Nippon AMR One Health Report (NAOR) 2017

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The AMR One Health Surveillance Committee

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1. Preface

Japan's "National Action Plan on Antimicrobial Resistance (AMR) 2016-2020" was published in April 2016, clearly indicating the implementation of integrated one health surveillance regarding antimicrobial-resistant bacteria that are isolated from humans, animals, food and the environment. This one health surveillance is endorsed as an important strategy for correctly identifying the current status and issues related to AMR, which leads to promoting appropriate national AMR policy. This document is the first surveillance report aimed at identifying the current status and trends of antimicrobial-resistant bacteria and national antimicrobial use in the areas of human health, animals, agriculture, food and the environment.

We hope that this report would provide the first step for presenting Japan's effort to fight against AMR with one health apprpach to both domestic and international stakeholders; moreover, related governmental agencies, organizations/associations, academic societies and other entities, our intended target readers, are welcome to utilize this report in order to accelerate and advance policy and research activities on AMR.

2. Abbreviations

AMED	Japan Agency for Medical Research and Development
AMU	Antimicrobial Use
AMR	Antimicrobial Resistance
AMRCRC	Antimicrobial Resistance Clinical Reference Center
AUD	Antimicrobial Use Density
BP	Break Point
CDI	*Clostridium Difficile* Infection
CLSI	Clinical and Laboratory Standards Institute
CRE	Carbapenem-resistant *Enterobacteriaceae*
DID	Defined Daily Dose per 1000 Inhabitants per Day
DDD	Defined Daily Dose
DOT	Days of Therapy
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAMIC	Food and Agricultural Materials Inspection Center
FAO	Food and Agricultural Organization of the United Nations
GLASS	Global Antimicrobial Resistance Surveillance System
HAI	Healthcare-associated Infection
ICU	Intensive Care Unit
JACS	Japan Antimicrobial Consumption Surveillance
JANIS	Japan Nosocomial Infections Surveillance
JVARM	Japanese Veterinary Antimicrobial Resistance Monitoring System
MIC	Minimum Inhibitory Concentration
MDRA	Multidrug-resistant *Acinetobacter* spp.
MDRP	Multidrug-resistant *Pseudomonas aeruginosa*
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
NDB	National Database for Prescription and National Health Check-up
NESID	National Epidemiological Surveillance of Infectious Disease
OIE	World Organisation for Animal Health (L'Office international des épizooties)
PPCPs	Pharmaceuticals and Personal Care Products
PRSP	Penicillin-resistant *Streptococcus pneumoniae*
RICSS	Regional Infection Control Support System
SSI	Surgical Site Infection
WHO	World Health Organization
VRE	Vancomycin-resistant *Enterococci*
VRSA	Vancomycin-resistant *Staphylococcus aureus*

3. Types and Abbreviations of Antimicrobials

Type			Nonproprietary name	Abbreviation*
Beta-lactam antibiotics	Penicillins		benzylpenicillin（penicillin G）	PCG
			ampicillin	ABPC
			ampicillin/sulbactam	ABPC/SBT
			piperacillin	PIPC
			piperacillin/tazobactam	PIPC/TAZ
			amoxicillin	AMPC
			amoxicillin/clavulanic acid	AMPC/CVA
	Cephalosporins	1st generation	cefazolin	CEZ
			cephalexin	CEX
		2nd generation	cefotiam	CTM
			cefaclor	CCL
	Cephamycins		cefmetazole†	CMZ
			cefoxitin†	CFX
	Oxacephems		flomoxef †	FMOX
	Cephalosporins	3rd generation	cefotaxime	CTX
			ceftazidime	CAZ
			ceftriaxone	CTRX
	Oxacephems		latamoxef §	LMOX
	Cephalosporins		cefoperazone/sulbactam	CPZ/SBT
			cefdinir	CFDN
			cefcapene pivoxil	CFPN-PI
			cefditoren pivoxil	CDTR-PI
			cefixime	CFIX
	Cephalosporins	4th generation	cefepime	CFPM
			cefpirome	CPR
			cefozopran	CZOP
	Monobactams		aztreonam	AZT
	Carbapenems		meropenem	MEPM
			doripenem	DRPM
			biapenem	BIPM
			imipenem/cilastatin	IPM/CS
			panipenem/betamipron	PAPM/BP
			tebipenem pivoxil	TBPM-PI
	Penems		faropenem	FRPM
ST			sulfamethoxazole-trimethoprim	ST, SMX/TMP
Macrolides			erythromycin	EM
			clarithromycin	CAM
			azithromycin	AZM
			tylosin	TS
Ketolides			telithromycin	TEL
Lincomycins			clindamycin	CLDM
			lincomycin	LCM
Streptogramins			quinupristin/dalfopristin	QPR/DPR
			virginiamycin	VGM
Tetracyclines			minocycline	MINO
			tetracycline	TC
			doxycycline	DOXY
			oxytetracycline	OTC
Aminoglycosides			streptomycin	SM

	tobramycin	TOB
	gentamicin	GM
	amikacin	AMK
	arbekacin	ABK
	kanamycin	KM
	spectinomycin	SPCM
	dihydrostreptomycin	DSM
Quinolones	ciprofloxacin	CPFX
	levofloxacin	LVFX
	pazufloxacin	PZFX
	norfloxacin	NFLX
	prulifloxacin	PUFX
	moxifloxacin	MFLX
	garenoxacin	GRNX
	sitafloxacin	STFX
	nalidixic acid	NA
	enrofloxacin	ERFX
	oxolinic acid	OA
	ofloxacin	OFLX
Glycopeptides	vancomycin	VCM
	teicoplanin	TEIC
Oxazolidinones	linezolid	LZD
Polypeptides	polymyxin B	PL-B
	colisitin	CL
	bacitracin	BC
Amphenicols	chloramphenicol	CP
	florfenicol	FF
Other antibacterial agents	fosfomycin	FOM
	salinomycin	SNM
	bicozamycin	BCM
Antitubercular antibiotics	isoniazid	INH
	ethambutol	EB
	rifampicin	RFP
	pyrazinamide	PZA
	rifabutin	RBT

* Quoted from the Glossary of Antimicrobial Chemotherapy (Japanese Society of Chemotherapy), the Annual Report of the Japanese Society of Antimicrobials for Animals 36 (2014), and the Guidelines for the Use of Antimicrobial Substances in Cooperative Livestock Insurances (2009, Ministry of Agriculture, Forestry and Fisheries)

† The spectrum of antibacterial activity is equivalent to that of 2nd generation cephalosporins

§ The spectrum of antibacterial activity is equivalent to that of 3rd generation cephalosporins

[Reference] There are multiple relevant terminologies with different definitions. However, in medical practice, the following four terms are often used interchangeably to refer drugs that act against bacteria: “antimicrobial agents,” “antibiotics,” “antibiotic agents,” and “antibacterial agents.” In the areas of agriculture and livestocks, the expressions "antibacterial agents" and "antimicrobial agents" are commonly used, because these agents are not only used for therapeutic purposes, but also in antibiotic feed additives.

Antimicrobial agents or antimicrobials: Antimicrobial agents, or antimicrobials, are active against microorganisms, which are generally categorized into bacteria, fungi, viruses and parasites. These are the general term for drugs to treat and prevent infectious diseases. They contain antibacterial agents, antifungal agents, antiviral agents and antiparasitic agents.

Antibacterial agents: Antimicrobial agents that are active against bacteria.

Antibiotics: informally defined as an agent that is derived from living organisms to inhibit and control cell activities of microorganisms

Antibiotic agents: Another term for drugs that use the antibacterial action of antibiotics

Reference: the Manual of Antimicrobial Stewardship, 1st edition

4. Executive Summary

Background: Japan's "National Action Plan on Antimicrobial Resistance (AMR) 2016-2020" endorses current status and monitoring of antimicrobial-resistant bacteria and national antimicrobial use as an important strategy for both evaluating the impact of the action plan on AMR and planning future national policy. For global monitoring and reporting, WHO has launched the Global Antimicrobial Resistance Surveillance System (GLASS) for the worldwide gathering and sharing of data on AMR in humans. Japan contributes to GLASS by providing our national data. Accordingly, it is crucial for Japan to show the current status and progress of our AMR policy to not only domestic stakeholders but also the global community in order to accelerate and advance the policy on AMR.

Method: The AMR One Health Surveillance Committee, comprised of experts on AMR in the areas of human health, animals, food and the environment, discussed current surveillance/monitoring systems and reviewed published research on AMR and antimicrobial use. Data on the proportion of antimicrobial resistance among major pathogens in the human medical setting were derived from the Japan Nosocomial Infections Surveillance (JANIS) program organized by the Ministry of Health, Labour and Welfare of Japan. Data on the proportion of antimicrobial resistance among animals and related antimicrobial sales were derived from the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) implemented by the Ministry of Agriculture, Forestry and Fisheries of Japan (MAFF). Moreover, we obtained data on sales and consumption of antimicrobials for human use from the Japan Antimicrobial Consumption Surveillance (JACS) program and the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB). Data on the distribution of antimicrobial feed additives were provided by the Food and Agricultural Materials Inspection Center (FAMIC) and the Japan Scientific Feeds Associations (JSFA). Data on the amount of domestic shipment of antimicrobials used as agricultural chemicals was from MAFF. Data on antimicrobial resistance patterns of pathogens, which are not monitored by current surveillance and monitoring systems but considered pertinent from a public health perspective, and public awareness toward AMR were obtained from individual published research. The latest data available, mostly up to 2015, are included.

Results: In Japan, the proportion of carbapenem resistance in *Enterobacteriaceae* such as *Escherichia coli* and *Klebsiella pneumoniae* remained at around 1% during the observed period, despite its global increase in humans. Likewise, the proportion of vancomycin-resistant enterococci in humans was less than 1%. The proportion of *Escherichia coli* resistant against the third generation cephalosporins and fluoroquinolones, however, was increasing; and that of methicillin-resistant *Staphylococcus aureus* (MRSA) accounted for approximately 50%. Penicillin-resistant *Streptococcus pneumoniae* (PRSP) accounted for approximately 40% of all detected pneumococcus in cerebral spinal fluid samples. Furthermore, oral antimicrobial agents accounted for about 90% of the total sales in Japan. Among all oral antimicrobial agents sold, rates of defined daily dose per 1,000 inhabitants per day (DID) of cephalosporins, macrolides and quinolones were higher than that of penicillins.

In animals, monitoring of resistant bacteria in cattle, pigs and chickens was conducted. The proportion of antimicrobial-resistant *Escherichia coli* and *Salmonella* spp. derived from diseased animals tended to be higher than those derived from healthy animals. It appeared that tetracycline resistance was more common, although the degree of the resistance depended on animal and bacterial species. The proportion of third generation cephalosporin- and fluoroquinolone-resistant *Escherichia coli*, the indicator bacteria, derived from health animals, was low and remained mostly less than 10% during the observed period. Monitoring of antimicrobial resistance in aquaculture and fisheries has been conducted since 2011: specifically, the resistance of *Lactococcus garvieae* and *Photobacterium*

damselae subsp. *picicida* taken from diseased fish (Seriola) and *Vibrio parahaemolyticus* obtained from aquaculture-environment sampling. The sales volume of antimicrobials used for animals including food-producing animals, fish and companion animals was calculated in tons of the active ingredients, which were based on the sales volume of antibiotics and synthetic antimicrobials mandated by the Regulations for Veterinary Drugs (Ordinance of the Ministry of Agriculture, Forestry and Fisheries No. 107 of 2004). The antimicrobials sales volume for veterinary use appeared to be decreasing over the years, with figures of 854.50 tons, 793.75 tons and 780.88 tons for 2009, 2011 and 2013, respectively. Tetracyclines represented the largest share of total antimicrobial sales volume, accounting for about 40%, whereas both the third generation cephalosporins and fluoroquinolones were less than 1% of the total sales volume.

Conclusion: The use of cephalosporins and quinolones and the proportion of resistance to those antimicrobials were higher in humans. In contrast, tetracyclines were more commonly used in animals and tetracycline resistance was high among animals. Overall, the surveillance and monitoring of antimicrobial resistance in human and animals are well established in Japan, whilst there is still much to be desired in terms of comprehensive monitoring systems for the environment and food. Further discussion is needed for new surveillance and monitoring systems in those areas. Regarding the current, already-implemented surveillance and monitoring systems, further discussions for new methods of analyses considering bias, enhancement of quality assurances and inter-surveillance comparisons are needed in order to improve the accuracy of those systems. By addressing each challenge, we hope that our effort can help uncover mechanisms and inter-connectivity with regard to the development and transmission of antimicrobial resistance among humans, animals, agriculture, food and the environment.

5. Outcome Indices for the Action Plan

Human-related indices for the Action Plan: proportion (%) of specified antimicrobial-resistant bacteria

	2015*	2020 Target value[†]
Proportion of penicillin-non-susceptible *Streptococcus pneumoniae*, CSF specimens[§]	40.5	15% or lower
Proportion of penicillin-non-susceptible *Streptococcus pneumoniae*, non-CSF specimens[§]	2.7	15% or lower
Proportion of fluoroquinolone-resistant *Escherichia coli*	38.0	25% or lower
Proportion of methicillin-resistant *Staphylococcus aureus*	48.5	20% or lower
Proportion of carbapenem-resistant *Pseudomonas aeruginosa* (Imipenem)	18.8	10% or lower
Proportion of carbapenem-resistant *Pseudomonas aeruginosa* (Meropenem)	13.1	10% or lower
Proportion of carbapenem-resistant *Escherichia coli* (Imipenem)	0.1	0.2% or lower (maintain at the same level)[¶]
Proportion of carbapenem-resistant *Escherichia coli* (Meropenem)	0.2	0.2% or lower (maintain at the same level)[¶]
Proportion of carbapenem-resistant *Klebsiella pneumoniae* (Imipenem)	0.3	0.2% or lower (maintain at the same level)[¶]
Proportion of carbapenem-resistant *Klebsiella pneumoniae* (Meropenem)	0.6	0.2% or lower (maintain at the same level)[¶]

CSF, cerebrospinal fluid
* Prepared based on JANIS data
[†] Target values were quoted from the National Action Plan on Antimicrobial Resistance (AMR).[1]
[§] The proportion of penicillin-non-susceptible *Streptococcus pneumoniae* in 2014, as indicated in the Action Plan, is based on the CLSI (2007) Criteria where those with penicillin MIC of 0.125 μg/mL or higher are considered resistant. The CLSI Criteria were revised in 2008, applying different standards to CSF and non-CSF specimens. Based on this revision, JANIS has divided data into CSF and non-CSF specimens since 2015.
[¶] The National Action Plan on Antimicrobial Resistance (AMR) [1] indicates that the respective proportion of carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* were at 0.1% and 0.2% in 2014, and the proportions should be maintained at the same level in 2020.

Human-related indices for the Action Plan: volume of use and sales of antimicrobials (DID)

Year	2013		2020 (target value*)
Data used	Volume of sales[†]	NDB[§]	
All antimicrobials	15.80	14.00	Reduce by 33%
Oral cephalosporins	3.85	3.09	Reduce by 50%
Oral fluoroquinolones	2.75	2.61	Reduce by 50%
Oral macrolides	4.84	4.82	Reduce by 50%
Intravenous antimicrobials	1.23	0.83	Reduce by 20%

DID: Defined daily dose per 1000 inhabitants per day
* Target values were quoted from [1].
[†] Prepared from [2] with partial modification
[§] Adpated from [3] [4] with partial modification

Animal-related indices for the Action Plan: proportion (%) of specified antimicrobial-resistant bacteria

	2014	2020 (target value*)
Propotion of tetracycline-resistant *Escherichia coli*	45.2	33% or lower
Proportion of third-generation cephalosporin-resistant *Escherichia coli*	1.5	The Same level as in other G7 nations
Proportion of fluoroquinolone-resistant *Escherichia coli*	4.7	The Same level as in other G7 nations

* Target values were quoted from [1].

6. Current Status of Antimicrobial-resistant Bacteria in Japan

(1) Humans

1) Gram-negative bacteria

Source: Japan Nosocomial Infections Surveillance (JANIS)

As for the recent status of gram-negative bacteria, despite recent global increase of carbapenem (IPM and MEPM)-resistant *Enterobacteriaceae* such as *Escherichia coli* and *Klebsiella pneumoniae*, the proportion of carbapenem-resistant *Escherichia coli* and *Klebsiella pneumoniae* in Japan remained low at less than 1%; and increment of those resistant organisims were not seen during the observed period, as in Table 1 and 2. On the other hand, the proportion of *Escherichia coli* resistant to third-generation cephalosporins, such as Cefotaxime (CTX), and those resistant to fluoroquinolones, such as Levofloxacin (LVFX), increased, calling for an action to address this issue.

The proportion of carbapenem-resistant *Enterobacter cloacae* (Table 3) and *Enterobacter aerogenes* (Table 4) remained around 1%; and the proportion of carbapenem-resistant *Pseudomonas aeruginosa* (Table 5) and *Acinetobacter* spp. (Table 6) remained at a level equivalent to or even lower than in other countries. In particular, the proportion of carbapenem-resistant *Acinetobacter* spp. remained low between around 1% and 3%.

i. *Escherichia coli*

Table 1. Trends in the proportion (%) of antimicrobial-resistant *Escherichia coli*

	BP (- 2013)	BP (2014-)	2011	2012	2013	2014	2015
ABPC	32	32	47.6 (116,097)	49.1 (133,330)	49.4 (150,867)	49.2 (170,597)	50.5 (257,065)
PIPC	128	128	40.1 (119,843)	41.6 (136,978)	42.5 (155,626)	42.5 (175,763)	44.1 (270,452)
TAZ/PIPC	4/128	4/128	-	-	2.2 (51,286)	1.7 (89,442)	1.7 (179,722)
CEZ*	32	8	24.4 (122,803)	26.2 (141,560)	26.9 (161,397)	33.3 (183,542)	35.8 (268,898)
CMZ	64	64	-	-	-	1.0 (163,342)	0.9 (260,844)
CTX*	64	4	14.8 (99,543)	16.6 (113,354)	17.8 (124,473)	23.3 (140,186)	24.5 (209,404)
CAZ*	32	16	5.2 (123,606)	5.2 (142,440)	5.5 (161,163)	9.5 (183,970)	10.8 (275,671)
CFPM	32	32	-	-	10.9 (81,456)	12.8 (129,606)	15.0 (236,705)
AZT*	32	16	8.5 (97,906)	9.4 (111,930)	10.2 (126,777)	16.1 (143,046)	17.6 (216,494)
IPM*	16	4	0.1 (113,820)	0.1 (128,289)	0.1 (146,007)	0.1 (163,181)	0.1 (251,050)
MEPM*	16	4	-	-	0.1 (95,180)	0.2 (144,913)	0.2 (269,893)
AMK	64	64	0.2 (123,464)	0.2 (141,114)	0.2 (161,406)	0.2 (184,788)	0.1 (281,641)
LVFX	8	8	31.4 (117,292)	34.3 (136,253)	35.5 (155,998)	36.1 (178,497)	38.0 (274,687)

The unit of BP is μg/mL.
Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.
Data for ST were not calculated.
* CLSI (2007)(M100-S17) Criteria was applied to detemine the BP up to 2013. CLSI (2012)(M100-S22) Criteria was applied to detemine BP after 2014.
-: Not under surveillance

ii. *Klebsiella pneumoniae*

Table 2. Trends in the proportion (%) of antimicrobial-resistant *Klebsiella pneumoniae*

	BP (-2013)	BP (2014-)	2011	2012	2013	2014	2015
ABPC	32	32	75.9	76.9	77.8	76.3	76.9
			(65,338)	(73,078)	(80,030)	(90,220)	(131,700)
PIPC	128	128	19.7	20.1	24.3	21.9	21.1
			(67,548)	(74,878)	(82,608)	(91,761)	(136,347)
TAZ/PIPC	4/128	4/128	-	-	2.2	2.0	2.0
					(27,279)	(46,941)	(91,503)
CEZ*	32	8	8.8	9.0	9.1	11.7	12.1
			(68,481)	(76,860)	(85,320)	(94,875)	(135,486)
CMZ	64	64	-	-	-	1.9	1.9
						(85,749)	(132,163)
CTX*	64	4	5.2	5.4	5.1	8.6	8.0
			(56,236)	(62,207)	(66,654)	(73,574)	(107,409)
CAZ*	32	16	3.4	2.9	2.7	3.8	4.0
			(68,916)	(76,961)	(84,761)	(94,878)	(138,191)
CFPM	32	32	-	-	3.0	3.5	4.0
					(41,143)	(66,399)	(119,563)
AZT*	32	16	4.1	3.7	3.5	5.1	5.3
			(54,680)	(60,606)	(67,253)	(75,340)	(110,259)
IPM*	16	4	0.2	0.2	0.1	0.3	0.3
			(63,825)	(70,284)	(77,193)	(85,253)	(126,997)
MEPM*	16	4	-	-	0.2	0.6	0.6
					(48,190)	(73,903)	(135,930)
AMK	64	64	0.3	0.2	0.2	0.1	0.1
			(68,995)	(76,293)	(84,916)	(95,643)	(141,710)
LVFX	8	8	2.7	2.4	2.5	2.4	2.6
			(66,466)	(74,718)	(83,063)	(92,993)	(138,428)

The unit of BP is μg/mL.
Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.
* CLSI (2007)(M100-S17) Criteria was applied to detemine the BP up to 2013. CLSI (2012)(M100-S22) Criteria was applied to detemine BP after 2014.
-: Not under surveillance

iii. *Enterobacter* spp.

