Nippon AMR One Health Report (NAOR) 2018

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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. In presenting the results of this surveillance, this report aims to identify the current status of and trends in antimicrobial-resistant bacteria and national antimicrobial use in the areas of human health, animals, agriculture, food and the environment, with the objective of assessing measures to combat antimicrobial-resistant bacteria and clarify challenges in this area.

We hope that this report would provide the first step for presenting Japan's effort to fight against AMR with one health approach 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	*Clostridioides* (*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
J-SIPHE	Japan Surveillance for Infection Prevention and Healthcare Epidemiology
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
PPCPs	Pharmaceuticals and Personal 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
			oxacillin	MPIPC
			piperacillin/tazobactam	PIPC/TAZ
			amoxicillin	AMPC
			amoxicillin/clavulanic acid	AMPC/CVA
	Cephalosporins	1st generation	cefazolin	CEZ
			cephalexin	CEX
		2nd generation	cefotiam	CTM
			cefaclor	CCL
			cefmetazole	CMZ
			cefoxitin	CFX
		3rd generation	cefotaxime	CTX
			ceftazidime	CAZ
			ceftriaxone	CTRX
			cefoperazone/sulbactam	CPZ/SBT
			cefdinir	CFDN
			cefcapene pivoxil	CFPN-PI
			cefditoren pivoxil	CDTR-PI
			cefixime	CFIX
		4th generation	cefepime	CFPM
			cefpirome	CPR
			cefozopran	CZOP
	Cephamycins		cefmetazole	CMZ
			cefoxitin	CFX
	Oxacephems		flomoxef	FMOX
			latamoxef	LMOX
	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 (◎fluoroquinolones)	◎ciprofloxacin	CPFX
	◎levofloxacin	LVFX
	◎pazufloxacin	PZFX
	◎norfloxacin	NFLX
	◎prulifloxacin	PUFX
	◎moxifloxacin	MFLX
	◎garenoxacin	GRNX
	◎sitafloxacin	STFX
	◎ofloxacin	OFLX
	◎enrofloxacin	ERFX
	oxolinic acid	OA
	nalidixic acid	NA
Glycopeptides	vancomycin	VCM
	teicoplanin	TEIC
Oxazolidinones	linezolid	LZD
Polypeptides	polymyxin B	PL-B
	colistin	CL
	bacitracin	BC
Amphenicols	chloramphenicol	CP
	florfenicol	FF
Other antibacterial agents	fosfomycin	FOM
	salinomycin	SNM
	bicozamycin	BCM
Antitubercular antibiotics	isoniazid	INH
	ethambutol	EB
	rifampicin (rifampin)	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)

[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

In terms of active ingredients (veterinary drugs), in terms of effective value (antibiotic feed additives), in terms of active ingredients (agrochemicals), antimicrobial consumption in terms of potency by weight (humans): Quantities in terms of the weight of active ingredients in veterinary drugs are calculated from sales data collected from marketing authorization holders for the volume of each drug sold. When doing so, the marketing authorization holders also submit estimates of the percentage of sales for each species of domestic animal, so the estimated volumes sold are calculated for each species based on those estimated percentages. As with the figures for veterinary drugs, quantities of antibiotic feed additives in terms of effective value, quantities of agrochemicals in terms of active ingredients, and human antimicrobial consumption in terms of potency by weight refer to active ingredient weight.

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. Japan also submits data to the World Organisation for Animal Health (OIE), which uses standardized methods for monitoring the volume of antimicrobial use in animals. 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 IQVIA Solutions Japan K.K. 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 findings by Health and Labor Sciences Research Groups, while the results of a survey by the Japan Livestock Industry Association were used for surveillance of awareness of animal AMR among clinical veterinarians and animal producers.

Results: In Japan, the carbapenem resistance rate in *Enterobacteriaceae*, particularly *Escherichia coli* and *Klebsiella pneumoniae* remained below 1% during the observed period, despite its global increase in humans. Likewise, the proportion of vancomycin-resistant enterococci in humans remained less than 1%. Penicillin resistance (non-susceptibility rate) in *Streptococcus pneumoniae* also has been on the decline in recent years. While the criteria for assessing carbapenem resistance in *Pseudomonas aeruginosa* changed in 2014, the resistance rate was trending downward. The rate of resistance against the third-generation cephalosporins and fluoroquinolones among *Escherichia coli*, however, was increasing. Although the percentage of methicillin-resistant *Staphylococcus aureus* (MRSA) has been declining in recent years, levels remained high. Clear similarities in the pattern of resistance rates to antimicrobials were observed in serotypes of *Salmonella* spp. isolated from food and from humans, strongly suggesting a link between resistant strains derived from food and from humans.

