edting from Nankodo Co., Ltd. and donation from Astellas Pharma Inc. Nobuki Aoki has received speaker's honorarium from Daiichi Sankyo Co., Ltd., Taisho Toyama Pharmaceutical Co.,Ltd., Kyorin Pharmaceutical Co., Ltd. and Bayer Yakuhin, Ltd. Tetsuya Matsumoto has received speaker's honorarium from Pfizer Japan Inc., Meiji Seika Pharma Co., Ltd. and MSD K.K. Masaki Yoshida is a consultant of Astellas Pharma Inc. Keisuke Sunakawa has received speaker's honorarium from Taisho Toyama Pharmaceutical Co.,Ltd. and Meiji Seika Pharma Co., Ltd. Akira Watanabe has received speaker's honorarium from MSD K.K., Glaxo SmithKline K.K., Shionogi & Co., Ltd., Daiichi Sankyo Co.,Ltd., Taisho Toyama Pharmaceutical Co., Ltd. and Pfizer Japan Inc.; grant support from Kyorin Pharmaceutical Co., Ltd., Shionogi & Co., Ltd., Taisho Pharmaceutical Co.,Ltd., Toyama Chemical Co., Ltd., Daiichi Sankyo Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Taiho Pharmaceutical Co.,Ltd. and Meiji Seika Pharma Co., Ltd. Satoshi Iwata has received speaker's honorarium from Astellas Pharma Inc., Pfizer Japan Inc., Taisho Toyama Pharmaceutical Co.,Ltd., MSD K.K., Meiji Seika Pharma Co., Ltd., Daiichi Sankyo Co., Ltd. and Japan Vaccine Co., Ltd., donation from Taisho Toyama Pharmaceutical Co.,Ltd. and supported, in part, by a fund from Nikon Corporation. Mitsuo Kaku has received speaker's honorarium from Taisho Toyama Pharmaceutical Co.,Ltd., Shionogi & Co., Ltd., Pfizer Japan Inc. and Sumitomo Dainippon Pharma Co., Ltd. and donation from Astellas Pharma Inc. Hideaki Hanaki is a member of a laboratory endowed chair from Kohjin Bio Co.,Ltd. Yoshihito Niki has received a speaker's honorarium from Astellas Pharma Inc., MSD K.K., Glaxo SmithKline K.K., Shionogi & Co., Ltd., Daiichi Sankyo Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., and Pfizer Japan Inc.; and grant support from Astellas Pharma Inc., Kyorin Pharmaceutical Co., Ltd., Shionogi & Co., Ltd., Taisho Pharmaceutical Co., Ltd., Toyama Chemical Co., Ltd, Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma, MSD K.K., Teva Pharma Japan Inc. Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation and Meiji Seika Pharma Co., Ltd. Koichiro Yoshida has received speaker's honorarium from Janssen Pharmaceutical K.K. and Astellas Pharma Inc. Hiroki Tsukada has received speaker's honorarium from Taisho Toyama Pharmaceutical Co.,Ltd. Seishi Asari has received speaker's honorarium from Pfizer Japan Inc., Naoyuki Miyashita has received speaker's honorarium from Daiichi Sankyo Co., Ltd., Taisho Toyama Pharmaceutical Co.,Ltd. and Astellas Pharma Inc. Yosuke Aoki has received speaker's honorarium from MSD K.K. and Taisho Toyama Pharmaceutical Co.,Ltd.

Acknowledgments

This investigation was supported by grants from following pharmaceutical companies (alphabetical order): Astellas Pharma Inc.,, Bayer Yakuhin, Ltd., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Glaxo SmithKline K.K., Kyorin Pharmaceutical Co., Ltd., Maruho Co.,Ltd., Meiji Seika Pharma Co., Ltd., MSD K.K., Pfizer Japan Inc., Sanofi-Aventis K.K., Shionogi & Co., Ltd., Taiho Pharmaceutical Co., Ltd., Taisho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Toyama Chemical Co., Ltd.

We are grateful to Taiji Nakae at the Kitasato Institute (Tokyo, Japan) for their encouragements on microbiological testing and Yumiko Suzuki, Harumi Endo, and Yukie Yamaguchi for their technical assistance in this surveillance.

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