Table 3. Trends in the proportion (%) of antimicrobial-resistant *Enterobacter cloacae*

	BP (-2013)	BP (2014-)	2013	2014	2015
ABPC	32	32	80.9	79.0	80.2
			(35,849)	(39,344)	(55,960)
PIPC	128	128	20.6	20.0	19.8
			(36,988)	(39,636)	(58,039)
TAZ/PIPC	4/128	4/128	10.3	8.6	8.9
			(11,895)	(21,091)	(40,315)
CEZ*	32	8	97.2	98.2	98.3
			(37,359)	(41,422)	(58,637)
CMZ	64	64	-	83.4	85.4
				(37,492)	(56,647)
CTX*	64	4	19.2	31.1	31.6
			(30,106)	(32,718)	(46,727)
CAZ*	32	16	20.6	24.7	25.0
			(37,202)	(41,456)	(59,533)
CFPM	32	32	4.2	4.2	4.2
			(17,900)	(29,836)	(52,218)

AZT*	32	16	16.8 (29,460)	23.8 (33,551)	24.0 (48,570)
IPM*	16	4	0.4 (34,403)	1.6 (37,396)	1.3 (54,926)
MEPM*	16	4	0.6 (21,164)	1.3 (32,589)	1.4 (59,009)
AMK	64	64	0.4 (37,947)	0.2 (42,005)	0.2 (61,086)
LVFX	8	8	4.2 (37,274)	3.5 (40,942)	3.7 (59,393)

The unit of BP is μg/mL.
Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.
* CLSI (2007)(M100-S17) Criteria was applied to detemine the BP up to 2013. CLSI (2012)(M100-S22) Criteria was applied to detemine BP after 2014.
-: Not under surveillance

Table 4. Trends in the proportion (%) of antimicrobial-resistant *Enterobacter aerogenes*

	BP (-2013)	BP (2014-)	2013	2014	2015
ABPC	32	32	76.5 (17,362)	77.1 (18,385)	78.9 (26,680)
PIPC	128	128	14.5 (18,029)	14.5 (18,550)	14.2 (27,189)
TAZ/PIPC	4/128	4/128	6.3 (5,568)	4.9 (9,568)	4.8 (18,731)
CEZ*	32	8	90.8 (17,945)	94.0 (19,173)	93.7 (27,526)
CMZ	64	64	-	84.8 (17,587)	86.8 (26,739)
CTX*	64	4	5.2 (14,452)	28.3 (15,173)	30.7 (21,985)
CAZ*	32	16	17.3 (17,992)	24.3 (19,439)	25.2 (27,886)
CFPM	32	32	1.0 (8,909)	1.2 (13,499)	1.1 (24,302)
AZT*	32	16	7.5 (14,639)	15.8 (15,846)	17.5 (23,225)
IPM*	16	4	0.4 (16,881)	1.7 (17,463)	1.9 (25,690)
MEPM*	16	4	0.2 (10,249)	0.9 (15,003)	0.8 (27,560)
AMK	64	64	0.2 (18,369)	0.2 (19,492)	0.1 (28,627)
LVFX	8	8	1.1 (18,111)	1.0 (19,068)	0.9 (28,012)

The unit of BP is μg/mL.
Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.
* CLSI (2007)(M100-S17) Criteria was applied to detemine the BP up to 2013. CLSI (2012)(M100-S22) Criteria was applied to detemine BP after 2014.
-: Not under surveillance

iv. *Pseudomonas aeruginosa*

Table 5. Trends in the proportion (%) of antimicrobial-resistant *Pseudomonas aeruginosa*

	BP (-2013)	BP (2014-)	2011	2012	2013	2014	2015
PIPC	128	128	12.1 (114,950)	11.9 (118,032)	11.4 (122,581)	10.8 (125,242)	10.5 (181,977)
TAZ/PIPC	4/128	4/128	-	-	9.0 (68,686)	8.8 (79,574)	8.8 (132,769)
CAZ	32	32	11.3 (116,596)	10.9 (120,473)	10.2 (124,864)	9.5 (126,718)	8.6 (180,479)
AZT	32	32	16.3 (96,435)	16.7 (100,964)	16.5 (105,681)	14.5 (107,167)	14.0 (146,841)
CFPM	32	32	9.7 (91,769)	8.9 (99,730)	8.0 (106,291)	7.5 (113,268)	6.6 (166,096)
IPM*	16	8	19.8 (112,596)	18.5 (116,193)	17.1 (119,979)	19.9 (119,323)	18.8 (168,471)
MEPM*	16	8	12.4 (109,453)	11.8 (113,996)	10.7 (119,330)	14.4 (123,976)	13.1 (180,850)
GM	16	16	7.0 (111,137)	6.1 (115,612)	5.3 (118,592)	5.1 (117,421)	4.5 (165,777)
AMK	64	64	3.1 (116,876)	2.6 (121,289)	2.1 (126,023)	1.9 (128,923)	1.5 (185,327)
LVFX	8	8	16.8 (111,005)	16.3 (115,478)	14.5 (119,162)	13.0 (120,691)	12.0 (174,301)

The unit of BP is μg/mL.
Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.
* CLSI (2007)(M100-S17) Criteria was applied to detemine the BP up to 2013. CLSI (2012)(M100-S22) Criteria was applied to detemine BP after 2014.
-: Not under surveillance

v. *Acintobacter* spp.

Table 6. Trends in the proportion (%) of antimicrobial-resistant *Acintobacter* spp.

	BP	2011	2012	2013	2014	2015
PIPC	128	13.2 (19,125)	13.2 (19,433)	12.9 (20,183)	12.4 (20,223)	11.5 (27,887)
TAZ/PIPC	4/128	-	-	7.8 (4,953)	7.8 (5,215)	8.1 (9,058)
SBT/ABPC	16/32	6.5 (2,942)	7.2 (3,601)	5.8 (4,498)	5.2 (6,462)	4.8 (11,356)
CAZ	32	10.3 (19,672)	10.6 (20,067)	10.0 (20,856)	9.3 (20,852)	8.0 (28,166)
CFPM	32	10.4 (13,013)	10.5 (14,093)	9.2 (15,394)	7.6 (17,424)	7.2 (25,412)
IPM	16	2.2 (18,048)	2.0 (18,238)	2.3 (16,947)	3.6 (11,147)	3.2 (13,942)
MEPM	16	2.9 (15,485)	2.4 (15,880)	2.3 (17,027)	2.0 (18,859)	1.8 (28,227)
GM	16	9.6 (18,276)	10.2 (18,842)	9.5 (19,422)	8.9 (18,832)	8.5 (25,689)
AMK	64	4.5 (19,348)	4.5 (19,793)	3.5 (20,863)	3.6 (20,851)	3.1 (28,568)
LVFX	8	9.5 (18,732)	9.8 (19,484)	8.3 (20,040)	8.5 (20,047)	7.7 (27,858)

The unit of BP is μg/mL.
Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.
-: Not under surveillance

2) Gram-positive bacteria

Source: Japan Nosocomial Infections Surveillance (JANIS)

As for the recent status of gram-positive bacteria, the proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) accounted for approximately 50%, which remained higher than that in other countries, though the proportion were declining over the past years (Table 9). Despite the global problem of increasing vancomycin-resistant enterococci, in Japan, the proportion of vancomycin-resistant *Enterococcus faecalis* remained lower than 0.05%, and that of *Enterococcus faecium* remained at 1% or lower as in Tables 10 and 11. The proportion of penicillin-resistant *Streptococcus pneumoniae* (PRSP) accounted for approximately 40% of all detected pneumoccous in cerebrospinal fluid (CSF) samples, though the figure varies from year to year, because only around 100 CSF samples are tested (Table 12). The proportion of PRSP was low for non-CSF samples at below 1% (Table 13), and below 5% even adding penicillin intermediate resistant bacteria.

i. *Staphylococcus aureus*

Table 7. Trends in the proportion (%) of methicillin-susceptible *Staphylococcus aureus* (MSSA)

	BP	2011	2012	2013	2014	2015
PCG	0.25	61.1	60.1	59.0	57.7	56.2
		(68,839)	(75,025)	(82,477)	(86,314)	(119,343)
CEZ	32	0.3	<0.05	0.2	0.2	0.1
		(77,483)	(84,520)	(93,945)	(103,603)	(146,254)
CVA/AMPC	4/8	0.3	0.1	0.2	0.2	0.1
		(11,696)	(9,466)	(11,230)	(11,666)	(19,163)
IPM	16	0.3	<0.05	0.2	0.2	<0.05
		(74,636)	(80,472)	(88,422)	(95,951)	(136,878)
EM	8	22.7	23.4	24.0	23.8	22.9
		(72,738)	(79,683)	(88,528)	(96,829)	(136,763)
CLDM	4	3.4	3.1	3.2	2.8	2.8
		(67,523)	(74,387)	(83,914)	(93,467)	(136,292)
MINO	16	0.7	0.6	0.5	0.6	0.6
		(77,872)	(84,595)	(94,425)	(104,145)	(151,493)
LVFX	4	9.3	10.2	10.6	10.7	11.6
		(73,163)	(79,857)	(89,641)	(99,898)	(144,083)

The unit of BP is μg/mL.
Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

Table 8. Trends in the proportion (%) of methicillin-resistant *Staphylococcus aureus* (MRSA)

	BP (since 2014)	2011	2012	2013	2014	2015
EM	8	91.3	90.6	88.4	86.0	84.1
		(105,936)	(109,521)	(108,607)	(107,836)	(149,851)
CLDM	4	76.8	73.5	67.3	60.3	56.0
		(102,895)	(106,124)	(105,503)	(106,910)	(153,329)
MINO	16	48.2	43.7	37.1	35.1	31.7
		(117,325)	(120,321)	(120,300)	(121,258)	(173,983)
VCM	16	0.0	0.0	0.0	0.0	0.0
		(115,679)	(119,111)	(119,441)	(120,535)	(172,083)
TEIC	32	<0.05	<0.05	<0.05	<0.05	<0.05
		(110,380)	(113,887)	(113,684)	(113,749)	(158,233)
LVFX	4	89.0	88.3	86.8	85.4	85.2
		(111,598)	(114,381)	(114,551)	(115,586)	(164,734)
LZD*	8	0.1	<0.05	<0.05	<0.05	0.1
		(76,632)	(84,550)	(85,223)	(88,255)	(127,278)
Daptomycin*	2	-	-	-	1.1	0.9
					(3,078)	(16,648)

The unit of BP is μg/mL.
Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.
As of 2015, no vancomycin-resistant *staphylococcus aureus* strains had been reported.
* CLSI (2007)(M100-S17) Criteria was applied to detemine the BP up to 2013. CLSI (2012)(M100-S22) Criteria was applied to detemine BP after 2014.
-: Not under surveillance

Table 9. The proportion of (%) of patients with MRSA among all patients with *Staphylococcus aureus* (*S.aureus*)

	2011	2012	2013	2014	2015
The number of patients with MRSA	114,933	117,209	118,539	120,702	169,528
The number of patients with *S. aureus*	210,382	221,239	231,909	246,030	349,743
The proportion of MRSA (%)*	54.6	53.0	51.1	49.1	48.5

Those detected in selective media were also included.
* The number of patients with MRSA / The number of patients with *S. aureus*

ii. *Enterococcus* spp.

Table 10. Trends in the proportion (%) of antimicrobial-resistant *Enterococcus faecalis*

	BP	2011	2012	2013	2014	2015
PCG	16	2.2	2.1	1.8	1.6	1.4
		(53,290)	(60,342)	(65,220)	(67,324)	(92,132)
ABPC	16	0.4	0.4	0.3	0.3	0.3
		(60,686)	(68,440)	(72,587)	(77,997)	(107,733)
EM	8	57.8	58.0	57.1	55.5	54.8
		(53,222)	(60,825)	(64,465)	(69,171)	(95,409)
MINO	16	47.8	47.7	47.7	52.1	49.7
		(61,549)	(69,421)	(74,880)	(81,925)	(115,648)
VCM	32	<0.05	<0.05	<0.05	<0.05	<0.05
		(61,747)	(69,719)	(75,162)	(81,867)	(115,100)
TEIC	32	<0.05	<0.05	<0.05	<0.05	<0.05
		(56,591)	(63,747)	(69,500)	(76,160)	(105,403)
LVFX	8	19.3	18.0	15.5	13.7	12.5
		(58,877)	(65,934)	(70,895)	(77,563)	(109,160)

The unit of BP is μg/mL.
Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

Table 11. Trends in the proportion (%) of antimicrobial-resistant *Enterococcus faecium*

	BP	2011	2012	2013	2014	2015
PCG	16	86.9	87.4	87.7	86.9	87.6
		(17,642)	(21,139)	(23,466)	(24,534)	(34,752)
ABPC	16	86.0	86.2	86.9	86.9	87.6
		(19,780)	(23,885)	(26,199)	(28,564)	(41,459)
EM	8	87.2	88.1	85.9	84.5	84.5
		(17,668)	(21,498)	(23,594)	(25,922)	(37,536)
MINO	16	26.9	28.8	29.3	32.2	35.1
		(21,877)	(25,961)	(28,387)	(31,550)	(46,351)
VCM	32	1.0	0.4	0.7	0.7	0.7
		(21,782)	(25,787)	(28,334)	(30,996)	(45,514)
TEIC	32	0.4	0.3	0.2	0.2	0.3
		(20,163)	(23,855)	(26,282)	(29,151)	(41,905)
LVFX	8	82.9	83.4	84.5	84.7	85.8
		(19,417)	(23,032)	(25,629)	(28,448)	(42,068)

LZD	8	0.0 (12,877)	0.1 (16,296)	<0.05 (18,561)	0.1 (22,044)	0.1 (33,382)

The unit of BP is μg/mL.
Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

iii. *Streptococcus pneumoniae*

Table 12. Trends in the proportion (%) of antimicrobial-resistant *Streptococcus pneumoniae* (CSF specimens)

	BP	2012	2013	2014	2015
PCG	0.125	38.6 (101)	47.4 (97)	47.0 (83)	40.5 (126)
CTX	2	3.7 (82)	1.2 (84)	2.9 (69)	2.0 (100)
MEPM	1	4.2 (95)	2.2 (92)	1.2 (83)	4.2 (119)
EM	1	82.5 (80)	82.7 (81)	92.5 (67)	84.9 (86)
CLDM	1	53.8 (65)	68.7 (67)	65.1 (63)	62.7 (83)
LVFX	8	0.0 (88)	0.0 (91)	1.3 (76)	0.0 (105)
VCM	2	0.0 (91)	0.0 (90)	0.0 (82)	0.0 (119)

The unit of BP is μg/mL.
Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.
CLSI (2012)(M100-S22) Criteria was applied to determine BP.

Table 13. Trends in the proportion (%) of antimicrobial-resistant*Streptococcus pneumoniae* (non-CSF specimens)

	BP	2012	2013	2014	2015
PCG*	4	3.2 (24,980)	2.7 (26,932)	2.5 (27,206)	2.7 (36,475)
CTX	4	2.4 (21,654)	2.0 (23,096)	1.8 (23,002)	1.6 (30,734)
MEPM	1	6.9 (22,989)	5.1 (24,986)	5.4 (25,760)	5.0 (34,461)
EM	1	87.0 (21,979)	86.2 (22,435)	86.7 (22,215)	85.5 (30,501)
CLDM	1	56.4 (17,513)	56.1 (19,719)	57.1 (20,296)	56.1 (27,555)
LVFX	8	3.0 (24,105)	3.1 (25,764)	3.3 (26,236)	3.5 (35,457)
VCM	2	0.0 (24,085)	0.0 (25,425)	0.0 (25,775)	0.0 (33,530)

The unit of BP is μg/mL.
Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.
* Each figure for PCG represents the sum of resistance (R: 8 μg/mL) and intermediate resistance (I: 4 μg/mL).
CLSI (2012)(M100-S22) Criteria was applied to determine BP.

3) Antimicrobial-resistant bacteria infection

Source: National Epidemiological Surveillance of Infectious Disease (NESID)

The number of cases reported under NESID through 2015 are open to public as of October 23, 2016. Cases reported since 2011 are listed below. The scope of reporting is limited to cases where the isolated bacteria is regarded as the cause of an infectious disease, or cases where it was detected from specimens that normally should be aseptic. Colonization is excluded from the scope of reporting.

As for a disease subject to notifiable disease surveillance (i.e. all cases are required to be reported), the annual number of reports of vancomycin-resistant enterococcal (VRE) infection remained under a hundred during the observed period. No case of vancomycin-resistant *Staphylococcus aureus* (VRSA) infection has been reported since November 5, 2003, when this disease became notifiable. Carbapenem-resistant *Enterobacteriaceae* (CRE) infection became a notifiable disease on September 19, 2014, and 1,671 cases were reported in 2015. Surveillance for multidrug-resistant *Acinetobacter* (MDRA) infection was started in Feburary 2011 and at first reporting of cases was limited to designated sentinel sites. Subsequently, it became a notifiable disease on September 19, 2014, and 38 cases were reported in 2015 (Table 14).

As for multidrug-resistant infections subject to reporting from designated sentinel sites (approximately 500 medical facilities across Japan that have 300 or more beds), penicillin-resistant *Streptococcus pneumoniae* (PRSP) infection, MRSA infection, and multidrug-resistant *Pseudomonas aeruginosa* (MDRP) are included. Both the absolute number of reports and reports per sentinel site declined for these diseases during the observation period (Table 15).

i. Diseases subject to notifiable disease surveillance

Table 14. Number of cases reported for diseases subject to notifiable disease surveillance

	2011	2012	2013	2014	2015
VRE	73	91	55	56	66
VRSA	0	0	0	0	0
CRE	-	-	-	314*	1671
MDRA	-	-	-	15*	38

* Reportable since September 19, 2014.
-: Not under surveillance

ii. Diseases reportable from designated sentinel sites

Table 15. Number of cases reported for diseases reportable from designated sentinel sites

		2011	2012	2013	2014	2015
PRSP	Cases	4,648	3,564	3,161	2,292	2,057
	Cases per sentinel site	9.87	7.53	6.65	4.79	4.29
MRSA	Cases	23,463	22,129	20,155	18,082	17,057
	Cases per sentinel site	49.82	46.78	42.43	37.83	35.61
MDRA*	Cases	5†	7	8	4	-
	Cases per sentinel site	0.01	0.01	0.02	0.01	-
MDRP	Cases	481	401	319	268	217
	Cases per sentinel site	1.02	0.85	0.67	0.56	0.45

* MDRA became reportable under notifiable disease surveillance on September 19, 2014.
† Reportable since February 1, 2011.
-: Not under surveillance

4) Other antimicrobial-resistant bacteria

i. *Campylobacter* spp.

Source: Tokyo Metropolitan Institute of Public Health

The Tokyo Metropolitan Institute of Public Health has conducted trend surveillance concerning the proportion of antimicrobial-resistant *Campylobacter* spp. Among the 129 outbreaks of food-borne illness that occurred in Tokyo in 2016, 32 outbreaks (24.8%) were caused by *Campylobacter* spp., being the largest cause of bacterial food-borne illness.[5] Among the *Campylobacter jejuni* (*C. jejuni*) isolated from patients with diarrhea in 2015, the proportion of quinolone-resistant strains accounted for 37.1%, the lowest since 2011 (Table 16). The proportion of quinolone-resistant *Campylobacter coli* (*C. coli*) strains accounted for 50% in 2015, higher than that of *C. jejuni*, but the lowest since 2011 (Table 17). Note that, however, the number of tested strains was smaller for *C.coli* and this shoul be taken into considration upon intepretation of the result.