Usage of antimicrobial agents in Japan based on total sales in 2017 fell by 7.3% from that in 2013 to a defined daily dose per 1,000 inhabitants per day (DID) of 13.8. Oral antimicrobial agents accounted for 90% of total sales, with oral cephalosporins, oral macrolides, and oral fluoroquinolones accounting for the highest shares. While the trend remained similar in 2017, steady progress toward achieving the numerical targets was observed, as the shares of each agent had declined since 2013, by 12.2%, 13.5%, and 9.1% respectively. However, use of parenteral antimicrobials saw a 9.3% increase from 2013.

In food-producing 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 food-producing animals. Tetracycline resistance appeared to be more common, although the degree of resistance depended on animal and bacterial species. Looking at resistance rates specified as outcome indices for the action plan, tetracycline resistance in the indicator bacteria, *Escherichia coli* derived from healthy animals, fell by approximately 5% from 2014 in 2015. Rates of indicator bacteria resistance to third-generation cephalosporins and fluoroquinolones were also low, remaining mostly below 10% during the observed period. Monitoring of antimicrobial resistance in aquaculture and fisheries began in 2011, focused specifically on the resistance of *Lactococcus garvieae* (lactococcosis and *Photobacterium damselae* subsp. *picicida* taken from diseased fish (*Seriola*) and *Vibrio parahaemolyticus* obtained from aquaculture-environment sampling. This monitoring was extended to cover all farmed fish species from 2017. In the area of companion

animals, nationwide surveillance of resistant bacteria isolated from diseased dogs and cats began in 2017. While *Escherichia coli* isolated from diseased dogs and cats demonstrated lower resistance to tetracyclines and aminoglycosides than those from food-producing animals, resistance rates to fluoroquinolones and cephalosporins tended to be higher.

The volume of sales of antimicrobials used for animals (including food-producing animals, fish and companion animals) was calculated in tons of the active ingredients, based on sales reports for antibiotics and synthetic antimicrobials mandated by the Regulations for Veterinary Drugs (Ordinance of the Ministry of Agriculture, Forestry and Fisheries No. 107 of 2004). These figures showed that sales of antimicrobials for veterinary use rose from 780.88 tons in 2013 to 832.56 tons in 2016. The increase in the volume of sales between 2013 and 2016 was attributed primarily to growth in sales of macrolides (erythromycin used in aquatic animals and 16-membered macrolides used in food-producing animals) and penicillin derivatives, with the rise in erythromycin used in aquatic animals presumed to have been triggered by an outbreak of streptococcal infection. Tetracyclines represented the largest share of antimicrobial sales, accounting for about 40%. In contrast, third-generation cephalosporins and fluoroquinolones each accounted for less than 1% of the total. Usage in each area between 2013 and 2016 was estimated from distribution volumes. Total usage in 2016 was 1,804.3 tons, comprising 591.0 tons for human use, 669.7 tons for food-producing animals, 155.1 tons for aquatic animals, 6.7 tons for companion animals, 228.2 tons for antibiotic feed additives, and 153.6 tons for agrochemicals.

Observations: This year's report includes data obtained after Japan's "National Action Plan on Antimicrobial Resistance (AMR) 2016-2020" was published. Figures for 2017 sales of oral antimicrobials, including oral cephalosporins, oral macrolides, and oral fluoroquinolones show that usage of these antimicrobials has fallen overall compared with the data for 2013. In addition, a clear downward trend in antimicrobial resistance rates has emerged among a number of bacterial species, thereby demonstrating progress toward achieving the numerical targets in the action plan. However, resistance rates in *Escherichia coli* to antimicrobials such as fluoroquinolone continue to climb. The data in this report demonstrate that further promotion of measures against AMR will be required to achieve the targets for 2020. In the case of animals, a rise in sales volumes was observed between 2013 and 2016, caused mainly macrolides (erythromycin used for aquatic animals and 16-membered macrolides used in food-producing animals) and penicillin derivatives, with no substantial increase observed among tetracyclines or the third-generation cephalosporins and fluoroquinolones that are critically important antimicrobials for human medicine. The rate of resistance to the third-generation cephalosporins and fluoroquinolones among *Escherichia coli* has been kept at a low level. While tetracycline resistance in *Escherichia coli* fell in 2015 from the year before, further efforts to ensure the prudent use of antimicrobials will be required if the 2020 targets are to be met.