Table 16. The proportion (%) of antimicrobial-resistant *Campylobacter jejuni isolated from diarrhea cases, Tokyo 2011-2015**

	2011 (n=108)	2012 (n=83)	2013 (n=85)	2014 (n=125)	2015 (n=116)
EM	3.7	2.4	1.2	0.8	0.9
Quinolones†	53.7	62.7	50.6	50.4	37.1

* Strains isolated from diarrhea cases in Tokyo
†NFLX, OFLX, CPFX, and NA were included.
Prepared from [5] with partial modification.

Table 17. The proportion (%) of antimicrobial-resistant *Campylobacter coli isolated from diarrhea cases, Tokyo 2011-2015**

	2011 (n=8)	2012 (n=9)	2013 (n=12)	2014 (n=7)	2015 (n=8)
EM	12.5	22.2	16.7	28.6	0.0
Quinolones†	87.5	66.7	75	57.1	50.0

* Strains isolated from the stool of sporadic diarrhea cases in Tokyo Prefecture.
† NFLX, OFLX, CPFX, and NA were included.
Prepared from [5] with partial modification.

ii. Non-typhoidal *Salmonella* spp.

Source: Public Health Institutes

The 18 Public Health Institutes across Japan conducted research on the multidrug-resistant status of the 917 *Salmonella* strains that were isolated in 2015 and 2016, using standardized methodology.[6] Table 18 lists the key serotypes of human-derived strains and food-derived strains.

About 40% of the 651 human-derived strains and 90% of the 266 food-derived strains, indicated resistance to one or more antimicrobials (Tables 19 and 20). Although this investigation was not conducted as a routine national surveillance operation, the results here are considered to reflect the current status in Japan, given the investigation covered all regions of Japan, and the proportion of resitance strains isolated in 2015 and 2016 was similar.

As for multidrug resistance, the proportion of three-drug resistance was large both among human-derived strains and among food-derived strains. Six among human-derived strains, and 22 among food-derived strains, indicated advanced resistance to as many as six to ten drugs. Furthermore, clear similarity was observed in the overall trends of resistance proportion between human-derived strains and food-derived strains, which were sampled independently from each other,

suggesting association between food-derived antimicrobial-resistant bacteria and human-derived antimicrobial-resistant bacteria. When the resistance status of human-derived strains was compared between serotypes that were isolated from food and serotypes that were not isolated, the respective proportion of strains that were resistant to at least one drug account for 56.7% in the former group, and at 23.1% in the latter group. Therefore, the former group indicated stronger similarity than the latter group in terms of resistance status of human-derived strains (Tables 21 and 22).

Table 18. Serotypes of human- and food-derived non-typhoidal *Salmonella* spp.*, Japan 2015 and 2016

Human-derived strains (n=651)	%	Food-derived strains (n=266)	%
S. Infantis	11.1	*S.* Infantis	36.8
S. Enteritidis	10.6	*S.* Schwarzengrund	31.6
S. Thompson	8.0	*S.* Manhattan	9.0
S. 4:i:-	7.8	*S.* Agona	4.5
S. Saintpaul	7.5	*S.* Typhimurium	3.0
S. Typhimurium	6.1	Others	15.0
S. Schwarzengrund	3.4		
S. Chester	3.1		
S. Manhattan	3.1		
S. Newport	2.8		
Others	36.6		

* The table lists the ten most common serotypes among human-derived strains, and the five most common serotypes among food-derived strains.
Prepared from [6] with partial modification.

Table 19. The proportion (%) of antimicrobial-resistant non-typhoidal *Salmonella* spp.* derived from patients, Japan 2015 and 2016

	2015 (n=388)	2016 (n=263)
ABPC	17.3	16.7
GM	0.3	0.4
KM	5.9	9.5
SM	27.1	30.0
TC	32.7	28.5
ST	4.4	6.5
CP	2.1	6.5
CTX	0.3	2.7
CAZ	0.3	2.3
CFX	0.0	1.5
FOM	0.0	0.4
NA	7.0	8.0
CPFX	0.3	1.1
NFLX	0.3	1.1
AMK	0.0	0.0
IPM	0.0	0.0
MEPM	0.0	0.0

* Status of strains isolated at the18 Public Health Institutes across Japan; 82.0% were isolated from stool. The remainder derived from blood, urine, abdominal drain, etc.
Prepared from [6] with partial modification.

Table 20. The proportion (%) of antimicrobial-resistant food-derived non-typhoidal *Salmonella* spp.*, Japan 2015 and 2016

	2015 (n=156)	2016 (n=110)
ABPC	16.9	13.3
GM	0.0	0.8
KM	44.6	42.5
SM	77.7	65.8
TC	80.7	70.0
ST	18.7	15.0
CP	6.6	9.2
CTX	4.8	5.0
CAZ	4.2	5.8
CFX	2.4	3.3
FOM	0.0	0.8
NA	17.5	17.5
CPFX	0.0	0.8
NFLX	0.0	0.0
AMK	0.0	0.0
IPM	0.0	0.0
MEPM	0.0	0.0

* Status of strains isolated at the18 Public Health Institutes across Japan; 90% were isolated from domestic chicken meat. The remaining 10% derived from foreign or unknown chicken meat, or from beef or pork.
Adapated from [6] with partial modification.

Table 21. The proportion (%) of antimicrobial-resistant non-typhoidal *Salmonella* spp. strains of serotypes derived from patints that were also detected from food samples

	2015 (n=190)	2016 (n=131)
ABPC	25.3	19.8
GM	0.5	0.8
KM	10.0	14.5
SM	42.6	41.2
TC	45.3	38.9
ST	7.4	6.1
CP	2.1	8.4
CTX	0.5	2.3
CAZ	0.5	2.3
CFX	0.0	0.8
FOM	0.0	0.8
NA	9.5	14.5
CPFX	0.0	0.8
NFLX	0.0	0.8
AMK	0.0	0.0
IPM	0.0	0.0
MEPM	0.0	0.0

Prepared from [6] with partial modification.

Table 22. The proportion (%) of antimicrobial-resistant human (symptomatic person)-derived non-typhoidal *Salmonella* spp. strains of serotypes that were not detected from food samples

	2015 (n=178)	2016 (n=117)
ABPC	6.2	8.5
GM	0.0	0.0
KM	2.2	3.4
SM	7.9	12.0
TC	15.7	10.3
ST	0.0	6.0
CP	1.1	3.4
CTX	0.0	3.4
CAZ	0.0	2.6
CFX	0.0	2.6
FOM	0.0	0.0
NA	4.5	1.7
CPFX	0.6	1.7
NFLX	0.6	1.7
AMK	0.0	0.0
IPM	0.0	0.0
MEPM	0.0	0.0

Prepared from [6] with partial modification.

iii. *Neisseria gonorrhoeae*

Source: National Institute of Infectious Diseases

The 618 and 675 *Neisseria gonorrhoeae* strains that were respectively isolated in 2015 and in 2016 were tested for antimicrobial susceptibility (Table 23). The proportion (%) of ceftriaxone (CTRX)-resistant strains respectively accounted for 6.2% and at 4.3% on the EUCAST standards. The respective proportion of strains assessed as resistant based on the CLSI Criteria (MIC ≥ 0.5 μg/mL) were 0.6% and 0.4%. No spectinomycin (SPCM)-resistant strains were present. On the other hand, the proportion (%) of azithromycin (AZM)-resistant strains increased from 13.0% in 2015 to 33.5% in 2016.

The CLSI Criteria do not provide a break point for azithiromycin. Based on the distribution of azithromycin MIC of strains with 23S rRNA gene mutation, the proportion of azithormycin reisitant were identified among strains that indicated 2 μg/mL or higher MIC ("non-wild type") (see Appendix (8)), at 3.2% in 2015 and at 4.0% in 2016. According to the clinical assessment in Japan, the strains that indicated azithromycin MIC of 1 μg/mL or higher can be resonably regarded as resistant. According to this criteria (R ≥ 1 μg/mL), the proportion of azithoromcyin resistant strains was 11% in 2015 and 9.3% in 2016. Among the other three antimicrobials, the proportion of cefixime (CFIX)-resistant strains accounted for approximately 30-40%, and that of ciprofloxacin (CPFX)-resistant strains accounted for approximately 80%. Penicillins (PCG) would not have therapeutic effect on about 90% of strains.

Table 23. The proportion (%) of antimicrobial-resistant *Neisseria gonorrhoeae*

	2015 (618 strains)	2016 (675 strains)
CTRX	6.2	4.3
SPCM	0.0	0.0
AZM	13.0	33.5
PCG	38.4 (96.6)*	36.3 (96.9)*

CFIX	36.2	43.2
CPFX	79.5	78.0

The EUCAST standards were used for susceptibility and resistance assessment.
* Figures in parentheses indicate the sum of resistance and intermediate resistance.

iv. *Salmonella* Typhi, *Salmonella* Paratyphi A, *Shigella* spp.
Source: National Institute of Infectious Diseases

The 32 and 46 *Salmonella* Typhi strains that were respectively isolated in 2015 and in 2016 were tested for antimicrobial susceptibility (Table 24). The proportion (%) of ciprofloxacin (CPFX)-resistant strains respectively accounted for 68.8% and at 63.0%. The figures included strains with advanced resistance (MIC ≥ 4) to ciprofloxacin at 12.5% and at 23.9%. Multidrug-resistant *Salmonella* Typhi that indicated resistance to ampicillin (ABPC), chloramphenicol (CP) and ST were isolated in both years (two strains in 2015 and one strain in 2016), including two strains (one each in 2015 and 2016) that were non-susceptible to ciprofloxacin (CPFX).

The 30 and 20 *Salmonella* Paratyphi A strains that were respectively isolated in 2015 and in 2016 were tested for antimicrobial susceptibility (Table 25). The proportion (%) of ciprofloxacin (CPFX)-non-susceptible strains respectively accounted for 83.3% and at 85.0%. No cefotaxime (CTX)-resistant strains were isolated among the *Salmonella* Typhi and *Salmonella* Paratyphi A. The 105 and 73 *Shigella* spp. strains that were respectively isolated in 2015 and in 2016 were tested for antimicrobial susceptibility (Table 26). The proportion (%) of ST-resistant strains respectively accounted for 81.0% and 80.8%. The proportion of ciprofloxacin (CPFX)-non-susceptible strains respectively accounted for 45.7% and for 35.6%. The proportion (%) of cefotaxime-resistant strains respectively accounted for 5.7% and for 16.4%.

Table 24. The proportion (%) of antimicrobial-resistant *Salmonella* Typhi

	2015 (32 strains)	2016 (46 strains)
ABPC	5.7	2.2
CP	5.7	2.2
ST	5.7	2.2
NA	68.8	63.0
CPFX	68.8 (12.5)*	63.0 (23.9)*
CTX	0.0	0.0

* Advanced resistance to fluoroquinolone

Table 25. The proportion (%) of antimicrobial-resistant *Salmonella* Paratyphi A

	2015 (30 strains)	2016 (20 strains)
ABPC	0.0	0.0
CP	0.0	0.0
ST	0.0	0.0
NA	80.0	80.0
CPFX	83.3	83.3
CTX	0.0	0.0

Table 26. The proportion (%) of antimicrobial-resistant *Shigella* spp.

	2015 (105 strains)	2016 (73 strains)
ABPC	21.9	42.5
CP	11.4	24.7
ST	81.0	80.8

NA	63.8	52.1
CPFX	45.7	35.6
CTX	5.7	16.4
FOM	1.9	0.0

5) *Mycobacterium tuberculosis*

Source: The Research Institute of Tuberculosis, Japan Anti-tuberculosis Association

Among patients with culture-positive pulmonary tuberculosis who were newly notified from 2011 to 2015, the proportion of resistance to major antituberculosis antibiotics:isoniazid (INH), rifampicin (RFP), streptomycin (SM), and ethambutol (EB) remained mostly at the same level. The number of newly reported cases with multidrug-resistant tublerclosis that are resistant at least to both INH and RFP remained from 50 to 60 per year.

Table 27. Newly Notified Patients with Culture-positive Pulmonary Tuberculosis: Trends in Drug Susceptibility at the Time of Notification

	2011	2012	2013	2014	2015
Culture-positive patients, N	10,915	11,261	10,523	10,259	10,035
INH-resistant, n	386	380	369	349	372
(%)*	(4.8)	(4.6)	(4.8)	(4.6)	(4.9)
RFP-resistant, n	86	73	64	76	77
(%)*	(1.1)	(0.9)	(0.8)	(1.0)	(1.0)
INH & RFP-resistant†, n	60	60	47	56	48
(%)*	(0.7)	(0.7)	(0.4)	(0.5)	(0.5)
SM-resistant, n	-	509	475	469	476
(%)§		(6.1)	(6.2)	(6.2)	(6.3)
EB-resistant, n	-	151	106	130	129
(%)¶		(1.8)	(1.4)	(1.7)	(1.7)

* The denominator was defined as the number of patients with recorded INH- and RFP-susceptibility testing results among all culture-positive patients: 8,046 patients in 2011, 8,347 patietints in 2012, 7,701 patietns in 2013, 7,645 patients in 2014, and 7,630 patients in 2015.

† INH- and RFP- resistant tuberculosis bacteria are referred to as "multidrug-resistant."

§ The proportion appeared here showed the share in patients with INH- and RFP-susceptibility testing results, excluding those who were not tested for SM-susceptibility or those with the unknown test result:54 patients in 2012, 48 patients in 2013, 52 patients in 2014, and 48 patients in 2015.

¶ The proportion appeared here showed the share in patients with INH- and RFP-susceptibility testing results, excluding those who were not tested for EB-susceptibility or those with the unknown test result:14 in 2012, 13 in 2013, 13 in 2014, and 19 in 2015).

-: Not under surveillance

6) Status of health care associated infection

Source: Japan Nosocomial Infections Surveillance (JANIS)

The number of medical institutions participating in the surgical site infection (SSI) division of JANIS nearly doubled over the past five years (Table 28). In 2015, among 251,832 surgical operations undertaken at 671 institutions, SSI were reported in 14,701 (5.8%) cases. The number of reported SSI declined from 2012 during the observed period.

In the intensive care unit (ICU) division of JANIS, the incidence of infection by ventilator-associated pneumonia remained 1.3 - 1.7 per 1,000 days of ICU stay over the past five years, and accounted for 1.5 per 1,000 days of ICU stay in 2015 (Table 29). The incidence of urinary tract infection and catheter related bloodstream infection remained at the same level over the past five years: 0.5-0.6 per 1,000 days of ICU stay and at 0.7-0.8 per 1,000 days of ICU stay respectively. JANIS monitors cases of infections that occured between 48 hours after admission to ICU and discharge from ICU.

i. Surgical site infection

Table 28. The trend of reported SSI cases, JANIS 2011-2015

	2011	2012	2013	2014	2015
Total SSI cases per total surgical operations (%)*	**6.0**	**6.8**	**6.5**	**6.0**	**5.8**
Participated medical institutions	333	363	442	552	671
Total surgical operations	127,731	129,825	161,077	207,244	251,832
Total SSI cases	7,719	8,771	10,445	12,508	14,701

* Total SSI cases per total sugical operations (%) = (Total SSI cases at medical facilities participated in JANIS) / (Total surgical operations at medical facilities participated in JANIS) times 100
Prepared from annual reports of the SSI division, JANIS.[7]

ii. Infections at ICU

Table 29. Incidence rates of infection at ICU

		2011	2012	2013	2014	2015
Ventilator-associated pneumonia	**Total infection incidence rate***	**1.7**	**1.4**	**1.3**	**1.4**	**1.5**
	Total infections at monitored medical institutions	382	327	324	395	522
Urinary tract infection	**Total infection incidence rate***	**0.5**	**0.5**	**0.6**	**0.5**	**0.5**
	Total infections at monitored medical institutions	111	124	143	148	190
Catheter-related bloodstream infection	**Total infection incidence rate***	**0.7**	**0.7**	**0.8**	**0.7**	**0.7**
	Total infections at monitored medical institutions	168	162	204	205	240

* Total infection incidence rate = (Total infections among applicable patients at medial facilities participated in JANIS) / (Total days of ICU stay of applicable patients medial facilities participated in JANIS) times 1000
Prepared from annual reports of the ICU section, JANIS.[8]

7) *Clostridium (Clostridioides) difficile* infection

Clostridium (Clostridioides) difficile is a spore-forming gram-positive anaerobic bacillus that colonizes the intestines of about 10% of healthy adults.[9] *Clostridium (Clostridioides) difficile* infection (CDI) is a major healthcare-associated infection that causes diarrhea at hospitals and long-term care facilities for the elderly. In addition, CDI has been recognized as a cause of diarrhea even in the community.[10]

In Japan, national surveillance for CDI has not been established, and a few studies have been performed to address the burden of the CDI in Japan .[11][12] The prospective multi-site study conducted at 12 sites in Japan showed that, among 653 inpatients who had diarrhea, 187 had CDI (incidence rate: 7.9 per 10,000 patient-day), and that more than 80% of CDI were hospital-aquired.[13]

(2) Animals

1) Bacteria derived from food-producing animal

Source: Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

Under the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM), antimicrobial susceptibility tests are performed using the broth microdilution method according to the CLSI guidelines. For agents with a BP established by the CLSI, susceptibility was interpreted using the CLSI Criteria. The BPs of the other antimicrobial agents were determined microbiologically (midpoint of a bimodal MIC distribution).

Bacteria derived from diseased animals

i. *Salmonella* spp.

Based on the monitoring on 11 agents from 2011 to 2015, the proportion (%) of antimicrobial-resistant strains respectively accounted for 0 to 66.1% in cattle, for 0 to 66.7% in pigs, and at 0 to 42.9% in chickens (Table 30). The tetracycline (TC) resistant strains were the most common among cattle, pigs and chickens. On the other hand, strains resistant to ciprofloxacin (CPFX) in those animals were not observed.

Table 30. The proportion (%) of antimicrobial-resistant *Salmonella* spp. isolated from diseased animals

Agent	BP	Animal	2011	2012	2013	2014	2015
ABPC	32*	Cattle	28.0	32.9	60.7	61.9	56.6
		Pigs	25.4	25.3	45.0	41.4	46.9
		Chickens	12.0	9.4	4.0	3.9	14.3
CEZ	32	Cattle	10.0	1.2	8.9	7.9	7.9
		Pigs	0.0	0.0	0.0	0.0	6.1
		Chickens	0.0	3.1	4.0	0.0	0.0
CTX	4*	Cattle	10.0	1.2	8.9	7.9	7.9
		Pigs	0.0	0.0	0.0	0.0	4.1
		Chickens	0.0	0.0	4.0	0.0	0.0
GM	16*	Cattle	0.0	0.0	0.0	3.2	7.9
		Pigs	6.3	3.6	15.0	15.5	8.2
		Chickens	0.0	0.0	2.0	0.0	0.0
KM	64*	Cattle	12.0	3.7	25.0	14.3	21.1
		Pigs	9.5	12.0	6.7	8.6	6.1
		Chickens	24.0	15.6	22.0	29.4	42.9
TC	16*	Cattle	30.0	32.9	66.1	50.8	55.3
		Pigs	61.9	53.0	66.7	60.3	61.2
		Chickens	36.0	34.4	30.0	39.2	42.9
NA	32*	Cattle	2.0	7.3	1.8	3.2	11.8
		Pigs	15.9	21.7	5.0	15.5	6.1
		Chickens	8.0	6.3	8.0	3.9	28.6
CPFX	4*	Cattle	0.0	0.0	0.0	0.0	0.0
		Pigs	0.0	0.0	0.0	0.0	0.0
		Chickens	0.0	0.0	0.0	0.0	0.0
CL	16	Cattle	0.0	0.0	0.0	0.0	0.0
		Pigs	0.0	0.0	1.7	0.0	0.0
		Chickens	0.0	3.1	2.0	0.0	0.0
CP	32*	Cattle	14.0	12.2	10.7	17.5	22.4
		Pigs	12.7	13.3	11.7	25.9	12.2
		Chickens	0.0	6.3	6.0	3.9	14.3
TMP (SMX/TMP in	16* (SMX/TMP:	Cattle	2.0	1.2	1.8	6.3	13.2
		Pigs	25.4	21.7	36.7	32.8	22.4

2011)	76/4*)	Chickens	20.0	15.6	14.0	29.4	42.9
Strains		Cattle	50	82	56	63	76
		Pigs	63	83	60	58	49
		Chickens	25	32	50	51	7

The unit of BP is μg/mL.
* BP follows CLSI Criteria .

ii. *Staphylococcus aureus*

Based on the monitoring conducted on 8 agents from 2011 to 2015, the proportion (%) of antimicrobial-resistant strains respectively accounted for 0 to 21.3% in cattle, and 0 to 55.0% in chickens (Table 31). The ampicillin (ABPC)- and erythromycin (EM)-resistant strains were the most common in cattle and chickens respectively.

Table 31. The proportion (%) of antimicrobial-resistant *Staphylococcus aureus* isolated from diseased animal

Agent*	BP	Animal	2011	2012	2013	2014	2015
ABPC	0.5	Cattle	5.5	13.6	11.0	11.1	21.3
		Chickens	0.0	25.0	0.0	15.4	50.0
SM	64	Cattle	6.4	2.3	2.8	1.1	2.7
		Chickens	0.0	10.0	0.0	7.7	16.7
GM	16†	Cattle	0.9	2.3	1.8	0.0	1.3
		Chickens	0.0	15.0	0.0	0.0	0.0
EM	8†	Cattle	1.8	3.4	5.5	0.0	6.7
		Chickens	50.0	55.0	0.0	15.4	16.7
TC	16†	Cattle	0.0	2.3	8.3	5.5	6.7
		Chickens	37.5	5.0	0.0	16.7	16.7
CP	32†	Cattle	0.0	0.0	0.9	0.0	1.3
		Chickens	0.0	0.0	0.0	15.4	33.3
CPFX	4	Cattle	0.0	0.0	0.9	0.0	1.3
		Chickens	25.0	0.0	4.2	15.4	33.3
Strains		Cattle	109	88	109	91	75
		Chickens	8	20	24	12	6

The unit of BP is μg/mL.
No data for pigs are listed, because the number of strains was smaller than 20 in each year.
* While NA was also included in the scope of monitoring, its proportion of NA-resitant strains was not listed because BP could not be established.
† BP follows CLSI Criteria .

iii. *Escherichia coli*

Based on the monitoring conducted on 12 agents from 2011 to 2015, the proportion (%) of antimicrobial-resistant strains respectively accounted for 0 to 78.7% in cattle, 0 to 79.1% in pigs, and 0 to 75.6% in chickens (Table 32). The highest proportion of resistance was observed for streptomycin (SM) in cattle, for tetracycline (TC) in pigs, and for ampicillin (ABPC) in chickens. On the other hand, the porpotion for colistin (CL)-resistant strains was maintained lower than 10% in all animal species.

Table 32. The proportion (%) of antimicrobial-resistant *Escherichia coli* isolated from diseased animals

Agent	BP	Animal	2012†	2013†	2014†	2015
ABPC	32*	Cattle	-	61.4	57.8	63.8
		Pigs	-	65.2	50.4	57.4
		Chickens	75.6	54.2	-	60.4
CEZ	32	Cattle	-	21.1	6.7	14.9
		Pigs	-	10.1	6.1	9.3
		Chickens	40.2	16.7	-	14.6
CTX	4*	Cattle	-	10.5	6.7	8.5
		Pigs	-	2.5	0.0	3.7
		Chickens	37.8	14.6	-	10.4
SM	32	Cattle	-	-	68.9	78.7
		Pigs	-	-	64.3	66.7
		Chickens	-	-	-	60.4
GM	16*	Cattle	-	17.5	6.7	12.8
		Pigs	-	24.1	8.7	19.4
		Chickens	6.1	3.1	-	2.1
KM	64*	Cattle	-	38.6	26.7	29.8
		Pigs	-	34.2	33.9	31.5
		Chickens	51.2	35.4	-	39.6
TC	16*	Cattle	-	50.9	66.7	66.0
		Pigs	-	79.1	75.7	75.9
		Chickens	74.4	61.5	-	70.8
NA	32*	Cattle	-	29.8	33.3	36.2
		Pigs	-	60.1	52.2	50.0
		Chickens	73.2	59.4	-	52.1
CPFX	4*	Cattle	-	19.3	24.4	34.0
		Pigs	-	36.1	23.5	32.4
		Chickens	22.0	25.0	-	8.3
CL	16	Cattle	-	5.3	6.7	0.0
		Pigs	-	3.2	0.0	2.8
		Chickens	2.4	1.0	-	0.0
CP	32*	Cattle	-	21.1	28.9	46.8
		Pigs	-	64.6	64.3	61.1
		Chickens	22	25	-	16.7
TMP	16	Cattle	-	22.8	33.3	44.7
		Pigs	-	49.4	59.1	64.8
		Chickens	31.7	33.3	-	33.3
Strains		Cattle	-	57	45	47
		Pigs	-	158	115	108
		Chickens	82	96	-	48

The unit of BP is μg/mL.
* BP follows CLSI Criteria .
†-: Not under surveillance.

Bacteria derived from healthy animals in farms

i. *Campylobacter jejuni*

Based on the monitoring on 8 agents from 2011 to 2015, the proportion (%) of antimicrobial-resistant strains respectively accounted for 0 to 68.3% in cattle, 0 to 53.1% in broilers, and 0 to 44.3% in layers (Table 33). The highest porpotion of resistance was observed for tetracycline (TC), in all animal species. On the other hand, the propotion for streptomycin (SM)-, erythromycin (EM)-, and chloramphenicol (CP)-resistant strains remained lower than 10%.

Table 33. The proportion (%) of antimicrobial-resistant *Campylobacter jejuni* derived from healthy animals

Agent*	BP	Animal	2011	2012	2013	2014	2015
ABPC	32	Cattle	0.0	6.4	1.4	13.3	4.4
		Broilers	25.5	6.3	26.8	20.8	26.5
		Layers	22.0	29.7	25.3	30.6	41.9
SM	32	Cattle	3.9	4.3	5.6	8.3	4.4
		Broilers	0.0	0.0	0.0	0.0	0.0
		Layers	2.2	0.0	0.0	0.0	0.0
EM	32†	Cattle	0.0	0.0	0.0	0.0	0.0
		Broilers	0.0	0.0	0.0	0.0	0.0
		Layers	0.0	0.0	0.0	0.0	0.0
TC	16†	Cattle	37.3	55.3	52.1	68.3	60.0
		Broilers	52.7	28.1	41.1	27.1	53.1
		Layers	39.6	21.6	44.3	40.8	21.0
CP	16	Cattle	0.0	0.0	2.8	6.7	0.0
		Broilers	0.0	0.0	0.0	0.0	0.0
		Layers	2.2	2.7	0.0	0.0	0.0
NA	32	Cattle	31.4	61.7	32.4	43.3	37.8
		Broilers	34.5	28.1	19.6	47.9	24.5
		Layers	22.0	10.8	16.5	24.5	19.4
CPFX	4†	Cattle	29.4	57.4	32.4	43.3	35.6
		Broilers	30.9	18.8	17.9	45.8	24.5
		Layers	17.6	5.4	16.5	24.5	16.1
Strains		Cattle	51	47	71	60	45
		Broilers	55	32	56	48	49
		Layers	91	37	79	49	62

The unit of BP is μg/mL.

No data for pigs was listed, because the number of strains was smaller than 20 in each year.

* While GM was also included in the scope of monitoring, the proportion to GM-resistant wass not listed because BP could not be established .

† BP follows CLSI Criteria .

ii. *Campylobacter coli*

Based on the monitoring conducted on 8 agents from 2011 to 2015, the proportion (%) of antimicrobial-resistant strains accounted for 0 to 86.4% in pigs (Table 34). The highest propotion of resitance was observed for tetracycline (TC). On the other hand, the proportion of ampicillin (ABPC)-resitant strains remained lower than 10%.

Table 34. The proportion (%) of antimicrobial-resistant *Campylobacter coli* derived from healthy animals

Agent*	BP	Animal	2011	2012	2013	2014	2015
ABPC	32	Pigs	2.2	3.4	4.8	5.1	7.9
SM	32	Pigs	55.6	62.1	57.1	54.2	71.1
EM	32†	Pigs	44.4	41.4	42.9	44.1	18.4

TC	16†	Pigs	73.3	72.4	78.6	86.4	78.9
CP	16	Pigs	17.8	29.3	19.0	16.9	0.0
NA	32	Pigs	73.3	29.3	47.6	49.2	57.9
CPFX	4†	Pigs	71.1	25.9	42.9	49.2	57.9
Strains		Pigs	45	58	42	59	38

The unit of BP is μg/mL.
No data for cattle, broilers, and layers were listed, because the number of strains was smaller than 20 in each year.
* While GM was also included in the scope of survey, the proportion of GM resistant strains was not listed because BP could not be established.
† BP follows CLSI Criteria .

iii. *Enterococcus* spp.

Based on the monitoring conducted on 13 agents from 2011 to 2015, the proportion (%) of antimicrobial-resistant strains respectively accounted for 0 to 34.8% in cattle, 0 to 73.0% in pigs, 0 to 75.0% in broilers, and 0 to 37.7% in layers (Table 35). The highest porpotion of resistance was observed for dihydrostreptomycin (DSM) in cattle, and for oxytetracycline (OTC) in pigs, broilers, and layers.

Table 35. The proportion (%) of antimicrobial-resistant *Enterococcus* spp. derived from healthy animals

Agent*	BP	Animal	2011	2012	2013	2014	2015
ABPC	16†	Cattle	0.0	0.0	0.0	0.7	0.0
		Pigs	0.0	0.8	0.0	1.4	0.0
		Broilers	1.4	1.9	0.7	1.6	0.0
		Layers	0.0	0.0	0.0	0.0	0.0
DSM	128	Cattle	34.8	23.4	31.5	26.6	26.8
		Pigs	53.8	38.1	40.5	37.9	37.0
		Broilers	32.1	32.2	47.8	31.9	51.8
		Layers	27.6	17.9	35.8	21.6	25.3
GM	32	Cattle	7.3	3.3	6.2	4.1	5.0
		Pigs	4.8	5.6	2.7	0.0	3.0
		Broilers	3.6	9.1	7.4	3.7	9.6
		Layers	6.7	2.9	8.5	1.5	2.7
KM	128	Cattle	18.6	14.2	10.0	10.7	9.1
		Pigs	31.7	27.8	24.3	29.3	19.0
		Broilers	33.6	34.1	56.6	41.0	43.9
		Layers	24.5	27.1	18.8	24.1	17.8
OTC	16	Cattle	24.7	17.2	28.2	17.9	19.5
		Pigs	70.2	52.4	59.5	56.4	73.0
		Broilers	60.0	66.3	75.0	61.7	63.2
		Layers	29.4	31.9	36.4	32.2	37.7
CP	32†	Cattle	1.2	0.0	0.0	0.7	0.5
		Pigs	12.5	19.8	9.9	11.4	10.0
		Broilers	5.0	7.2	11.8	9.6	18.4
		Layers	0.6	1.9	3.0	1.0	0.7
EM	8†	Cattle	6.1	2.2	2.5	5.9	2.3
		Pigs	31.7	28.6	38.7	22.1	36.0
		Broilers	30.0	39.4	36.8	28.2	41.2
		Layers	14.1	14.0	15.2	9.0	10.3
LCM	128	Cattle	3.2	1.5	1.2	5.5	1.4
		Pigs	41.3	49.2	45.0	37.9	49.0
		Broilers	32.9	39.4	41.2	29.8	43.9
		Layers	11.7	11.1	13.3	10.1	9.6
ERFX	4	Cattle	9.7	10.6	3.7	7.2	6.8
		Pigs	14.4	15.1	9.0	17.9	15.0

		Broilers	28.6	30.3	36.8	41.0	20.2
		Layers	12.3	22.2	12.7	21.6	8.9
TS[§]	64	Cattle	2.4	1.5	1.2	5.2	0.5
		Pigs	30.8	27.0	35.1	21.4	35.0
		Broilers	24.3	37.0	33.1	23.9	40.4
		Layers	9.8	12.1	11.5	7.0	11.0
Strains		Cattle	247	274	241	290	220
		Pigs	104	126	111	140	100
		Broilers	140	208	136	188	114
		Layers	163	207	165	199	146

The unit of BP is μg/mL.

* While BC, SNM and VGM were also included in the scope of survey, the propotion of BC-, SNM- and VM-resistant strains were not listed because BP could not be established.

[†] BP follows CLSI Criteria .

[§] The BP for TS was set at 8 μg/mL in 2010 and 2011, but was changed to 64 μg/mL in 2012. The resistance proportion in the table were calculated using cut-off of 64 μg/mL.

iv. *Escherichia coli*

Based on the monitoring conducted on 12 agents from 2011 to 2015, the proportion (%) of antimicrobial-resistant strains respectively accounted for 0 to 2.5% in cattle, 0 to 64.2% in pigs, 0 to 61.1% in broilers, and 0 to 38.5% in layers. The highest propotion of resistance was observed for tetracycline (TC) in all animal species. On the other hand, the proportion of cefazolin (CEZ)-, cefotaxime (CTX)-, gentamicin (GM)-, ciprofloxacin (CPFX)-, and colistin (CL)-resistant strains remained mostly lower than 10%. The proportionof cefazolin (CEZ)- and cefotaxime (CTX)-resistant strains in broilers had declined from 2012. This decline is perhaps explained by the intervention to related associations: explaining JVARM data and ordering to withdraw the off-label use of third-generation cephalosporin.[32]

Table 36. The proportion (%) of antimicrobial-resistant *Escherichia coli* derived from healthy animals

Agent	BP	Animal	2011	2012	2013	2014	2015
ABPC	32*	Cattle	5.9	6.4	7.1	5.6	4.2
		Pigs	22.1	28.7	26.5	24.6	30.8
		Broilers	42.9	44.9	47.3	44.5	41.8
		Layers	14.0	12.3	16.9	18.4	19.8
CEZ	32	Cattle	0.7	1.7	0.0	1.1	0.0
		Pigs	2.1	1.4	1.5	0.0	0.0
		Broilers[†]	19.9	9.7	5.3	3.8	3.6
		Layers	1.7	3.1	2.9	0.0	0.8
CTX	4*	Cattle	0.4	1.0	0.0	1.1	0.0
		Pigs	1.4	1.4	0.8	0.0	0.0
		Broilers[†]	18.6	8.8	4.6	3.3	2.7
		Layers	0.0	3.1	2.9	0.0	0.0
SM	32	Cattle	12.8	15.1	20.0	13.4	16.7
		Pigs	43.4	39.9	43.9	47.0	37.4
		Broilers	28.6	38.0	38.9	47.8	33.6
		Layers	14.5	19.0	14.7	9.5	18.2
GM	16*	Cattle	0.0	0.0	0.4	0.0	1.4
		Pigs	1.4	2.8	1.5	3.7	1.9
		Broilers	3.7	3.4	0.8	1.6	0.9
		Layers	0.6	1.0	0.0	1.1	0.0
KM	64*	Cattle	1.8	2.3	2.5	1.8	1.4
		Pigs	6.9	7.0	7.6	9.7	11.2
		Broilers	14.3	27.7	24.4	30.2	29.1
		Layers	4.1	3.1	5.9	1.7	7.4

TC	16*	Cattle	18.3	22.4	22.5	20.4	19.0
		Pigs	58.6	60.1	53.8	64.2	55.1
		Broilers	47.2	58.5	61.1	51.1	45.5
		Layers	23.8	38.5	24.3	24.6	22.3
CP	32*	Cattle	2.9	3.3	4.6	2.5	3.7
		Pigs	18.6	26.6	22.0	25.4	25.2
		Broilers	9.3	16.5	22.1	14.3	16.4
		Layers	1.2	9.7	6.6	2.8	4.1
CL	16	Cattle	0.0	0.0	0.0	0.0	0.0
		Pigs	2.1	0.0	0.0	0.0	0.0
		Broilers	0.6	0.5	0.0	0.0	0.0
		Layers	1.7	1.0	0.0	0.0	0.0
NA	32*	Cattle	2.9	3.7	1.3	2.8	0.9
		Pigs	9.7	9.8	9.8	8.2	9.3
		Broilers	31.7	30.2	35.1	38.5	32.7
		Layers	9.9	16.4	9.6	10.6	17.4
CPFX	4*	Cattle	0.7	1.0	0.0	0.0	0.5
		Pigs	2.8	0.7	0.8	1.5	1.9
		Broilers	5.0	7.8	7.6	12.6	9.1
		Layers	0.6	1.0	0.0	4.5	4.1
TMP	16*	Cattle	3.3	2.3	4.6	3.2	3.2
		Pigs	26.2	35.0	28.0	34.3	28.0
		Broilers	23.6	33.0	40.5	36.8	30.0
		Layers	14.5	13.3	12.5	17.9	18.2
Strains		Cattle	273	299	240	284	216
		Pigs	145	143	132	134	107
		Broilers	161	205	131	182	110
		Layers	172	195	136	179	121

The unit of BP is μg/mL.

* BP follows CLSI Criteria .

† The proportion of CEZ- and CTX- resistant strains in broilers in 2010 accounted for 20.5% and 17.9% respectively

Bacteria derived from food-producing animals in animal and poultry slaughterhouses

i. *Escherichia coli*

Based on the monitoring conducted on 12 agents from 2012 to 2015, the proportion (%) of antimicrobial-resistant strains respectively accounted for 0 to 19.8% in cattle, 0 to 62.2% in pigs, and 0 to 54.9% in chickens (Table 37). The highest proportion of resistance was observed for tetracycline (TC), in all animal species. On the other hand, the proportion of cefazolin (CEZ)-, cefotaxime (CTX)-, gentamicin (GM)-, ciprofloxacin (CPFX)-, and colistin (CL)- resistant strains remained lower than 10%.

Table 37. The proportion (%) of antimicrobial-resistant *Escherichia coli* derived from animal and poultry slaughterhouses

Agent	BP	Animal	2012	2013	2014	2015
ABPC	32*	Cattle	2.4	6.5	3.0	5.5
		Pigs	32.3	26.0	43.0	34.4
		Chickens	30.8	35.5	40.1	43.5
CEZ	32	Cattle	0.4	0.3	0.0	0.0
		Pigs	1.0	0.8	1.1	1.0
		Chickens	3.0	7.8	5.8	3.8
CTX	4*	Cattle	0.0	0.0	0.4	0.0
		Pigs	0.0	0.0	1.1	0.0
		Chickens	1.5	4.8	4.1	2.2
SM	32	Cattle	14.9	12.3	17.1	12.4
		Pigs	44.1	44.9	52.7	39.6
		Chickens	39.1	38.6	44.8	41.8
GM	16*	Cattle	0.0	0.3	0.0	0.0
		Pigs	0.5	2.4	6.5	2.1
		Chickens	1.5	1.8	2.9	2.2
KM	64*	Cattle	1.2	1.5	0.4	0.7
		Pigs	9.7	7.9	9.7	8.3
		Chickens	24.1	24.1	33.1	37.5
TC	16*	Cattle	19.0	16.4	19.8	18.6
		Pigs	58.5	62.2	59.1	45.8
		Chickens	49.6	44.0	43.6	54.9
NA	32*	Cattle	2.4	1.8	2.3	2.6
		Pigs	4.1	11.0	9.7	5.2
		Chickens	39.8	36.1	45.3	35.9
CPFX	4*	Cattle	0.0	0.6	0.8	0.0
		Pigs	1.5	0.8	2.2	3.1
		Chickens	6.0	5.4	9.9	4.9
CL	16	Cattle	0.0	0.0	0.8	0.0
		Pigs	0.0	0.0	0.0	0.0
		Chickens	0.8	0.6	0.0	0.5
CP	32*	Cattle	5.2	2.3	3.8	2.9
		Pigs	23.6	23.6	34.4	25.0
		Chickens	11.3	11.4	15.1	9.8
SMX/TMP	76/4*	Cattle	2.0	2.9	5.3	2.9
		Pigs	23.6	26.8	34.4	30.2
		Chickens	24.8	31.9	30.2	28.3
Strains		Cattle	248	341	263	274
		Pigs	195	127	93	96
		Chickens	133	166	172	184

The unit of BP is μg/mL.
* BP follows CLSI Criteria .

ii. *Campylobacter jejuni*

Based on the monitoring on 8 agents from 2012 to 2015, the proportion (%) of antimicrobial-resistant strains respectively accounted for 0 to 52.4% in cattle, and 0 to 48.1% in chicken (Table 38). The highest proportion of resistance was observed for tetracycline (TC) in cattle, and for nalidixic acid (NA) in chickens. On the other hand, the proportion of streptomycin (SM)-, erythromycin (EM)-, and chloramphenicol (CP)- resistant strains remained lower than 10%.