5. Outcome Indices for the Action Plan

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

	2013	2015*	2017	2020 (target value†)
Proportion of penicillin-non-susceptible *Streptococcus pneumoniae*, CSF specimens§	47.4	40.5	29.1	15% or lower
Proportion of penicillin-non-susceptible *Streptococcus pneumoniae*, non-CSF specimens§	3.2	2.7	2.1	
Proportion of fluoroquinolone-resistant *Escherichia coli*	35.5	38.0	40.1	25% or lower
Proportion of methicillin-resistant *Staphylococcus aureus*	51.1	48.5	47.7	20% or lower
Proportion of carbapenem-resistant *Pseudomonas aeruginosa* (Imipenem)	17.1	18.8	16.9	10% or lower
Proportion of carbapenem-resistant *Pseudomonas aeruginosa* (Meropenem)	10.7	13.1	11.4	10% or lower
Proportion of carbapenem-resistant *Escherichia coli* (Imipenem)	0.1	0.1	0.1	0.2% or lower (maintain at the same level)¶
Proportion of carbapenem-resistant *Escherichia coli* (Meropenem)	0.1	0.2	0.1	0.2% or lower (maintain at the same level)¶
Proportion of carbapenem-resistant *Klebsiella pneumoniae* (Imipenem)	0.3	0.3	0.2	0.2% or lower (maintain at the same level)¶
Proportion of carbapenem-resistant *Klebsiella pneumoniae* (Meropenem)	0.6	0.6	0.4	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: antimicrobials of use based on sales data (DID)

	2013		2017	Change from 2013	2020 (target value*)
Data source	Sales†	NDB§	Sales	Sales	
All antimicrobials	14.89	13.25	13.8	7.3% ↓	33% ↓
Oral cephalosporins	3.91	3.44	3.43	12.2% ↓	50% ↓
Oral fluoroquinolones	2.82	2.71	2.57	9.1% ↓	50% ↓
Oral macrolides	4.83	4.55	4.18	13.5% ↓	50 % ↓
Intravenous antimicrobials	0.96	0.71	1.05	9.3% ↑	20% ↓

DID: Defined daily dose per 1000 inhabitants per day

* Target values were quoted from [1].

† Prepared from [2] with partial modification

§ Prepared from [3], NDB: national database

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

	2014*	2015*	2020 (target value**)
Proportion of tetracycline-resistant *Escherichia coli*	45.2	39.9	33% or lower
Proportion of third-generation cephalosporin-resistant *Escherichia coli*	1.5	0.9	The Same level as in other G7 nations
Proportion of fluoroquinolone-resistant *Escherichia coli*	4.7	3.8	The Same level as in other G7 nations

* Prepared from [35] with partial modification

JVARM "Results of Monitoring of Antimicrobial Resistant Bacteria Isolated from Food-producing Animals on Farms"

** 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 organisms 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 *Klebsiella (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	2016	2017
ABPC	32	32	47.6 (116,097)	49.1 (133,330)	49.4 (150,867)	49.2 (170,597)	50.5 (257,065)	51.2 (288,052)	51.7 (307,143)
PIPC	128	128	40.1 (119,843)	41.6 (136,978)	42.5 (155,626)	42.5 (175,763)	44.1 (270,452)	44.9 (305,604)	45.2 (327,773)
TAZ/ PIPC	4/128	4/128	-	-	2.2 (51,286)	1.7 (89,442)	1.7 (179,722)	1.8 (218,008)	1.7 (241,519)
CEZ*	32	8	24.4 (122,803)	26.2 (141,560)	26.9 (161,397)	33.3 (183,542)	35.8 (268,898)	36.8 (303,608)	37.3 (324,109)
CMZ	64	64	-	-	-	1.0 (163,342)	0.9 (260,844)	1.0 (300,089)	0.9 (325,296)
CTX*	64	4	14.8 (99,543)	16.6 (113,354)	17.8 (124,473)	23.3 (140,186)	24.5 (209,404)	26.0 (230,911)	26.8 (241,843)
CAZ*	32	16	5.2 (123,606)	5.2 (142,440)	5.5 (161,163)	9.5 (183,970)	10.8 (275,671)	11.6 (310,281)	12.0 (330,029)
CFPM	32	32	-	-	10.9 (81,456)	12.8 (129,606)	15.0 (236,705)	15.8 (273,587)	16.1 (296,143)
AZT*	32	16	8.5 (97,906)	9.4 (111,930)	10.2 (126,777)	16.1 (143,046)	17.6 (216,494)	18.4 (239,952)	18.7 (258,193)
IPM*	16	4	0.1 (113,820)	0.1 (128,289)	0.1 (146,007)	0.1 (163,181)	0.1 (251,050)	0.1 (284,316)	0.1 (304,633)
MEPM*	16	4	-	-	0.1 (95,180)	0.2 (144,913)	0.2 (269,893)	0.2 (317,987)	0.1 (340,687)
AMK	64	64	0.2 (123,464)	0.2 (141,114)	0.2 (161,406)	0.2 (184,788)	0.1 (281,641)	0.1 (317,913)	0.1 (339,871)
LVFX	8	8	31.4 (117,292)	34.3 (136,253)	35.5 (155,998)	36.1 (178,497)	38.0 (274,687)	39.3 (310,705)	40.1 (336,310)