Table 38. The proportion (%) of antimicrobial-resistant *Campylobacter jejuni* derived from animal and poultry slaughterhouses

Agent*	BP	Animal	2012	2013	2014	2015
ABPC	32	Cattle	0.0	9.1	12.9	8.9
		Chickens	19.7	19.8	17.5	19.1
SM	32	Cattle	2.4	3.5	3.8	3.2
		Chickens	1.4	0.0	3.5	2.1
EM	32†	Cattle	0.0	0.7	0.0	1.3
		Chickens	0.0	0.0	0.0	0.0
TC	16†	Cattle	45.1	52.4	49.2	52.2
		Chickens	38.0	44.4	38.6	28.7
CP	16	Cattle	0.0	6.3	0.0	1.3
		Chickens	0.0	0.0	1.8	0.0
NA	32	Cattle	34.1	33.6	50.8	42.7
		Chickens	39.4	48.1	29.8	27.7
CPFX	4†	Cattle	34.1	29.4	49.2	40.8
		Chickens	39.4	39.5	29.8	26.6
Strains		Cattle	82	143	132	157
		Chickens	71	81	57	94

The unit of BP is μg/mL.
* While GM was also included in the scope of monitoring, the proportion of GM-resistant strains was not listed because BP could not be established.
† BP follows CLSI Criteria .

iii. *Campylobacter coli*

Based on the monitoring conducted on 8 agents from 2012 to 2015, the proportion (%) of antimicrobial-resistant strains respectively accounted for 1.2 to 80.9% in cattle, and 3.8 to 93.4% in pigs (Table 39). The highest proportion of resistance was observed for nalidixic acid (NA) in cattle-derived strains, and for tetracycline (TC) for pig-derived strains. On the other hand, the proportion of chloramphenicol (CP)-resistant strain remained mostly lower than 10%.

Table 39. The proportion (%) of antimicrobial-resistant *Campylobacter coli* derived from animal slaughterhouses

Agent*	BP	Animal	2012	2013	2014	2015
ABPC	32	Pigs	23.3	25.5	36.6	24.6
SM	32	Pigs	67.4	78.3	69.9	72.3
EM	32†	Pigs	32.6	44.3	43.0	26.2
TC	16†	Pigs	84.5	93.4	80.6	87.7
CP	16	Pigs	10.9	3.8	7.5	9.2
NA	32	Pigs	46.5	53.8	52.7	47.7
CPFX	4†	Pigs	46.5	46.2	50.5	47.7
Strains		Pigs	129	106	93	65

The unit of BP is μg/mL.
* While GM was also included in the scope of monitoring, the proportion of GM-resistant strains was not listed because BP could not be established.

† BP follows CLSI Criteria .

iv. *Enterococcus* spp.

Based on the monitoring conducted on 13 agents from 2012 to 2014, and on 14 agents adding VCM to the above in 2015, the proportion (%) of antimicrobial-resistant bacteria respectively accounted for 0 to 85.6% in cattle, 0 to 82.0% in pigs, and 0 to 72.2% in chickens. The highest proportion of resistance was observed for dihydrostreptomycin (DSM) in cattle and pigs, and for oxytetracycline (OTC) in chickens. On the other hand, the ampicillin (ABPC)- or vancomycin (VCM)-resistant strains were not observed in all animal species.

Table 40. The proportion (%) of antimicrobial-resistant *Enterococcus* spp. derived from animal slaughterhouses

Agent*	BP	Animal	2012	2014†	2015
ABPC	16§	Cattle	0.0	0.0	0.0
		Pigs	0.0	0.0	0.0
		Chickens	0.0	0.6	0.0
DSM	128	Cattle	85.6	31.2	14.9
		Pigs	82.0	55.7	34.4
		Chickens	69.2	30.9	49.2
GM	32	Cattle	61.2	4.2	2.2
		Pigs	43.3	3.4	3.1
		Chickens	29.3	5.5	9.4
KM	128	Cattle	55.2	5.0	4.1
		Pigs	56.2	20.5	31.3
		Chickens	68.4	37.0	47.0
OTC	16	Cattle	24.4	21.2	27.1
		Pigs	61.9	54.5	59.4
		Chickens	72.2	58.0	63.0
CP	32§	Cattle	1.5	0.0	0.0
		Pigs	17.5	17.0	10.4
		Chickens	13.5	8.8	7.2
EM	8§	Cattle	5.0	3.8	1.5
		Pigs	41.8	28.4	30.2
		Chickens	50.4	43.1	42.5
LCM	128	Cattle	27.9	3.1	0.7
		Pigs	59.8	50.0	34.4
		Chickens	52.6	34.3	43.1
ERFX	4	Cattle	6.0	1.2	0.4
		Pigs	22.7	9.1	2.1
		Chickens	9.8	3.9	13.3
TS	64	Cattle	2.0	2.3	0.7
		Pigs	33.0	21.6	19.8
		Chickens	49.6	42.0	35.9
VCM	32	Cattle	-	-	0.0
		Pigs	-	-	0.0
		Chickens	-	-	0.0
Strains		Cattle	201	260	269
		Pigs	194	88	96
		Chickens	133	181	181

The unit of BP is μg/mL.
* While BC, SNM, and VGM were also included in the scope of monitoring, the propotion of BC-, SNM- and VGM-reisitant strains were not listed because BP could not be established.
† The monitoring was not conducted on *Enterococcus* spp. derived from animal slaughterhouses in fiscal year (FY)2013.
§ BP follows CLSI Criteria .

-: Not under surveillance.

v. *Salmonella* spp.

Based on the monitoring conducted on 12 agents with chicken-derived strains from 2011 to 2015, the proportion (%) of antimicrobial-resistant strains accounted for 0 to 85.9%. The highest proportion of resistance was observed for streptomycin (SM). On the other hand, the proportion of cefazolin (CEZ)-, cefotaxime (CTX)-, gentamicin (GM)-, chloramphenicol (CP)-, colistin (CL)-, and ciprofloxacin (CPFX)-resistant strains remained lower than 10%. In particular, no resistant strains were observed for gentamicin (GM), colistin (CL), and ciprofloxacin (CPFX).

Table 41. The proportion (%) of antimicrobial-resistant *Salmonella* spp. derived from poultry slaughterhouses

Agent	BP	Animal	2012	2013	2014	2015
ABPC	32*	Chickens	31.9	22.9	17.2	13.0
CEZ	32	Chickens	7.4	5.9	3.1	1.6
CTX	4*	Chickens	7.4	5.1	2.3	1.6
SM	32	Chickens	77.7	84.7	85.9	76.4
GM	16*	Chickens	0.0	0.0	0.0	0.0
KM	64*	Chickens	31.9	42.4	57.8	69.1
TC	16*	Chickens	74.5	82.2	85.2	83.7
CP	32*	Chickens	0.0	0.8	1.6	1.6
CL	16	Chickens	0.0	0.0	0.0	0.0
NA	32*	Chickens	29.8	19.5	17.2	15.4
CPFX	4*	Chickens	0.0	0.0	0.0	0.0
SMX/TMP	76/4*	Chickens	31.9	48.3	51.6	57.7
Strains		Chickens	94	118	128	123

The unit of BP is μg/mL.
* BP follows CLSI Criteria.

2) Aquatic animal farming

Source: Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

For the monitoring and surveillance of antimicrobial resistance in aquaculture under the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM), antimicrobial susceptibility monitoring are conducted focusing on *Lactococcus garvieae* and *Photobacterium damselae* subsp. *picicida* that are derived from diseased fish (Seriola) and on *Vibrio parahaemolyticus* that is derived from aquaculture envrionment. Strains that were isolated and identified from diseased fish at prefectural fisheries experiment stations were mainly used for testing. In antimicrobial susceptibility tests, MIC values were measured using an agar plate dilution method based on the CLSI guidelines. BP was defined as microbial BP: midpoint of a bimodal MIC distribution.

To further enhance the trend surveillance of antimicrobial resistance in aquaculture, the expantion of the scope of surveillance to all farmed fish species was planned in FY2017, and the antimicrobial susceptibility monitoring of *Lactococcus garvieae* and *Vibrio* spp. will be conducted.

i. *Lactococcus garvieae* derived from diseased fish (Seriola)

The monitoring was conducted on 4 agents that had efficacy on the streptococcal diseases from 2011 to 2014. Antimicrobial resistance was 0-92.6%, with the highest proportion of resistance observed for lincomycin (LCM), whereas the proportion of erythromycin (EM)-resistant strains remained lower than 10%. Given the fact that no bimodal MIC distribution was observed for florfenicol (FF), the proportion of resistance was not calculated. MIC values, however, were low (≤

4) in all strains, suggesting that the susceptibility was maintained.

Table 42. The proportion (%) of antimicrobial-resistant *Lactococcus garvieae*

Agent*	BP	2011	2012	2013	2014
EM	8	0.0	10.3	0.0	0.0
LCM	4	92.6	76.9	71.4	62.5
OTC	8	0.0	12.8	0.0	0.0
Strains		27	39	21	16

The unit of BP is μg/mL.
* While FF was also included in the scope of survey, the proportion of FF-resistant strains was not listed because BP could not be established.

ii. *Photobacterium damselae* subsp. *picicida* derived from diseased fish (Seriola)

A resistant testing was conducted on five agents that had efficacy against photobacteriosis from 2011 to 2014. The number of tested strains was small, and the proportion of resistance varied particularly for ampicillin (ABPC) and for oxolinic acid (OA). However, the proportion of the resistance remained at 7.1% or lower both for bicozamycin (BCM) and for fosfomycin (FOM). Although the proportion of florfenicol (FF)-resistant strain was not calculated given that no bimodal MIC distribution was observed, MIC values were low (≤ 1) in all strains, suggesting that the susceptibility was maintained.

Table 43. The proportion (%) of antimicrobial-resistant pseudotuberculosis-causing bacteria (*Photobacterium damselae* subsp. *picicida*)

Agent*	BP	2011	2012	2013	2014
ABPC	2	11.8	17.6	7.1	59.4
FOM	32	0.0	0.0	7.1	0.0
BCM	64	0.0	0.0	0.0	0.0
OA	1	100.0	82.4	92.9	3.1
Strains		17	17	14	32

The unit of BP is μg/mL.
* While FF was also included in the scope of survey, its resistance proportion is not listed because BP cannot be established.

iii. *Vibrio parahaemolyticus* derived from aquaculture environment

Using the 53 and 50 strains that were respectively isolated in 2011 and in 2012, MIC values were measured for five agents (EM, LCM, OTC, OA and FF) that were approved as aquatic drugs.

Given that no bimodal MIC distribution was observed for all of these agents, the proportion of the strain that were resistant to those agents were not calculated. MIC values, however, were low (≤ 2 for erythromycin (EM), ≤ 1 for oxytetracycline (OTC) and florfenicol (FF), and ≤ 0.5 for oxolinic acid (OA)) in all strains, excluding lincomycin (LCM), which suggested that the susceptibility was maintained to these agents.

3) Companion animal

Source: Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

In FY2016, the Ministry of Agriculture, Forestry and Fisheries organized a "Working Group for the Surveillance of Antimicrobial Resistance (AMR) in Companion Animals," in order to collect inputs from experts concerning monitoring methods for antimicrobial-resistant bacteria in companion animals, and to conduct a pilot surveillance. Based on these results, the routine monitoring of antimicrobial-resistant bacteria in companion animals will be launched in FY2017.

(3) Food

Shinomiya et. al. conducted a reserach regarding antimicrobial-resistant bacteria in food.[6] An outline of this research was presented under (1)-4)-ii, “Non-typhoidal *Salmonella* spp.” in this report.

(4) Environment

In several cases reported from around the world, antimicrobial-resistant factors have been detected in the environment (e.g. soil, river), in addition to hospitals, communities and food-producing animals.[14][15][16][17] For instance, in the neighborhood of Hyderabad, India, where global manufacturing plants of generic drugs were located, there was remarkable contamination of the environment by antimicrobials, and a concern was reported on the risk of the selective emergence of antimicrobial-resistant bacteria and the environmental hazard.[18]

Based on an idea that a large part of environmental contamination is caused by sewage from domestic wastewater, a global project of surveillance on antimicrobial-resistant bacteria in sewage has been conducted with a support from WHO (Global Sewage Surveillance Project),[19] with 90 participating countries. By Jaunuary 2018, a report comparing the antimicrobial-resistant bacteria collected from wastewater entering sewerage systems and thier genetic information around the world, will be published.

In concurrence with this project, a pilot research experiment was launched to evaluate the current status in Japan, by next-generation sequencers (metagenomic analysis), in order to exhaustively detect antimicrobial-resistant genes from rivers and other environmental water. Developing a standardized protocol for the local authorities with Public Health Institutes to continuously monitor such antimicrobial-resistant gene is underway in FY2017.

In the area of health care assoicated infections, thus far, field epidemiology and molecular epidemiological analysis of isolated strains are used for identifying mode of transmission and quantifing the risk on health effects. In contrast, a paucity of data exsits on the impacts of antimicrobial-resistant bacteria derived from the environment on human and animal health, and there have been no established perspecitives whether antimicrobial resistance in the environment may pose health risks on human and animal. A global effort to linking risk assessment and field suvey is expected to be accelated globally, as a workshop for the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) [20] was held in September 2017 in order to assess how antimicrobial-resistant bacteria in the environment can have impact on human health risks.

7. Current Volume of Use of Antimicrobials in Japan

(1) Antimicrobials for humans

Source: Japan Antimicrobial Consumption Surveillance (JACS) and others

The status of consumption of oral and parenteral antimicrobials in 2009, 2011 and 2013, based on the volume of sales in Japan, are summerized in Table 44 and 45.[2] The overall volume of use of antimicrobials in Japan (15.8 DID in 2013) was mostly at the same level as in EU member countries (14.7 DID in 2014), and is relatively lower than in South Korea (21.7 DID in 2012) and in the United States (24.9 DID in 2014).[2] Of note, oral antimicrobials accounted for 90% of total consumption in Japan. The share of penicillins was small, while cephalosporins, macrolides, and fluoroquinolones accounted for large shares.

The research to identify trends in antimicrobial consumption at medical institutions that utilized National Databae for Prescription and National Health Check-up (also known as national data base, NDB) was conducted.[3][4] When actual consumption estimated via NDB was compared to the sales data, no substantial difference exsited between two databse (i.e. sales data and NDB) at 14.0 DID for all antimicrobials, at 2.93 for oral third-generation cephems, at 2.61 for oral fluoroquinolones, at 4.82 for oral macrolides, and at 0.83 for intravenous antimicrobials.

Table 44. Trends in oral antimicrobial consumption, based on the volume of sales, Japan*

	2009	2011	2013
Tetracyclines	0.66	0.77	0.78
Amphenicols	0.00	0.00	0.00
Penicillins with extended spectrum	0.80	0.80	0.88
Beta lactamase-sensitive penicillins	0.01	0.01	0.01
Combination of penicillins including beta lactamaseinhibotors	0.19	0.24	0.25
1st generatoin cephalosproins	0.10	0.08	0.07
2nd generation cephalosporins	0.37	0.33	0.3
3rd genration cephalosporins	3.57	3.57	3.47
Other cephalosporins and penems	0.11	0.13	0.13
Combination of Sulfonamides and trimethroprim, including derivative	0.62	0.79	0.98
Macrolide	4.85	5.19	4.84
Lincosamide	0.02	0.02	0.02
Fluoroquinolones	2.20	2.63	2.75
Polymyxins	0.03	0.03	0.03
Others	0.09	0.10	0.10
Total	13.62	14.66	14.61

* As a unit, defined daily dose per 1000 inhabitants per day (DID) is used.
Prepared from [2] with partial modification.

Table 45. Trends in parenteral antimicrobial consumption, based on the volume of sales, Japan*

	2009	2011	2013
Tetracyclines	0.004	0.004	0.004
Amphenicols	0.000	0.000	0.000
Penicillins with extended spectrum	0.021	0.025	0.027
Beta lactamase-sensitive penicillins	0.024	0.022	0.019
Combination of penicillins including beta lactamaseinhibotors	0.257	0.316	0.389
1st generatoin cephalosproins	0.113	0.121	0.130
2nd generation cephalosporins	0.138	0.124	0.111
3rd genration cephalosporins	0.171	0.199	0.211
4th generation cephalosporins	0.071	0.064	0.055
Monobactams	0.001	0.001	0.001
Carbapenems	0.098	0.105	0.109
Combination of Sulfonamides and trimethroprim, including derivative	0.003	0.003	0.004
Lincosamide	0.030	0.028	0.022
Streptogramins	0.000	0.000	0.000
Other aminigoglycosides	0.069	0.061	0.052
Fluoroquinolones	0.015	0.030	0.036
Gylocopeptides	0.036	0.037	0.033
Others	0.019	0.019	0.022
Total	1.070	1.159	1.255

* As a unit, defined daily dose per 1000 inhabitants per day (DID) is used.
Prepared from [2] with partial modification.

(2) Veterinary drugs

Source: Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

Based on the volumes of sales of antibiotics and synthesized antimicrobials, as reported under the Veterinary Drug Control Regulations, the amounts of veterinary antimicrobials were calculated in terms of active ingredients (unit: tons). The volume of sales of veterinary antimicrobials was 854.50 tons in 2009, 793.75 in 2011, and 780.88 in 2013, indicating a slightly downward trend. Tetracyclines took up largest share in the overall volume of sales, acounting for 43.5 to 46.2%.

On the other hand, third-generation cephalosporins and fluoroquinolones, though important drugs for human medicine, accounted for less than 1% of overall volume of sales.

Table 46. Amounts of veterinary antimicrobials in terms of active ingredients (unit: tons)

	2009	2011	2013
Penicillins	95.96	95.82	78.17
Cephalosporins (total)	3.73	4.09	5.58
1st generation cephalosporins	(3.06)*	(3.40)	(4.71)
2nd generation cephalosporins	(0.13)	(0.14)	(0.19)
3rd generation cephalosporins	(0.53)	(0.55)	(0.68)
Aminoglycosides	47.88	33.61	39.52
Macrolides	74.88	76.36	77.70
Lincosaminids	43.69	38.67	38.99
Tetracyclines	372.48	367.19	340.52
Peptides	8.83	5.70	11.78
Other antibacterials	17.48	19.72	25.98
Sulfonamides	141.49	105.81	103.90
Quinolones	2.37	1.23	1.01
Fluoroquinolones	6.04	7.22	5.53
Thiamphenicol and derivateives	19.70	21.34	21.53
Furan and derivatives	3.03	3.34	14.46
Other synthetic antibacterials	16.85	13.59	15.02
Antifungal antibiotics	0.10	0.09	1.18
Total	854.50	793.75	780.88

* The figures in parentheses are included in the Cephalosporins (total).

1) Food-producing animals

The estimated volumes of sales of veterinary antimicrobials used for food-producing animals (cattle, pigs, horses, chickens, and others) in terms of active ingredients are listed in Table 47. The volume of sales were estimated at 720.54 tons in 2009, at 654.64 in 2011, and at 650.19 in 2013. Tetracyclines (313.51 tons in 2009, 301.56 in 2011, and 286.74 in 2013) took up the largest share in the overall volume of sales of antimicrobials for food-producing animals, accounting for 43.5 to 46.1%. In contrast, the volume of sales of the third-generation cephalosporins and fluoroquinolones that are important for human health remained about 0.5 tons and 5 tons respectively, accounting for only 0.068 to 0.98% of total volume of sales in food-producing animals.

Table 47. The estimated volumes of sales of veterinary antimicrobials used for food-producing animals (cattle, pigs, horses, chickens, and others) in terms of active ingredients (unit: tons)

	2009	2011	2013
Penicillins	81.39	78.02	59.50

Cephalosporins (total)	2.82	2.85	3.12
1st generation cephalosporins	(2.19)*	(2.21)	(2.45)
2nd generation cephalosporins	(0.13)	(0.14)	(0.19)
3rd generation cephalosporins	(0.49)	(0.50)	(0.49)
Aminoglycosides	47.66	31.52	37.40
Macrolides	45.35	53.69	54.93
Lincosaminids	37.11	34.81	35.88
Tetracyclines	313.51	301.56	286.74
Peptides	8.82	5.69	11.77
Other antibacterials	17.13	19.72	25.71
Sulfonamides	126.28	87.60	95.63
Quinolones	0.34	0.14	0.22
Fluoroquinolones	5.26	6.41	4.64
Thiamphenicol and derivateives	18.09	19.08	19.66
Furan and derivatives	0.00	0.00	0.00
Other synthetic antibacterials	16.78	13.53	14.98
Antifungal antibiotics	0.00	0.00	0.00
Total	720.54	654.64	650.19

* The figures in parentheses are included in the Cephalosporins (total).

2) Aquatic animals

The estimated volumes of sales of veterinary antimicrobials used for aquatic animals (saltwater fish, freshwater fish, and aquarium fish) in terms of active ingredients are summerized in Table 48. The volume of sales was 130.17 tons in 2009, 131.04 in 2011, and 119.92 in 2013, which accounted for 15.2 to 16.5% of the overall volume of sales of veterinary antimicrobials. Tetracyclines (58.99 tons in 2009, 65.65 in 2011, and 53.78 in 2013) took up the largest share in the overall volume of sales of aquatic antimicrobials, accounting for 44.8 to 50.0%.

Third-generation cephalosporins and fluoroquinolones that are important for human health are not approved for aquatic animal use.

Table 48. The estimated volumes of sales of veterinary antimicrobials used for aquatic animals (saltwater fish, freshwater fish, and aquarium fish) in terms of active ingredients (unit: tons)

	2009	2011	2013
Penicillins	13.99	15.95	16.31
Cephalosporins (total)	0.00	0.00	0.00
1st generation cephalosporins	0.00	0.00	0.00
2nd generation cephalosporins	0.00	0.00	0.00
3rd generation cephalosporins	0.00	0.00	0.00
Aminoglycosides	0.00	0.00	0.00
Macrolides	29.53	22.67	21.70
Lincosaminids	6.37	3.81	3.02
Tetracyclines	58.99	65.65	53.78
Peptides	0.00	0.00	0.00
Other antibacterials	0.15	0.00	0.27
Sulfonamides	14.44	16.25	7.68
Quinolones	2.03	1.09	0.79

Fluoroquinolones	0.00	0.00	0.00
Thiamphenicol and derivateives	1.60	2.26	1.87
Furan and derivatives	3.03	3.34	14.46
Other synthetic antibacterials	0.05	0.03	0.02
Antifungal antibiotics	0.00	0.00	0.00
Total	130.17	131.04	119.92

3) Companion animals

The estimated volumes of sales of veterinary antimicrobials used for companion animals (dogs and cats) in terms of active ingredients are summerized in Table 49. The volume of sales were 3.86 tons in 2009, 8.10 in 2011, and 10.74 in 2013, which accounted for 0.5 to 1.4% of the overall volume of sales of veterinary antimicrobials. The consumptions of human antimicrobials in companion animals are not monitored under JVARM, and are excluded from values in the Table 49. Hence, further discussion is needed including how to monitor the consumptions of human antimicrobials in companion animals.

Table 49. The estimated volumes of sales of veterinary antimicrobials used for companion animals (cats and dogs) in terms of active ingredients (unit: tons)

	2009	2011	2013
Penicillins	0.64	1.84	2.36
Cephalosporins (total)	0.91	1.24	2.45
1st generation cephalosporins	(0.88)*	(1.19)	(2.26)
2nd generation cephalosporins	(0.00)	(0.00)	(0.00)
3rd generation cephalosporins	(0.04)	(0.05)	(0.20)
Aminoglycosides	0.23	2.08	2.07
Macrolides	0.00	0.00	1.07
Lincosaminids	0.21	0.05	0.09
Tetracyclines	0.00	0.00	0.00
Peptides	0.01	0.01	0.01
Other antibacterials	0.20	0.00	0.00
Sulfonamides	0.77	1.96	0.60
Quinolones	0.00	0.00	0.00
Fluoroquinolones	0.78	0.81	0.90
Thiamphenicol and derivateives	0.00	0.00	0.00
Furan and derivatives	0.00	0.00	0.00
Other synthetic antibacterials	0.03	0.02	0.02
Antifungal antibiotics	0.09	0.08	1.18
Total	3.86	8.10	10.74

* The figures in parentheses are included in the Cephalosporins (total).

(3) Antimicrobial feed additives

Source: Food and Agricultural Materials Inspection Center (FAMIC) and Japan Scientific Feeds Association

The volumes of distribution of antimicrobial feed additives, based on surveys by the Food and Agricultural Materials Inspection Center and by the Japan Scientific Feeds Association, are indicated in Table 50. The overall volume of distribution were 233.3 tons in 2009, 233.9 in 2011, and 235.1 in 2013, trending at mostly the same level. Comparison among the types of antimicrobials indicated that polyethers were on an increasing trend.

Table 50. Volume of distribution of antibiotic feed additives in terms of effective value (unit: tons)

	2009	2011	2013
Aminoglycosides	4.0	0.0	0.0
Polypeptides	39.3	36.4	35.0
Tetracyclines	8.1	2.4	1.6
Macrolides	1.1	5.4	5.6
Polysaccharides	0.0	0.0	0.2
Polyethers	107.8	130.2	136.0
Other antimicrobials	15.0	20.8	20.8
Synthetic antimicrobials	58.0	38.7	35.9
Total	233.3	233.9	235.1

(4) Agrochemicals

Source: Plant Products Safety Division, Food Safety and Consumer Affairs Bureau, Ministry of Agriculture, Forestry and Fisheries

Table 51 indicates the volume of shipment in Japan of antimicrobials that are used as agrochemicals, in terms of active ingredients (unit: tons). The estimated volume of shipment was 145.30 tons in 2009, 148.24 in 2011, and 146.59 in 2013.

Table 51. The volume of shipment in Japan of antimicrobials that are used as agrochemicals, in terms of active ingredients (unit: tons).

	2009	2011	2013
Streptomycin	35.59	40.71	36.12
Oxytetracycline	10.35	10.15	10.52
Kasugamycin	20.88	20.02	20.53
Validamycin	23.56	23.60	23.11
Oxolinic acid	37.30	38.87	40.08
Polyoxins	17.60	14.90	16.24
Total	145.30	148.24	146.59

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(5) Environment

Pharmaceutical products including antimicrobials, drugs and daily necessities, are collectively referred to as “Pharmaceuticals and Personal Care Products (PPCPs).” PPCPs may have physiological activity even at low concentration, causing concerns about effect on aquatic ecosystems.[21] Regarding antimicrobials as a type of PPCPs, several studies have indicated the measurements of antimicrobial concentrations in the environment (e.g. sewage, treated wastewater, recycled water, environmental water, and sludge).[22]

In some cases, a part of sewage sludge (biomass) that is generated from sewage treatment is reused as agricultural fertilizers through anaerobic digestion and composting. The extent to which PPCPs are degraded in the sewage treatment process or in the sewage sludge digestion process varies by the type of PPCPs. For example, among other antimicrobials, most sulfonamides are decomposed, while fluoroquinolones, such as ofloxacin and norfloxacin, reside in sludge at high concentrations without being degraded.[23] The biodegradation process of PPCPs is affected by water temperature. The removability of PPCPs is affected by treatment conditions in the sewage treatment process, such as hydraulic retention time, the processing concentration and retention time of activated sludge. To further promote removal, research is in progress to improve the removability of antimicrobials using

membrane biorector.[22] Many research activities are also undertaken both in Japan and overseas to improve efficiency in removing antimicrobials, by introducing ozone and advanced oxidation process. It is required to identify the current status of discharge and developmental trends in Japan.[21]

A study that measured the concentrations of antimicrobials detected in Japanese urban rivers, based on influent sewage at sewage treatment plants, reported that the actual measurements of ciprofloxacin and clarithromycin indicated certain similarity to concentrations expected from the volumes of shipment or sales of these antimicrobials, and pointed out that it may be possible to predict sewage concentrations of antimicrobials based on their volumes of shipment or sales.[24] The study reported that, for example, ciprofloxacin and clarithromycin were contained in sewage at the respective concentrations of 51 to 442 ng/L and 886 to 1866 ng/L. However, no research results have been reported that these antimicrobials in the environment are affecting the health of humans and other living things.

In the coming years, further progress is expected in related research activities, by utilizing and sharing information concerning residual PPCPs that are under the Environmental Survey and Monitoring of Chemicals (so-called "the black book survey"), conducted by Ministry of the Environment.

8. Public Awareness regarding Antimicrobial Resistance in Japan

(1) Survey in the general public

Omagari et al. conducted a survey of the public awareness concerning antimicrobial resistance, with Grants for research from the Ministry of Health, Labour and Welfare of Japan.[25] As a specific survey method, monitors (excluding healthcare professionals) registered with INTAGE Research Inc. responeded to an on-line questionnaire sheet during a period from March 18 to 21, 2017. Among the 21,039 persons who were contacted for the survey, valid responses were received from 3,390 (16%). By gender, 48.8% of respondents were females. By age group, more than 90% of all respondents were aged 35 to 69 years. About half of all respondents experienced taking antibiotics because of cold (Table 52). Similarly, approximately 40% of respondents thought that antibiotics were effective for cold and influenza (Table 53). Approximately 20% discontinued taking antibiotics based on their own judgment; and approximately 10% kept the remaining antibiotics at home (Table 54). Among the respondents who kept antibiotics at home, approximately 80% used them based on their own judgment (Table 55).

Table 52. Reasons for internally taking antibiotics (%)

n=3,390 (select all that applied)	%
Cold	45.5
Others/unknown	24.3
Influenza	11.6
Fever	10.7
Nasopharyngitis	9.5
Cough	9.0
Sore throat	7.7
Skin or wound infection	6.5
Bronchitis	5.4
Headache	4.3
Diarrhea	3.1
Urinary tract infection	2.3
Pneumonia	1.4

Table 53. Do you think each of the following statement is correct or incorrect? (%)

n=3,390	Correct	Incorrect	Do not know
Antibiotics beat viruses	46.8	21.9	31.3
Antibiotics have effect on cold and influenza	40.6	24.6	34.8
Unnecessary use of antibiotics may result in the loss of their effect	67.5	3.1	29.4
Adverse effects are involved in the use of antibiotics	38.8	12.7	48.6

Table 54. Does each statement below apply to you? (%)

n=3,390	Yes	No
I have discontinued taking antibiotics, or adjusted a dose or freuqency based on my own judgment	23.6	76.4
I keep antibiotics in my house	11.7	88.3

Table 55. Does each statement below apply to you? (%)

(n=396)*	Yes	No
I have used antibiotics that I kept at home for myself	75.8	24.2
I have given antibiotics that I kept at home to my family or friend	26.5	73.5

* Only respondents with valid responses that kept antibiotics at home.

(2) Survey in healthcare providers

Nakahama et al. conducted an awareness survey among clinicians regarding the administration of oral antimicrobials for the common cold syndrome.[26] The survey was conducted through internet research from January 6 to February 13, 2017. On-line questionnaire sheets were sent to physicians whom the research team knew, members of mailing lists of primary care physicians, members of university alumni associations, members of mailing lists of local medical associations, and so on. The responeded physicians were also able to distribute the questionnaire sheets to others. In total, 612 physicians responded to the questionnaire: 40% answered as self-employed physicians and 60% answered as employed physicians. Physicians in their 30's to 60's, actively seeing patients, accounted for the largest part of respondents, and male physicians accounted for 87%. By specialty, the share of internal medicine was the largest at 69%, followed by pediatrics at 16%, and by orthopedics and urology.

With respect to the administration of antimicrobials for the common cold syndrome, the most frequent response was "0 to less than 10% of patients with cold" at around 60% (Table 57). As the reason for administering antimicrobials for the common cold syndrome, the most frequent response was "it is difficult to distinguish whether the cause is viral or bacterial" at more than 30%, followed by "patients' requests" at approximately 20% (Table 59). As for response to patients' requests for antimicrobials, more than half of physicians prescribed antimicrobials when patients insisted on the need for antimicrobials despite patient education (Table 60). The largest number of respondents, which acounted for about 30%, believed that priority in the antimicrobial resistance in the outpatient setting should be placed on enhanced public relation and awareness activities, targeting general public and clinicians (Table 61).

Table 56. The proportion of physicians as to proper use of oral antimicrobials for the common cold syndrome in clinical practice (%)

	Total (n=612)	Self-employed physicians (n=244)	Employed physicians (n=368)
Have never considered	9.6	5.7	12.2
Consider occasionally	27.9	29.9	26.6
Consider actively	42.6	48.0	39.1
Observe strictly	18.5	15.2	21.2
Others	1.0	1.2	0.8

Table 57. The proportion of patients with the common cold syndrome to whom oral antimicrobials were administered (%)

	Total (n=612)	Self-employed physicians (n=244)	Employed physicians (n=368)
<10%	60.1	50.0	66.8
>=10% and <30%	21.7	22.1	21.5
>=30% and < 40%	9.6	13.1	6.3
>=40% and <70%	4.7	7.0	3.3
>=70% and < 90%	3.1	6.1	1.1
>=90%	0.7	1.6	0.0

Table 58. Oral antimicrobials that are the most frequently administered to patients with the common cold syndrome (%)

	Total (n=612)	Self-employed physicians (n=244)	Employed physicians (n=368)
Penicillins	27.8	24.6	29.9
β-lactamase inhibitor combinations with penicillins	6.4	4.1	7.9

Cephems	14.5	18.0	12.2
Macrolides	35.0	38.9	32.3
New quinolones	7.5	9.0	6.5
Others	8.5	5.3	11.1

Table 59. Reasons for administering oral antimicrobials to patients with the common cold syndrome (%)

	Total (n=612)	Self-employed physicians (n=244)	Employed physicians (n=368)
To prevent secondary bacterial infection	17.7	18.0	17.5
To prevent worsening of infection	15.4	16.8	14.5
Difficult to distinguish whether the cause is viral or bacterial	35.1	35.3	35.0
Patients' requests	17.7	15.8	19.0
Habitual administration	0.8	1.3	0.5
Others	13.3	13.0	13.5

Table 60. Response to requests for the off-label administration of antimicrobials from patients with the common cold syndrome or their families (%)

	Total (n=612)	Self-employed physicians (n=244)	Employed physicians (n=368)
Prescribe as requested	8.2	12.7	5.2
Prescribe if they do not accept explanation	56.4	56.1	56.5
Explain and do not prescribe	33.0	27.5	36.7
Others	2.5	3.7	1.6

Table 61. Activities that should be prioritized to improve antimicrobial resistance issues in outpatient setting (%)

Multiple answers	Total (n=1739)	Self-employed physicians (n=688)	Employed physicians (n=1,051)
Strengthened public relations and awareness improvement for the general public and clinicians	31.2	31.7	30.8
More stringent restrictions on the application of medical insurance to antimicrobials	12.3	8.9	14.6
Strengthened surveillance of antimicrobial-resistant bacteria	13.2	13.2	13.2
Preparation of a treatment manual for outpatient infections	13.5	16.9	11.2
Guidance to physicians with inadequate prescriptions	5.9	4.8	6.6
More stringent administration of commercial antimicrobials to food-producing animal	12.7	12.2	13.0
Promotion of the development of new antimicrobials	2.7	2.5	2.9
Promotion of international information exchange and cooperation	6.1	7.6	5.1
Others	2.5	2.3	2.6

9. Way Forward

This document is the first report in Japan, representing information on the current status of antimicrobial resistance in the areas of human health, animals, agriculture, food and the environment, as well as the volumes of use (or of sales) of human and veterinary antimicrobials. It is a great achievement to compile those data into one report. This report also featured the special monitoring systems in aquaculture and companion animals, proving that a number of monitoring systems that can be globally shared exist in Japan. Based on this current report, it is expected that AMR-related measures will be further advanced by promoting multi-disciplinary cooperation and collaboration. It is also considered crucial to continue with advanced surveillance activities, in order to take the leadership in global policy in AMR.

In contrast, according to the comprehensive collection of information, the current detection status of antimicrobial-resistant bacteria in each area and the current status of use of antimicrobials revealed that the quality of each surveillance was variable. Upon analyzing relationships among different areas regarding the antimicrobial-resistant bacteria and the use of antimicrobials, it is necessary to consider the difference in each area and make the data compatible. The future challenge include standardization of measurement methods, verification of the representativeness of data in each morniting systems, establishment of quality assuarance in each surveillance systems, and continuity of monitoring systems that are conducted as research activities. Further research is warranted to uncover mechanisms and inter-connectivity with regard to the development and transmission of antimicrobial resistance among humans, animals, agriculture, food and the environment.

Appendix

(1) Japan Nosocomial Infections Surveillance (JANIS)

1) Overview

JANIS (Japan Nosocomial Infection Surveillance) is conducted for the purpose of having an overview of nosocomial infections in Japan, by surveying the status of health care associated infections at medical institutions in Japan, the isolation of antimicrobial-resistant bacteria, and the status of infections caused by antimicrobial-resistant bacteria, while providing useful information for the control of health care associated infections in medical settings. The aggregated data of information from all medical institutions partipated are published on the website of the National Institute of Infectious Diseases (https://janis.mhlw.go.jp/english/index.asp). A result of the analysis is reported back to each instiiution so that such a feedback can be utilized for the formulation and evaluation of infection control measures at each institution. JANIS participation is voluntary with approximately 1,800 participating medical institutions at present.

Clinical Laboratory Division of JANIS collects the laboratory data of bacteria that are isolated at hospitals across Japan, and publish aggregated data regarding the proportion of clinically important bacterial species that are resistant to major antimicrobials. In 2015, 1,482 hospitals participated in the laboratory section. The aggregated data include data from hospitals with at least 20 beds, and exclude clinics and facilities for the elderly. Only bacteria that are isolated from specimens from hospialized patients at participating hospitals are included into aggregated data, and specimens from ambulatory sections are excluded. To provide more representative information as a national surveillance system, protocols of sampling including selection of sentinel sites and their stratification need to be improved further. The assessment of antimicrobial susceptibility tests is interpretted based on CLSI Criteria.

Quality control for antimicrobial susceptibility tests depends on medical institutions. To improve the quality of antimicrobial susceptibility tests at hospital laboratories, a quality control program was developed under the leadership of the Japanese Society for Clinical Microbiology and it has been piloted since 2016.

JANIS is a surveillance program regulated by the Statistics Act and it differs from the National Epidemiological Surveillance of Infectious Diseases based on the Infectious Diseases Control Act. While participation is voluntary, from 2014, Premiums for infection control 1 in medical reimbursement requires participation in JANIS or equivalent surveillance programs. JANIS is organized and operated by the Ministry of Health, Labour and Welfare, and its operating policy is determined at the operation council that comprises of experts in infectious diseases, antimicrobial resistance and other relevant professional fields. Section II, Laboratory of Antimicrobial Resistance Survailance, National Institute of Infectious Diseases functions as a secretariat office for JANIS

Under the Global Antimicrobial Resistance Surveillance System (GLASS), launched by WHO in 2015, individual countries are encouraged to submit data regarding resistant bacterias in the human health area.[27] Japan has provided necessary data from JANIS and other pertinent monitoring sysmtems to GLASS. Of note, data for 2014 and 2015 have already been submitted. Under GLASS, the expansion of the scope of surveillance to food-producing animal and other areas are discussed.[27] It is expected that the data from this national one health report can be contributed to GLASS.

2) Methods for submission

JANIS consists of five divisions: (1) Clinical Laboratory, (2) Antimicrobial-Resistannt Bacterial Infection, (3) SSI, (4) ICU and (5) NICU. Medical institutions select divisions to participate in, in accordance with their purposes and conditions. Among the five divisions, Clinical Laboratory division handles surveillance regarding antimicrobial resistance. In Clinical Laboratory division, all data concerning isolated bacteria are collected from bacteriological examination units installed in the laboratories of medical institutions, computerized systems, and other sources, and converted into the JANIS format before submitted online. The submitted data are aggregated, and the shares of clinically important bacterial species that are resistant to key antimicrobials are calculated, and published as the national data of Japan.

3) Prospect

Most medical institutions participating in JANIS are of a relatively large scale with 200 or more beds. The data in the laboratory division only include specimens from hospitalized patients, and exclude specimens from ambulatory sections. Data are not collected from clinics. The bias based on this sampling policy in JANIS should be addressed.

(2) National Epidemiological Surveillance of Infectious Disease (NESID)

1) Overview

The National Epidemiological Surveillance of Infectious Disease (NESID) program collects and publishes domestic information regarding infectious diseases, and monitors the occurrence of and trends in infectious diseases, based on reports from physicians and veterinarians. At present, the NESID program is conducted in accordance with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (hereinafter referred

to as "Infectious Diseases Control Law"), which took effect in April 1999. The goal of NESID is to accurately identify and analyze information regarding the occurrence of infectious diseases and to rapidly provide and publish the results to the general public and healthcare practitioners, thereby promoting measures for the effective and adequate prevention, diagnosis and treatment of infectious diseases, and preventing the occurrence and spread of various infectious diseases, while verifying the detection status and characteristics of circulating pathogens, and facilitating appropriate infection control measures, through the collection and analysis of pathogen information.

As of June 2017, the following seven antimicrobial-resistant bacteria infections are designated as reportable under NESID, which are all classified as Category V Infectious Diseases. The four diseases that are subject to notifiable disease surveillance, which requires reporting by all physicians, are vancomycin-resistant enterococcal infection (VRE, designated in April 1999), vancomycin-resistant *Staphylococcus aureus* infection (VRSA, designated in November 2003), carbapenem-resistant *Enterobacteriaceae* infection (CRE, designated in September 2014), and multidrug-resistant *Acinetobacter* infection (MDRA, designated as a disease reportable from designated sentinel sites in February 2011, and changed to a disease reportable under notifiable disease surveillance in September 2014). The three diseases that are reportable from approximately 500 designated sentinel sites (medical institutions that have 300 or more beds, with internal medicine and surgery departments) across Japan are penicillin-resistant *Streptococcus pneumoniae* infection (PRSP, designated in April 1999), methicillin-resistant *Staphylococcus aureus* infection (MRSA, designated in April 1999), and multidrug-resistant *Pseudomonas aeruginosa* infection (MDRP, designated in April 1999).