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.
-: Not under surveillance
* CLSI (2007) (M100-S17) Criteria was applied to determine the BP up to 2013. CLSI (2012)(M100-S22) Criteria was applied to determine BP after 2014.

ii. *Klebsiella pneumoniae*

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

	BP (-2013)	BP (2014-)	2011	2012	2013	2014	2015	2016	2017
ABPC	32	32	75.9 (65,338)	76.9 (73,078)	77.8 (80,030)	76.3 (90,220)	76.9 (131,700)	76.3 (147,500)	77.4 (152,477)
PIPC	128	128	19.7 (67,548)	20.1 (74,878)	24.3 (82,608)	21.9 (91,761)	21.1 (136,347)	21.8 (154,260)	21.8 (161,254)

TAZ/ PIPC	4/128	4/128	-	-	2.2 (27,279)	2.0 (46,941)	2.0 (91,503)	2.2 (110,189)	2.2 (118,796)
CEZ*	32	8	8.8 (68,481)	9.0 (76,860)	9.1 (85,320)	11.7 (94,875)	12.1 (135,486)	13.1 (152,973)	13.4 (157,849)
CMZ	64	64	-	-	-	1.9 (85,749)	1.9 (132,163)	1.7 (152,086)	1.5 (159,375)
CTX*	64	4	5.2 (56,236)	5.4 (62,242)-	5.1 (66,654)	8.6 (73,574)	8.0 (107,409)	8.9 (118,057)	8.9 (119,672)
CAZ*	32	16	3.4 (68,916)	2.9 (76,961)	2.7 (84,761)	3.8 (94,878)	4.0 (138,191)	4.6 (155,293)	5.0 (160,619)
CFPM	32	32	-	-	3.0 (41,143)	3.5 (66,399)	4.0 (119,563)	4.8 (138,737)	5.1 (145,745)
AZT*	32	16	4.1 (54,680)	3.7 (60,606)	3.5 (67,253)	5.1 (75,340)	5.3 (110,259)	5.9 (122,600)	6.2 (127,491)
IPM*	16	4	0.2 (63,825)	0.2 (70,284)	0.1 (77,193)	0.3 (85,253)	0.3 (126,997)	0.2 (143,813)	0.2 (149,546)
MEPM*	16	4	-	-	0.2 (48,190)	0.6 (73,903)	0.6 (135,930)	0.5 (159.623)	0.4 (166,298)
AMK	64	64	0.3 (68,995)	0.2 (76,293)	0.2 (84,916)	0.1 (95,643)	0.1 (141,710)	0.1 (159,871)	0.1 (166.081)
LVFX	8	8	2.7 (66,466)	2.4 (74,718)	2.5 (83,063)	2.4 (92,993)	2.6 (138,428)	2.7 (156,249)	2.8 (163,688)

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
* CLSI (2007)(M100-S17) Criteria was applied to determine the BP up to 2013. CLSI (2012)(M100-S22) Criteria was applied to determine BP after 2014.

iii. *Enterobacter* spp.