2) Reporting criteria

A physician who has diagnosed a reportable disease listed above (the manager of a designated notification facility in the case of a disease subject to sentinel surveillance) should report to a Public Health Center using a designated reporting form. The scope of reporting includes cases where bacteria that satisfy the laboratory findings specified in Table A are detected, and the isolated bacteria are regarded as the cause of the relevant infectious disease, or caseswhere it was detected from specimens that normally should be aseptic. Carriers are excluded from the scope of reporting.

3) Reporting criteria

A physician who has diagnosed a reportable disease listed above (the manager of a designated notification facility in the case of a disease subject to sentinel surveillance) should report to a Public Health Center using a designated reporting form. The scope of reporting includes cases where bacteria that satisfy the laboratory findings specified in Table A are detected, and the isolated bacteria are regarded as the cause of the relevant infectious disease, or cases of detection from specimens that normally should be aseptic. Colonizations are excluded from the scope of reporting.

Table A. Reporting criteria

Reportable disease	Summary of reporting criteria
VRE	*Enterococcus* is isolated and identified, and the MIC value of vancomycin is ≥ 16 μg/mL.
VRSA	*Staphylococcus aureus* is isolated and identified, and the MIC value of vancomycin is ≥ 16 μg/mL.
CRE	*Enterobacteriaceae* is isolated and identified, and either A) or B) below is satisfied: A) The MIC value of meropenem is ≥ 2 μg/mL, or the diameter of the inhibition circle of the meropenem susceptibility disk (KB) is ≤ 22 mm. B) It is confirmed that both the following conditions are satisfied: a) The MIC value of imipenem is ≥ 2 μg/mL, or the diameter of the inhibition circle of the imipenem susceptibility disk (KB) is ≤ 22 mm. b) The MIC value of cefmetazole is ≥ 64 μg/mL, or the diameter of the inhibition circle of the cefmetazole susceptibility disk (KB) is ≤ 12 mm.
MDRA	*Acinetobacter* spp. is isolated and identified, and all three conditions below are satisfied: A) The MIC value of imipenem is ≥ 16 μg/mL, or the diameter of the inhibition circle of the imipenem susceptibility disk (KB) is ≤ 13 mm. B) The MIC value of amikacin is ≥ 32 μg/mL, or the diameter of the inhibition circle of the amikacin susceptibility disk (KB) is ≤ 14 mm. C) The MIC value of ciprofloxacin is ≥ 4 μg/mL, or the diameter of the inhibition circle of the ciprofloxacin susceptibility disk (KB) is ≤ 15 mm.
PRSP	*Streptococcus pneumoniae* is isolated and identified, and the MIC value of penicillin is ≥ 0.125 μg/mL, or the diameter of the inhibition circle of the oxacillin susceptibility disk (KB) is ≤ 19 mm.
MRSA	*Staphylococcus aureus* is isolated and identified, and the MIC value of oxacillin is ≥ 4 μg/mL, or the diameter of the inhibition circle of the oxacillin susceptibility disk (KB) is ≤ 10 mm.

MDRP	*Pseudomonas aeruginosa* is isolated and identified, and all three conditions below are satisfied: A) The MIC value of imipenem is ≥ 16 μg/mL, or the diameter of the inhibition circle of the imipenem susceptibility disk (KB) is ≤ 13 mm. B) The MIC value of amikacin is ≥ 32 μg/mL, or the diameter of the inhibition circle of the amikacin susceptibility disk (KB) is ≤ 14 mm. C) The MIC value of ciprofloxacin is ≥ 4 μg/mL, or the diameter of the inhibition circle of the ciprofloxacin susceptibility disk (KB) is ≤ 15 mm.

4) System

Public Health Centers confirm reported information, and enter the data into NESID. The registered information is further confirmed and analyzed, and additional information is collected, by local infectious disease surveillance centers, the Infectious Diseases Surveillance Center of NIID as the central infectious disease surveillance center, and other relevant bodies. Patient information (e.g. the reported numbers of patients, and trends) that is collected under the Infectious Diseases Control Law, and other related information, are provided to the general public through the Infectious Diseases Weekly Reports (IDWRs) and other media.

5) Prospect

A certain level of quality is considered to be guaranteed in the reporting of antimicrobial-resistant bacteria infections under NESID, since reporting is based on case definitions specified by the Infectious Diseases Control Law. Although cases may be underestimated in notifiable disease surveillance, an overall picture of trends in occurrence can be monitored. This surveillance system is also considered useful because, when an unusual trend is observed, it may trigger an intervention (e.g. investigation, guidance) at the relevant medical institution by the Public Health Center. Trends in diseases reportable from designated sentinel sites have been recorded since the launch of the NESID program in 1999, and considered useful for monitoring medium- to long-term trends in the occurrence of the target diseases.

In June 2011, a notification was issued by the Director of the Guidance of Medical Service Division, Health Policy Bureau, MHLW, stating that it was deemed important to strengthen the Public Health Institutes' capacity to enable the testing of microorganisms causing helathcare-assoicated infections. In March 2017, a notification was issued by the Director of the Tuberculosis and Infectious Diseases Control Division, Health Service Bureau, MHLW, requiring that, when CRE or other specified infections are reported, Public Health Institutes and other organizations should conduct testing on the relevant antimicrobial-resistant bacteria. In the coming years, the framework of the NESID system will enable access to information of higher quality that is useful for measures against antimicrobial-resistant bacteria, through the comprehensive collection and analysis of carbapenemase genes and other information. It will also become possible to identify the regional spread of antimicrobial-resistant bacteria and their carriers, as well as the disease burden and regional distribution of antimicrobial-resistant bacteria infections, by combining the data from the NESID system with the information of Clinical Laboratory Division in JANIS and other antimicrobial-resistant bacteria surveillance systems. Based on these consolidated data, high quality information can be returned to the health care system.

(3) Trend surveillance of antimicrobial-resistant *Mycobacterium tuberculosis*

1) Overview

A registered tuberculosis patient information system is a part of NESID including: new tuberculosis patients and latent tuberclosis patients who are registered from January 1 to December 31 of a registration year; and all tuberculosis patients who are registered as of December 31 of the calender year. In principle, information in this system pertains to tuberculosis patients, and focuses on the number of incidence case and incidence rate, the number of patients with tubercosis, treatment status, the number of deaths from tuberculosis, and so on. Information regarding tuberculosis bacillus as the causal bacteria is limited to the smear positive ratio, the number of culture-positive patients, drug-susceptibility testing data, and so on. Though limited, this report exclusively provides routine national information regarding antimicrobial-resistant tuberculosis bacillus.

2) Survey methods

Based on the registered tuberculosis patient information, the results of drug-susceptibility testing in newly registered patients with culture-positive pulmonary tuberculosis are aggregated. The entry of this information item used to be optional, before the Ordinance for the Partial Revision of the Enforcement Regulation of the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (MHLW Ordinance No. 101 of 2015, effective May 21, 2015) added "the results of drug-susceptibility testing" under "Conditions of disease" in Item 4, Paragraph 1, Article 27-8.

3) System

When physicians diagnose and report a tubercolosis case to Public Health Center collect, corresponding public health nurses collect detailed information from patients and physicians. Drug-susceptibility testing data are considered to be collected mostly from hospital and commercial laboratories. Those individual data are entered by Public Health

Centers across Japan into NESID.

4) Prospect

The surveillance based on the registered tuberculosis patient information system contains the susceptibility results of newly registered patients with culture-positive pulmonary tuberculosis, as reported from all medical institutions. Therefore, data are considered nationally representative. Improvement in the entry rate of drug-susceptibility testing results (approximately 75% at present); the establishment of a system for nationwide quality assurance for drug-susceptibility testing; and the quality control of data entry are warranted.

(4) Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

1) Overview

The Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) is a nationwide monitoring of antimicrobial-resistant bacteria in the animal area, conducted by the Ministry of Agriculture, Forestry and Fisheries since 1999 through its network with livestock hygiene service centers across Japan. JVARM provides globally important information, and is cited as one of the examples of monitring systems in "Antimicrobial resistance: global report on surveillance 2014," published by WHO.

Figure 1. Overview of veterinary antimicrobial resistance monitoring

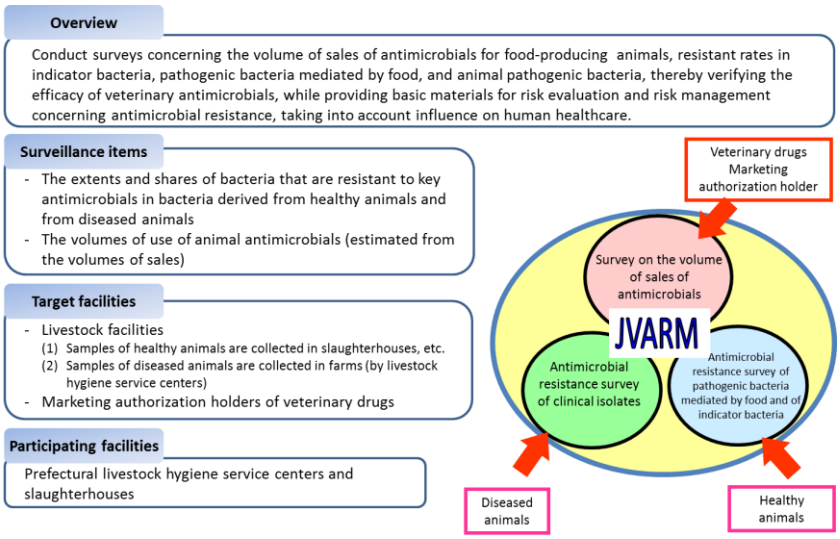


Figure 2. Antimicrobial resistance monitoring in food-producing animals in farms

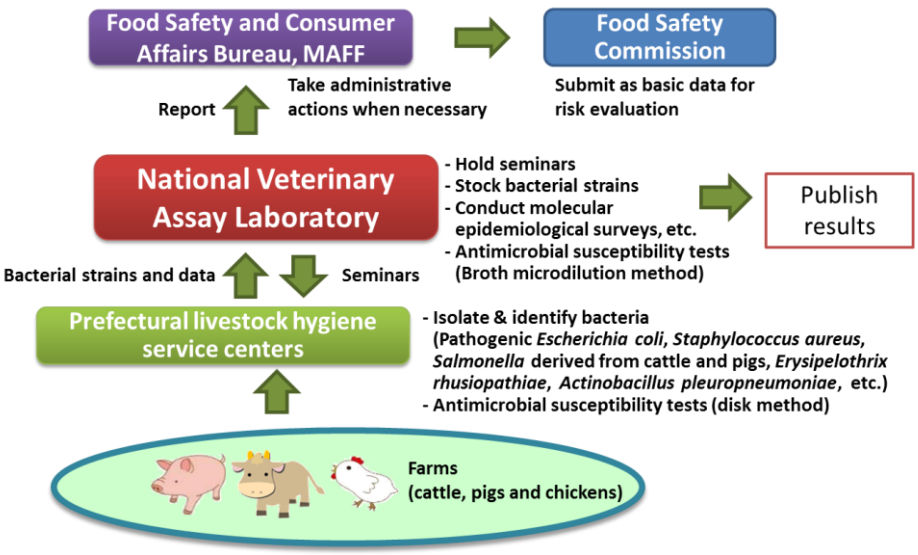
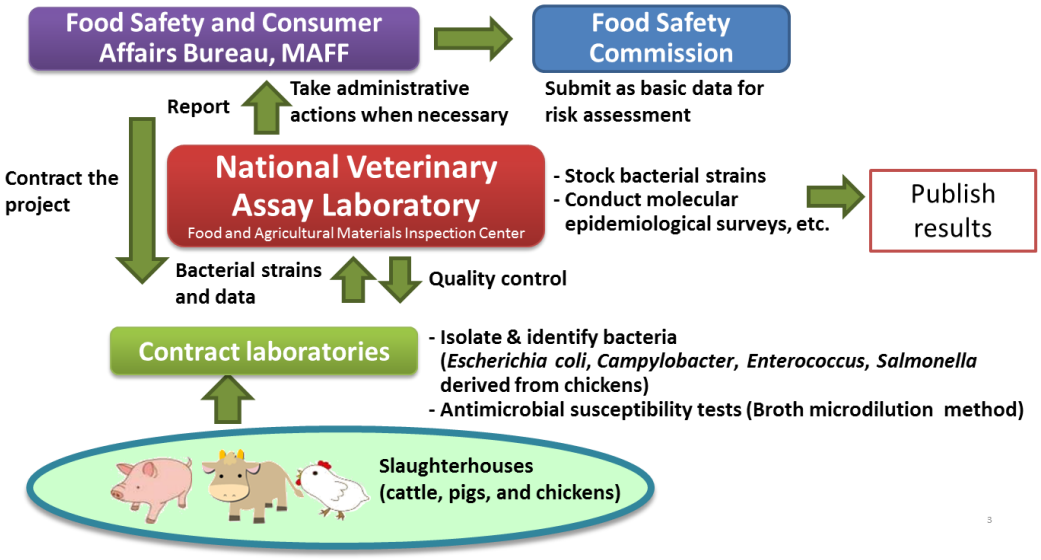


Figure 3. Antimicrobial resistance monitoring in food producing animals in slaughterhouses



Under JVARM, three monitorings are conducted: (1) monitoring of the volumes of use of antimicrobials (estimated from the volumes of sales); (2) monitoring of antimicrobial resistance among indicator bacteria derived from healthy animals, and among pathogenic bacteria mediated by food; and (3) monitoring of antimicrobial resistance among pathogenic bacteria (clinical isolates) derived from diseased animals. While verifying the efficacy of veterinary antimicrobials, JVARM also provides basic data for risk assessment and risk management concerning antimicrobial resistance, taking into account influence on human healthcare (Figures 1, 2 and 3). The results of JVARM are published on the website of the National Veterinary Assay Laboratory, Ministry of Agriculture, Forestry and Fisheries.[28] In FY2016, reviews were performed concerning how to strengthen antimicrobial resistance surveillance on aquatic animals, and how to conduct antimicrobial resistance surveillance on companion animals, in response to the strategies of the National Action Plan on Antimicrobial Resistance (AMR).

2) Monitoring details on the volumes of sales of antimicrobials

An annual monitoring is conducted on the volumes of sales of veterinary antimicrobials, based on the reported quantities of veterinary drugs handled by marketing authorization holders, pursuant to Article 71-2 of the Veterinary Drug Control Regulations (MAFF Ordinance No. 107 of 2004). Starting 2000, the scope of monitoring has included the volume of sales by active pharmaceutical ingredient and by the route of administration, and the estimated volume of sales by animal type, in addition to the volumes of sales by antimicrobial type and by dosage form. As is stated in Chapter 6.8 of the OIE Terrestrial Animal Health Code concerning the monitoring of antimicrobial agents used,[29] data are required regarding the volumes of use of active ingredients by animal type, in order to identify and compare the volumes of use in individual countries. Therefore, reports have been issued based on the relevant survey results.

3) Monitoring details on antimicrobial resistance

For the monitoring of clinical isolates, bacterial strains are isolated and identified from materials for pathological appraisal by prefectural livestock hygiene service centers, and the MIC values for these strains are measured by the National Veterinary Assay Laboratory using a broth microdilution method based on the CLSI Criteria. For the monitoring of pathogenic bacteria mediated by food and indicator bacteria, antimicrobial susceptibility tests have been conducted by livestock hygiene service centers since 1999, isolating *Salmonella* and *Campylobacter* as pathogenic bacteria mediated by food, and *Escherichia coli* and *Enterococcus* as indicator bacteria, via feces from beef-cattle, pigs, and broilers and layers in farms. Annual continued education are conducted at the National Veterinary Assay Laboratory in order to standardize the isolation and identification of bacterial strains and antimicrobial susceptibility testing. National Veterinary Assay Laboratory also conducts monitoring regarding source farms of samples, dates of sampling, the status of use of therapeutic antimicrobials and antibiotic feed additives, and so on. As described in the later in the section, sampling locations for the survey of pathogenic bacteria mediated by food and indicator bacteria were switched from farms to animal and poultry slaughterhouses in FY2016.

As of 2016, the scope of monitoring broadly includes active ingredients that are considered important in antimicrobials for animals, for both animals and human health, and antimicrobial feed additives: ampicillin, cefazolin, cefotaxime, streptomycin, dihydrostreptomycin, gentamicin, kanamycin, erythromycin, tylosin, lincomycin, tetracycline, oxytetracycline, chloramphenicol, colistin, bacitracin, virginiamycin, salinomycin, nalidixic acid, ciprofloxacin, enrofloxacin, and trimethoprim. Antimicrobial agents subject to monitoring are selected for each bacterial species, according to the past monitoring results and Chapter 6.7 of the OIE Terrestrial Animal Health Code.[30]

4) System for the antimicrobial resistance monitoring

Currently, there are 170 prefectural livestock hygiene service centers across Japan, which have cooperated in establishing the nationwide JVARM network. For the monitoring of clinical isolates, bacterial strains are isolated and identified from diseased animals by livestock hygiene service centers, and the MIC values for these strains are measured by the National Veterinary Assay Laboratory (Figure 2). From 2000 to 2016, pathogenic bacteria mediated by food and indicator bacteria derived from healthy animals were isolated and identified from the feces of specified animals, and subsequently the relevant MIC values were measured, by livestock hygiene service centers. The submitted data were aggregated and analyzed by the National Veterinary Assay Laboratory, and were published as JVARM data.

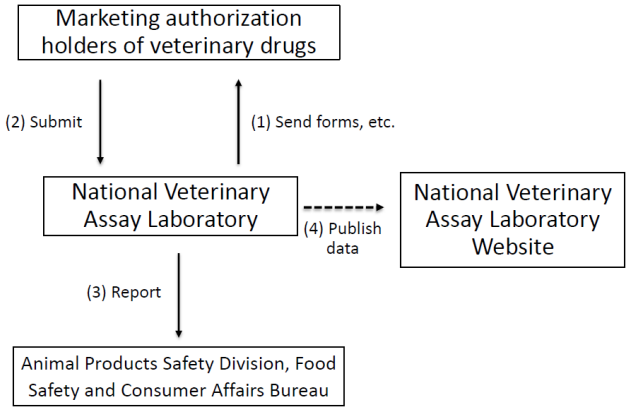
In contrast, animal and poultry slaughterhouses have been selected as sampling locations for antimicrobial resistance monitoring in Europe and the U.S., since they are proximal to food and are capable of more integrated collection of feces. Therefore, sampling of feces from healthy animals in animal and poultry slaughterhouses started in FY2012 (Figure 3), and sampling of feces in farms was discontinued in FY2016. Accordingly, sampling locations for the monitoring of pathogenic bacteria mediated by food and indicator bacteria from healthy animals were switched to animal and poultry slaughterhouses.

Isolated strains collected under JVARM are examined and stocked by the National Veterinary Assay Laboratory, which also performs the analysis of genetic properties and the clarification of antimicrobial resistance mechanism, in order for the molecular epidemiological survey of antimicrobial-resistant strains. Antibiotic feed additives are analyzed by the Food and Agricultural Materials Inspection Center (FAMIC). Data collected through JVARM are published on the website of the National Veterinary Assay Laboratory every year. The data are also utilized for risk assessment by the Food Safety Commission as well as for science-based risk management measures.

5) Monitoring on the sales volumes of antimicrobials

Each marketing authorization holder of veterinary drugs annualy submit, to the National Veterinary Assay Laboratory, the sales volume of antimicrobials from January 1 to December 31, using a designated reporting form. The data are aggregated and published on the website of the National Veterinary Assay Laboratory as “Annual Report of Sales Amount and Sales Volume of Veterinary drugs, Quasi-drugs and Medical Devices.”