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

	BP (-2013)	BP (2014-)	2013	2014	2015	2016	2017
ABPC	32	32	80.9 (35,849)	79.0 (39,344)	80.2 (55,960)	79.3 (61,667)	79.8 (61,970)
PIPC	128	128	20.6 (36,988)	20.0 (39,636)	19.8 (58,039)	20.1 (63,580)	20.8 (64,217)
TAZ/ PIPC	4/128	4/128	10.3 (11,895)	8.6 (21,091)	8.9 (40,315)	8.9 (47,390)	9.4 (48,775)
CEZ*	32	8	97.2 (37,359)	98.2 (41,422)	98.3 (58,637)	98.3 (64,634)	98.3 (64,693)
CTX*	64	4	19.2 (30,106)	31.1 (32,718)	31.6 (46,727)	31.2 (50,311)	32.4 (50,022)
CAZ*	32	16	20.6 (37,202)	24.7 (41,456)	25.0 (59,533)	24.9 (65,317)	25.8 (65,027)
CFPM	32	32	4.2 (17,900)	4.2 (29,836)	4.2 (52,218)	4.0 (58,298)	4.0 (59,398)
AZT*	32	16	16.8 (29,460)	23.8 (33,551)	24.0 (48,570)	23.9 (52,951)	24.3 (53,374)
IPM*	16	4	0.4 (34,403)	1.6 (37,396)	1.3 (54,926)	1.2 (60,602)	1.1 (60,689)
MEPM*	16	4	0.6 (21,164)	1.3 (32,589)	1.4 (59,009)	1.2 (67,250)	1.1 (67,392)
AMK	64	64	0.4 (37,947)	0.2 (42,005)	0.2 (61,086)	0.1 (67,133)	0.1 (67,125)
LVFX	8	8	4.2 (37,274)	3.5 (40,942)	3.7 (59,393)	3.4 (65,161)	3.5 (65,690)

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
* CLSI (2007)(M100-S17) Criteria was applied to determine the BP up to 2013. CLSI (2012)(M100-S22) Criteria was applied to determine BP after 2014.

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

	BP (-2013)	BP (2014-)	2013	2014	2015	2016	2017
ABPC	32	32	76.5 (17,362)	77.1 (18,385)	78.9 (26,680)	77.9 (29,228)	79.1 (30,844)
PIPC	128	128	14.5 (18,029)	14.5 (18,550)	14.2 (27,189)	15.8 (29,852)	17.1 (31,802)
TAZ/PIPC	4/128	4/128	6.3 (5,568)	4.9 (9,568)	4.8 (18,731)	4.8 (21,767)	5.7 (24,082)

CEZ**	32	8	90.8 (17,945)	94.0 (19,173)	93.7 (27,526)	94.2 (30,088)	94.5 (31,800)
CMZ	64	64	-	84.8 (17,587)	86.8 (26,739)	87.1 (29,681)	88.0 (31,915)
CTX**	64	4	5.2 (14,452)	28.3 (15,173)	30.7 (21,985)	31.1 (23,572)	32.9 (24,195)
CAZ**	32	16	17.3 (17,992)	24.3 (19,439)	25.2 (27,886)	25.7 (30,388)	26.7 (32,030)
CFPM	32	32	1.0 (8,909)	1.2 (13,499)	1.1 (24,302)	1.1 (27,146)	1.3 (29.464)
AZT**	32	16	7.5 (14,639)	15.8 (15,846)	17.5 (23,225)	17.5 (25,023)	18.0 (26,772)
IPM**	16	4	0.4 (16,881)	1.7 (17,463)	1.9 (25,690)	1.9 (28,307)	1.9 (29,869)
MEPM**	16	4	0.2 (10,249)	0.9 (15,003)	0.8 (27,560)	0.8 (31,311)	0.8 (33,150)
AMK	64	64	0.2 (18,369)	0.2 (19,492)	0.1 (28,627)	0.1 (31,338)	0.1 (33,074)
LVFX	8	8	1.1 (18,111)	1.0 (19,068)	0.9 (28,012)	1.0 (30,451)	0.9 (32,503)

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
*_Enterobacter aerogenes_ has been renamed _Klebsiella aerogenes_ (Int. J. Syst. Evol. Microbiol. 67, 502-504, 2017).
** CLSI (2007)(M100-S17) Criteria was applied to determine the BP up to 2013. CLSI (2012)(M100-S22) Criteria was applied to determine BP after 2014.

iv. *Pseudomonas aeruginosa*

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

	BP (-2013)	BP (2014-)	2011	2012	2013	2014	2015	2016	2017
PIPC	128	128	12.1 (114,950)	11.9 (118,032)	11.4 (122,581)	10.8 (125,242)	10.5 (181,977)	10.5 (201,764)	10.3 (205,165)
TAZ/ PIPC	4/128	4/128	-	-	9.0 (68,686)	8.8 (79,574)	8.8 (132,769)	8.4 (155,724)	8.3 (165,402)
CAZ	32	32	11.3 (116,596)	10.9 (120,473)	10.2 (124,864)	9.5 (126,718)	8.6 (180,479)	8.7 (199,597)	8.6 (202,025)
AZT	32	32	16.3 (96,435)	16.7 (100,964)	16.5 (105,681)	14.5 (107,167)	14.0 (146,841)	13.8 (158,737)	13.7 (162,952)
CFPM	32	32	9.7 (91,769)	8.9 (99,730)	8.0 (106,291)	7.5 (113,268)	6.6 (166,096)	6.5 (185,283)	6.3 (191,502)
IPM*	16	8	19.8 (112,596)	18.5 (116,193)	17.1 (119,979)	19.9 (119,323)	18.8 (168,471)	17.9 (186,380)	16.9 (188,981)
MEPM*	16	8	12.4 (109,453)	11.8 (113,996)	10.7 (119,330)	14.4 123,976)	13.1 (180,850)	12.3 (201,991)	11.4 (206,368)
GM	16	16	7.0 (111,137)	6.1 (115,612)	5.3 (118,592)	5.1 (117,421)	4.5 (165,777)	4.1 (182,343)	3.3 (184,453)
AMK	64	64	3.1 (116,876)	2.6 (121,289)	2.1 (126,023)	1.9 (128,923)	1.5 (185,327)	1.3 (204,892)	1.1 (208,098)
LVFX	8	8	16.8 (111,005)	16.3 (115,478)	14.5 (119,162)	13.0 (120,691)	12.0 (174,301)	11.6 (193,366)	10.8 (197,890)

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
* CLSI (2007)(M100-S17) Criteria was applied to determine the BP up to 2013. CLSI (2012)(M100-S22) Criteria was applied to determine BP after 2014.

v. *Acinetobacter* spp.

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

	BP	2011	2012	2013	2014	2015	2016	2017
PIPC	128	13.2 (19,125)	13.2 (19,433)	12.9 (20,183)	12.4 (20,223)	11.5 (27,887)	10.9 (29,776)	10.9 (27,468)
TAZ/ PIPC	4/128	-	-	7.8 (4,953)	7.8 (5,215)	8.1 (9,058)	8.6 (10,551)	9.0 (10,983)
SBT/	16/32	6.5	7.2	5.8	5.2	4.8	5,4	4.7

ABPC		(2,942)	(3,601)	(4,498)	(6,462)	(11,356)	(12,831)	(12,241)
CAZ	32	10.3	10.6	10.0	9.3	8.0	7.6	7.9
		(19,672)	(20,067)	(20,856)	(20,852)	(28,166)	(29,844)	(27,308)
CFPM	32	10.4	10.5	9.2	7.6	7.2	7.4	7.6
		(13,013)	(14,093)	(15,394)	(17,424)	(25,412)	(27,386)	(25,631)
IPM	16	2.2	2.0	2.3	3.6	3.2	3.1	2.5
		(18,048)	(18,238)	(16,947)	(11,147)	(13,942)	(15,147)	(14,383)
MEPM	16	2.9	2.4	2.3	2.0	1.8	1.9	1.3
		(15,485)	(15,880)	(17,027)	(18,859)	(28,227)	(30,489)	(28,064)
GM	16	9.6	10.2	9.5	8.9	8.5	8.5	8.2
		(18,276)	(18,842)	(19,422)	(18,832)	(25,689)	(27,313)	(24,887)
AMK	64	4.5	4.5	3.5	3.6	3.1	2.3	2.3
		(19,348)	(19,793)	(20,863)	(20,851)	(28,568)	(30,279)	(27,835)
LVFX	8	9.5	9.8	8.3	8.5	7.7	8.2	8.0
		(18,732)	(19,484)	(20,040)	(20,047)	(27,858)	(29,702)	(27,360)