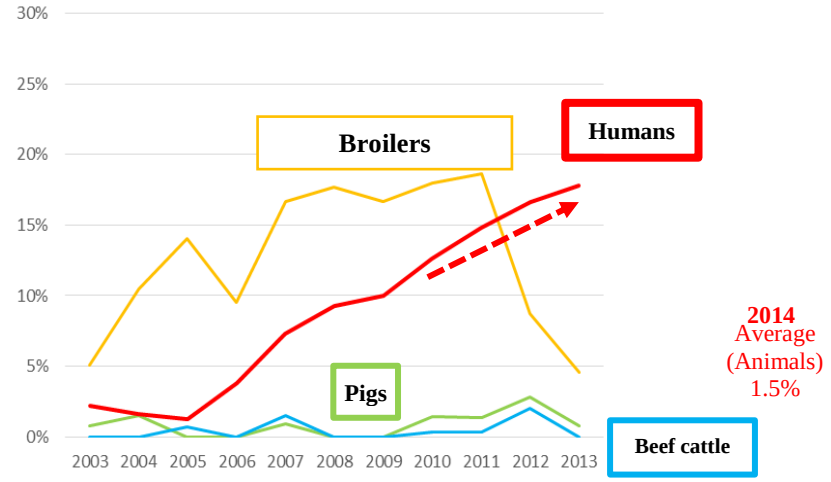
Figure 4.



6) Collaboration with JANIS

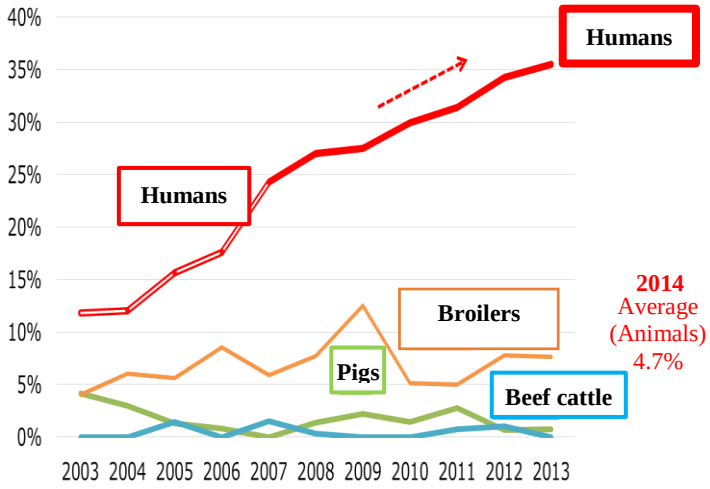
Since FY2012, collaboration has been promoted between JVARM and JANIS (Japan Nosocomial Infections Surveillance). The data of *Escherichia coli* derived from healthy animals collected under JVARM are converted into a format comparable with JANIS data, and the results are published as antibiograms on the website of the National Veterinary Assay Laboratory.[31] These data enable the comparison of trends in antimicrobial-resistant bacteria between humans and animals.

Figure 5 Comparison of the proportion of third-generation cephalosporin-resistant *Escherichia coli* derived from humans and those derived from food-producing animal



The proportion of third-generation cephalosporin-resistant strains derived from humans and those derived from broilers had an increase trend until 2011. The proportion, however, has rapidly decreased in broilers since 2012. This is probably due to the withdrawal of the off-label use of the third-generation cephalosporin after the explanation of the JVARM data to related associations. [32] On the other hand, the proportion still continues to rise in humans, indicating different trends between humans and broilers.

Figure 6 Comparison of the proportion of fluoroquinolone-resistant *Escherichia coli* derived from humans and those derived from food-producing animal



While a consistent increase was observed in fluoroquinolone-resistant strains derived from humans from 2003 to 2013, the proportion of fluoroquinolone-resistant strains derived from food-producing animal remained low, indicating different trends between humans and food-producing animal.

7) Prospect

The key issues in JVARM are that 1) only limited fish species are included in the scope of monitoring of aquaculture; 2) no monitoring is implemented concerning companion animals; 3) only limited monitoring and analysis are conducted regarding antimicrobial-resistant genes; and 4) no monitroing is implemented regarding the volume of use of human antimicrobials on companion animals. The existing monitoring in food-producing animal will be continued under JVARM. Several steps will be taken to address the issues from 2017, which include 1) increasing fish species included in the scope of monitoring of aquaculture; 2) implementing monitoring of companion animals; 3) performing analysis on antimicrobial-resistant genes, including whole genome analysis using next-generation sequencers; and 4) implementing monitoring on the volume of use of human antimicrobials on companion animals. To further promote one health monitoring, further collaboration with JANIS will be pursued by comparing antimicoribal-resistant bacterias at a

genetic level through whole genome analysis data. Those data accumulated will lay the ground for risk assessment and risk management, by clarifying the transmission process of antimicrobial-resistant bacteria, through linkage with other areas.

(5) Japan Antimicrobial Consumption Surveillance (JACS)

1) Overview

Japan Antimicrobial Consumption Surveillance (JACS) is aimed at establishing a network for identifying the volume of use of antimicrobials and infection status in Japan over time, and at further upgrading the quality of infection control in order to benefit the general public, by providing collected information as materials for enhancing regional collaboration in infection control.

2) Monitoring methods

i. Identification of the status of use of parenteral antimicrobials at medical institutions and thier demographics

A web-based system was established (service rendered by: DOMO Inc.) and published in April 2015. In November 2015, a pilot survey request was issued concerning the volume of use in 2014. At the end of FY2016, a survey request was issued concerning the volume of use from 2010 to 2015. Aggregated results are to be provided in FY2017.

ii. Identification of the status of use of parenteral and oral antimicrobials based on sales data

The volumes of use of antimicrobials in 2009, 2011 and 2013 were obtained from IMS Japan, and DID recommended by WHO were calculated. Each antimicrobial was aggregated in Level 3 and Level 4 based on the ATC classification system, and were compared with data from other countries.

3) System

To evaluate two elements ((1) the frequency of isolation of antimicrobial-resistant bacteria does not increase, that is, infection control and treatment are properly undertaken; (2) resistance does not proceed, that is, selection pressure is adequately controlled), the JACS system consists of (1) online data collection by pharmacists concerning infection control, aimed at the identification of actual administration to patients with antimicrobial-resistant bacteria infection at medical institutions; and (2) data collection that includes clinics and ambulatory care, based on sales and other data from wholesalers.

As for the onle data collection by pharamacists, the titers or days of use of parenteral antimicrobials at medical institutions are entered into an integrated online form. The entered data are automatically calculated in AUD (Antimicrobial Used Density) and DOT (Day of Therapy), as indicators recommended by WHO and CDC, and provided as aggregated data. As for ambulatory use, the data of volume of sales are purchased from IMS Japan, and the volume of use of antimicrobials over time is aggregated. Subsequently, data are calculated in DDD (Defined Daily Dose), as defined by WHO, and in DID (DDD per 1,000 inhabitants per day), after correction by the population of Japan.

4) Indicators for the volume of use of parenteral antimicrobials

- Antimicrobial use density (AUD)

AUD is calculated by dividing the total titer of antimicrobials in a specified period by DDD (defined daily dose) as defined by the World Health Organization (WHO), and correcting the DDDs with the total patient days. Units used for AUD are DDDs per 100 bed-days, DDDs per 1000 patient-days, etc. Outpatient prescription may also be calculated by dividing the volume of use (titer) by DDD, and correcting the denominator with regional inhabitants per day (DID; DDDs per 1,000 inhabitants per day). While the term AUD is common in Japan, DDDs are interchagibly used in overseas journals. Although AUD used in Europe is relatively easy to handle and can be utilized for cost calculaition via computing titers, AUD cannot be adapted to pediatric population. Furthermore, AUD may cause underestimation or overestimation in comparison among facilities, when the defined DDDs differ from the local dosage or recommended amount.

- Day of therapy (DOT)

DOT is calculated by correcting the total days of therapy (DOTs) using antimicrobials in a specified period with the total patient-days. Units used for DOT are DOTs per 100 bed-days, DOTs per 1,000 patient-days, etc. DOT is used as a standard indicator in the U.S., and can also be used for pediatric population. On the other hand, the treatment period cannot be estimated, since DOT does not incorporate a concept of dosage and DOT can be inaccurate if a patient is on more than one antimicrobial. There are also cases where the number of inpatients is used as the denominator, instead of the total patient-days. In such cases, some reports indicate that correlation with propotion of resistance is improved, compared to when the total patient-days is used as the denominator.

5) Prospect

Currently a program is under development for automatically calculating the status of antimicrobial use at medical institutions mentioned above, based on medical prescription request files (EF files). Preparations are in progress to archive automatically calculated files in servers for the Regional Infection Control Support System (RICSS), which is

installed in the AMR Clinical Reference Center (AMRCRC) established in April 2017 at the National Center for Global Health and Medicine (NCGM). RICSS allow a facility to compare the status of the antimicrobial use among the given groups. By utilizing NDB, identification of antimicrobial use based on various demographic inforamtion stratified by age, prefecture and medical area are under progress; and the identification of status of use in pediatric population are underway.

(6) Monitoring on the antimicrobial-resistant *Campylobacter* spp. isolated from humans

1) Overview

Currently the monitoring regarding the emergence of antimicrobial-resistant *Campylobacter* spp. derived from humans is undertaken as research activities by the Tokyo Metropolitan Institute of Public Health, as part of the food safety assurance and promotion research project, with Grants for research from the Ministry of Health, Labour and Welfare of Japan.[5]

2) Survey methods

Antimicrobial susceptibility tests were conducted by the disk method, in accordance with the CLSI standards in US.[5] The 116 *C. jejuni* strains and 8 *C. coli* strains that were isolated from the stool of diarrhea cases at hospitals in Tokyo in 2015 were tested using imicrobials such as tetracycline (TC), nalidixic acid (NA), ciprofloxacin (CPFX), norfloxacin (NFLX), ofloxacin (OFLX), and erythromycin (EM).

3) Prospect

To identify the emergence of antimicrobial-resistant *C. jejuni /C. coli* on a wide-area basis, it is required to standardize tested antimicrobials, implementation methods, assessment criteria, and other details. However, no standardized methods have been indicated regarding antimicrobial susceptibility tests for *Campylobacter*spp. It is required to conduct antimicrobial susceptibility tests using common methods not only for strains isolated from humans, but also for strains isolated from food and food-producing animal, in order to know the emergence of antimicrobial-resistant bacteria nationwide.

(7) Monitoring on the antimicrobial-resistant non-typhoidal *Salmonella* spp. isolated from humans and from food

1) Overview

Many Public Health Institutes conducted resistance monitoring regarding antimicrobial-resistant bacteria derived from food. Several Public Health Institutes were organized to undertake the monitoring of antimicrobial-resistant bacteria derived from food as research activities, as part of the food safety assurance and promotion research project, with Grants for research from the Ministry of Health, Labour and Welfare of Japan.[6] This is likely the first monitoring in Japan regarding antimicrobial-resistant bacteria derived from food on a nationwide scale, conducted by standardized methods. The collected data were also reported to GLASS, which was launched by WHO.

2) Methods

With cooperation from 18 Public Health Institutes across Japan, an antimicrobial resistance monitoring was conducted using the common protocol, antimicrobials, instruments, etc., concerning bacteria, particularly *Salmonella* spp., derived from human patients and from food, as collected by these Public Health Institutes.[6] The monitoring was targeted at *Salmonella* spp. strains that were isolated from human patients and from food in 2015 and 2016. Strains derived from humans included those isolated from specimens of patients with infectious gastroenteritis or with food poisoning. For each strain derived from food, the type of source food and the date of isolation were identified. When the source food was chicken meat, information was collected concerning the country of production (domestic, imported (country name), and unknown). The 18 cooperating Public Health Institutes performed antimicrobial susceptibility tests by the CLSI disk diffusion method, in accordance with the Public Health Institute Group Protocol for Antimicrobial Susceptibility Tests, using strains that were assessed as *Salmonella* spp. All Public Health Institutes used common reagents (e.g. susceptibility disks) and instruments (e.g. disk dispensers, vernier calipers) for the tests. Susceptibility disks were laid out on an agar plate as indicated in the layout drawing in the protocol, so that inhibition circles would not be coalesced. The diameters of inhibition circles were measured, and the measurements were assessed based on the susceptibility assessment chart in the protocol.

3) Prospect

Clear similarity was observed in the proportion of antimicrobial-resistant strains derived from humans and of those derived from food. These data are important in the one health approach that combines the environment, animals, food and human health. A system is being established for linking this monitoring with JANIS and JVARM through interconversion software, thereby enabling the integrated evaluation of the three different monitoring

(8) Monitoring on the antimicrobial-resistant *Neisseria gonorrhoeae*

1) Overview

In the diagnosis of gonococcal infection, the utilization of nucleic acid testing has been promoted. Isolation culture is only implemented for some patients. Because antimicrobial susceptibility tests for *Neisseria gonorrhoeae* cannot be easily implemented in general laboratories or laboratory companies, it is difficult for JANIS to monitor trends in this bacteria. Therefore, a monitoring on the antimicrobial-resistant *Neisseria gonorrhoeae* has been undertaken as research activities at AMED since 2015. The collected data are also reported to GLASS, which is operated by WHO.

2) Survey methods

More than 40 cooperating clinics are designated across Japan. Antimicrobial susceptibility tests were performed at five facilities capable of testing across Japan, after collecting specimens from the cooperating clinics, or collecting strains through laboratory companies. Antimicrobial susceptibility tests were performed using an agar plate dilution method, recommended by CLSI or EUCAST, or using Etest. MIC values were measured for ceftriaxone (CTRX) and spectinomycin (SPCM) as recommended agents; for azithromycin (AZM), which was used as part of the two-drug combination therapy overseas; and for penicillin (PCG), cefixime (CFIX), and ciprofloxacin (CPFX), which had been used as recommended agents in the past. The EUCAST standards were used for susceptibility and resistance assessment (Table B). For reference, the proportion of resistant strain based on CLSI Guidelines(M100-S25) (Table C) are indicated in Table D. The figures for AZM in the tables are based on the MIC distribution of strains that have antimicrobial-resistant gene, as indicated by CLSI Guideline (M100-S27).

3) Prospect

Physicians need to empirically choose therapeutic agents for gonococcal infection according to the result of the monitoring given the difficulty in routinely performing antimicrobial susceptibility tests.

For empiric treatment, it is recommended to use an agent with the potential success rate of 95% or higher. At present, ceftriaxone and spectinomycin are the only recommendable agents in Japan. Because *Neisseria gonorrhoeae* that are present in the pharynx are an important source of infection, *Neisseria gonorrhoeae* in pharynx should be treated. Due to its *in vivo* pharmacokinetics, spectinomycin does not have effect on *Neisseria gonorrhoeae* present in the pharynx. Therefore, ceftriaxone is the only practically recommendable agent.

In sporadic cases, strains are isolated in Japan that indicate the ceftriaxone MIC of 0.5 μg/mL in antimicrobial susceptibility tests. Ceftriaxone is administered by intramuscular injection overseas, and therefore subject to dose limitation. Therefore, if strains that indicate the ceftriaxone MIC of 0.5 μg/mL are transmitted to overseas, it is likely that ceftriaxone loses its effect. Hence, it is required to continue with the careful monitoring of isolated strains in coming years.

Table B. Antimicrobial susceptibility assessment criteria based on EUCAST (μg/mL) for *Neisseria gonorrhoeae*

	Susceptible		Resistant
PCG	0.06	0.125–1	1
CFIX	0.125	-	0.125
CTRX	0.125	-	0.125
SPCM	64	-	64
AZM	0.25	0.5	0.5
CPFX	0.03	0.06	0.06

Table C. Antimicrobial susceptibility assessment criteria based on CLSI (μg/mL) for *Neisseria gonorrhoeae*

	Susceptible		Resistant
PCG	0.06	0.125–1	2
CFIX	0.25	-	-
CTRX	0.25	-	-
SPCM	32	64	128
AZM*	-	-	-
CPFX	0.06	0.12-0.5	1

* Epidemiological cutoff value indicated in CLSI Standards (M100-S27): wild type (WT) ≤ 1; non-WT ≥ 2

Table D. The proportion (%) of antimicrobial-resistant *Neisseria gonorrhoeae* based on the CLSI (M100-S25)

	2015	2016
CTRX	0.6	0.4
SPCM	0	0
AZM	3.2*	4*
PCG	36.0 (96.1) †	35.8 (96.7) †
CFIX	16.1	11.0
CPFX	79.0 (79.4)	77.9 (78.3)

* The figures are based on the epidemiological cutoff value (non-WT ≥ 2 μg/mL) indicated in CLSI Standards (M100-S27), and differ from resistance proportion.

† * Figures in parentheses indicate the sum of resistance and intermediate resistance.

(9) Monitoring on the antimicrobial-resistant *Salmonella* Typhi, *Salmonella* Paratyphi A, and *Shigella* spp.

1) Overview

For typhoid, paratyphoid, and shigellosis, definitive diagnosis is undertaken based on bacterial isolation. Given there are no routine antimicrobial resistance monitorings regarding *Salmonella* Typhi, *Salmonella* Paratyphi A, and *Shigella* spp, susceptibility tests are performed at the National Institute of Infectious Diseases, using strains submitted based on the Notification for Epidemiological Surveillance. Antimicrobial resistance information concerning *Shigella* spp. is also used as data reported to GLASS.

2) Methods

Antimicrobial susceptibility tests are performed using strains that are submitted based on the Notification for Epidemiological Surveillance (HSB/TIDCD Notification No. 100901, PFSB/ISD Notification No. 100902). In antimicrobial susceptibility tests, assessment was performed in accordance with CLSI standards, using a broth microdilution method for *Salmonella* Typhi and *Salmonella* Paratyphi A, and using a disk diffusion method for *Shigella* spp.

3) Prospect

Treatment with antimicrobials is essential for typhoid and paratyphoid. To enable the proper selection of effective therapeutic agents, it is necessary to conduct continuous monitoring. The proportion of strains that are resistant to quinolones and other commonly used antibacterials are high in *Shigella* spp, and therefore recurrence is also possible even after administering antimicrobials. Careful monitoring is required to prevent possible spread of infection in Japan.

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Websites of Key Trend Surveys

Japan Nosocomial Infections Surveillance (JANIS)
https://janis.mhlw.go.jp/english/index.asp

National Epidemiological Surveillance of Infectious Disease (NESID)
https://www.niid.go.jp/niid/images/epi/nesid/nesid_en.pdf
https://www.niid.go.jp/niid/ja/allarticles/surveillance/2270-idwr/nenpou/6980-idwr-nenpo2015.html

Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)
http://www.maff.go.jp/nval/yakuzai/yakuzai_p3.html

The Tuberculosis Surveillance Center, The Research Institute of Tuberculosis, Japan Anti-tuberculosis Association
http://www.jata.or.jp/rit/ekigaku/en

Japan Antimicrobial Consumption Surveillance (JACS)
https://www.jacs.asia/

The Antimicrobial Resistance One health Surveillance Comittee: Terms of Refrences

January 16, 2017

1. Objective

As a sentiment is being elevated to promote antimicrobial resistance (AMR)-related measures, an integrated AMR trend surveillance with human health, animals, food, and the environment is regarded as important.

The National Action Plan on Antimicrobial Resistance (AMR), enacted on April 5, 2016, also requires to establish systems for such one health AMR surveillance.

Under these circumstances, the Antimicrobial Resistance One health Surveillance Comittee (hereinafter referred to as "Comittee") is to be held, requesting the participation of experts under the Director-General of the Health Service Bureau, Ministry of Health, Labour and Welfare (MHLW), in order to review necessary technical matters that pertain to one health AMR surveillance.

2. Structure of the Comittee

(1) The Comittee should consist of experienced experts and other stakeholders.
(2) The Chair should be elected from members by mutual voting.
(3) The Comittee should be presided over by the Chair.
(4) The Director-General of the Health Service Bureau may request non-member experts to participate at Comittee when necessary.

3. Term of office

(1) In principle, the term of office of a member should be two years. The term of office of a member elected to fill a vacancy should be the remaining term of his/her predecessor.
(2) A member may be re-elected.

4. Others

(1) Sessions of the Comittee should be held by the Director-General of the Health Service Bureau, MHLW.
(2) Clerical affairs for the Comittee should be handled by the Tuberculosis and Infectious Diseases Control Division, Health Service Bureau, MHLW, with cooperation from the Animal Products Safety Division, Food Safety and Consumer Affairs Bureau, Ministry of Agriculture, Forestry and Fisheries, and from the General Affairs Division, Environmental Management Bureau, Ministry of the Environment .
(3) Sessions of the Comittee should be held openly in principle.
(4) Necessary matters concerning the operation of the Comittee, other than those specified in this Overview, should be determined at the Comittee.

The Process of Preparation of This Report

This report was drafted through discussion at the a series of the AMR One Health Surveillance committee in cooperation with addtinal expers and cooporating govemental agencies:1st meeting on on 2/3/2017, 2nd meeting on 3/8/2017, 3rd meeting on 3/8/2017, 4th meeting on 8/21/2017, and 5th meeting on 10/2/2017.

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