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-susceptible *Staphylococcus aureus* (MSSA) varied among antimicrobials (Table 7), and 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 8, 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 pneumococcus 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	2016	2017
PCG	0.25	61.1	60.1	59.0	57.7	56.2	55.0	53.9
		(68,839)	(75,025)	(82,477)	(86,314)	(119,343)	(126,394)	(129,943)
CEZ	32	0.3	<0.05	0.2	0.2	0.1	<0.05	<0.05
		(77,483)	(84,520)	(93,945)	(103,603)	(146,254)	(157,917)	(161,831)
CVA/	4/8	0.3	0.1	0.2	0.2	0.1	0.1	0.1
AMPC		(11,696)	(9,466)	(11,230)	(11,666)	(19,163)	(21,783)	(24,713)
IPM	16	0.3	<0.05	0.2	0.2	<0.05	<0.05	<0.05
		(74,636)	(80,472)	(88,422)	(95,951)	(136,878)	(146,433)	(149,014)
EM	8	22.7	23.4	24.0	23.8	22.9	23.3	23.5
		(72,738)	(79,683)	(88,528)	(96,829)	(136,763)	(146,280)	(148,795)
CLDM	4	3.4	3.1	3.2	2.8	2.8	2.9	2.9
		(67,523)	(74,387)	(83,914)	(93,467)	(136,292)	(148,439)	(151,841)
MINO	16	0.7	0.6	0.5	0.6	0.6	0.5	0.6
		(77,872)	(84,595)	(94,425)	(104,145)	(151,493)	(163,214)	(167,178)
LVFX	4	9.3	10.2	10.6	10.7	11.6	12.3	13.1
		(73,163)	(79,857)	(89,641)	(99,898)	(144,083)	(154,868)	(159,066)

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 (2014-)	2011	2012	2013	2014	2015	2016	2017
EM	8	91.3	90.6	88.4	86.0	84.1	83.8	82.9
		(105,936)	(109,521)	(108,607)	(107,836)	(149,851)	(155,587)	(157,708)
CLDM	4	76.8	73.5	67.3	60.3	56.0	51.6	46.3
		(102,895)	(106,124)	(105,503)	(106,910)	(153,329)	(160,500)	(164,301)
MINO	16	48.2	43.7	37.1	35.1	31.7	29.1	27.1
		(117,325)	(120,321)	(120,300)	(121,258)	(173,983)	(182,306)	(185,770)
VCM	16	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		(115,679)	(119,111)	(119,441)	(120,535)	(172,083)	(181,288)	(185,948)
TEIC	32	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
		(110,380)	(113,887)	(113,684)	(113,749)	(158,233)	(165,213)	(167,342)

LVFX	4	89.0 (111,598)	88.3 (114,381)	86.8 (114,551)	85.4 (115,586)	85.2 (164,734)	85.8 (172,494)	86.5 (176,790)
LZD*	8	0.1 (76,632)	<0.05 (84,550)	<0.05 (85,223)	<0.05 (88,255)	0.1 (127,278)	<0.05 (136,468)	<0.05 (139,785)
Daptomycin*	2	-	-	-	1.1 (3,078)	0.9 (16,648)	0,8 (23,217)	0.7 (26,874)

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
As of 2015, no vancomycin-resistant *staphylococcus aureus* strains had been reported.
* CLSI (2007)(M100-S17) Criteria was applied to determine the BP up to 2013. CLSI (2012)(M100-S22) Criteria was applied to determine BP after 2014.

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

Table 9-1. All participating medical institutions

	2011	2012	2013	2014	2015	2016	2017
Number of participating medical institutions	594	660	745	883	1435	1653	1795
The number of patients with MRSA	114,933	117,209	118,539	120,702	169,528	177,768	182,619
The number of patients with *S. aureus*	210,382	221,239	231,909	246,030	349,743	372,787	383,006
The proportion of MRSA (%)*	54.6	53.0	51.1	49.1	48.5	47.7	47.7

Table 9-2. Participating medical institutions with 200 or more beds

	2011	2012	2013	2014	2015	2016	2017
Number of participating medical institutions	-	-	-	791	1177	1269	1312
The number of patients with MRSA	-	-	-	115,757	157,419	160,060	160,714
The number of patients with *S. aureus*	-	-	-	237,343	328,540	341,822	344,543
The proportion of MRSA (%)*	-	-	-	48.8	47.9	46.8	46.6

Table 9-3. Participating medical institutions with fewer than 200 beds

	2011	2012	2013	2014	2015	2016	2017
Number of participating medical institutions	-	-	-	92	258	384	483
The number of patients with MRSA	-	-	-	4,945	12,109	17,708	21,905
The number of patients with *S. aureus*	-	-	-	8,687	21,203	30,965	38,463
The proportion of MRSA (%)*	-	-	-	56.9	57.1	57.2	57.0

Those detected in selective media were also included.
* The number of patients with MRSA / The number of patients with *S. aureus*
-: Not under surveillance

ii. *Enterococcus* spp.

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

	BP	2011	2012	2013	2014	2015	2016	2017
PCG	16	2.2 (53,290)	2.1 (60,342)	1.8 (65,220)	1.6 (67,324)	1.4 (92,132)	1.1 (98,465)	1.0 (98,478)
ABPC	16	0.4 (60,686)	0.4 (68,440)	0.3 (72,587)	0.3 (77,997)	0.3 (107,733)	0.2 (115,548)	0.2 (116,493)
EM	8	57.8 (53,222)	58.0 (60,825)	57.1 (64,465)	55.5 (69,171)	54.8 (95,409)	54.3 (101,036)	53.8 (101,379)
MINO	16	47.8 (61,549)	47.7 (69,421)	47.7 (74,880)	52.1 (81,925)	49.7 (115,648)	48.9 (123,860)	50.3 (125,728)
VCM	32	<0.05 (61,747)	<0.05 (69,719)	<0.05 (75,162)	<0.05 (81,867)	<0.05 (115,100)	<0.05 (124,305)	<0.05 (126,510)
TEIC	32	<0.05 (56,591)	<0.05 (63,747)	<0.05 (69,500)	<0.05 (76,160)	<0.05 (105,403)	<0.05 (112,636)	<0.05 (113,501)

LVFX	8	19.3	18.0	15.5	13.7	12.5	11.9	11.2
		(58,877)	(65,934)	(70,895)	(77,563)	(109,160)	(117,297)	(120,136)

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	2016	2017
PCG	16	86.9	87.4	87.7	86.9	87.6	88.2	87.8
		(17,642)	(21,139)	(23,466)	(24,534)	(34,752)	(38,060)	(39,478)
ABPC	16	86.0	86.2	86.9	86.9	87.6	88.0	87.9
		(19,780)	(23,885)	(26,199)	(28,564)	(41,459)	(45,069)	(47,046)
EM	8	87.2	88.1	85.9	84.5	84.5	84.0	83.1
		(17,668)	(21,498)	(23,594)	(25,922)	(37,536)	(40,509)	(42,259)
MINO	16	26.9	28.8	29.3	32.2	35.1	34.7	36.2
		(21,877)	(25,961)	(28,387)	(31,550)	(46,351)	(50,325)	(52,494)
VCM	32	1.0	0.4	0.7	0.7	0.7	0.9	0.8
		(21,782)	(25,787)	(28,334)	(30,996)	(45,514)	(49,618)	(52,127)
TEIC	32	0.4	0.3	0.2	0.2	0.3	0.6	0.4
		(20,163)	(23,855)	(26,282)	(29,151)	(41,905)	(45,388)	(47,321)
LVFX	8	82.9	83.4	84.5	84.7	85.8	86.6	86.5
		(19,417)	(23,032)	(25,629)	(28,448)	(42,068)	(45,834)	(48.995)
LZD	8	0.0	0.1	<0.05	0.1	0.1	0.1	<0.05
		(12,877)	(16,296)	(18,561)	(22,044)	(33,382)	(37,099)	(39,584)

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	2016	2017
PCG	0.125	38.6	47.4	47.0	40.5	36.4	29.1
		(101)	(97)	(83)	(126)	(140)	(117)
CTX	2	3.7	1.2	2.9	2.0	1.0	2.1
		(82)	(84)	(69)	(100)	(105)	(97)
MEPM	1	4.2	2.2	1.2	4.2	0.7	5.0
		(95)	(92)	(83)	(119)	(134)	(120)
EM	1	82.5	82.7	92.5	84.9	75.5	82.4
		(80)	(81)	(67)	(86)	(98)	(91)
CLDM	1	53.8	68.7	65.1	62.7	61.2	49.5
		(65)	(67)	(63)	83)	(98)	(91)
LVFX	8	0.0	0.0	1.3	0.0	0.0	0.9
		(88)	(91)	(76)	(105)	(123)	(111)
VCM	2	0.0	0.0	0.0	0.0	0.0	0.0
		(91)	(90)	(82)	(119)	(134)	(116)

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	2016	2017
PCG*	4	3.2	2.7	2.5	2.7	2.1	2.1
		(24,980)	(26,932)	(27,206)	(36,475)	(35,960)	(34,415)
CTX	4	2.4	2.0	1.8	1.6	1.4	1.6
		(21,654)	(23,096)	(23,002)	(30,734)	(29,405)	(27,773)
MEPM	1	6.9	5.1	5.4	5.0	5.7	6.0
		(22,989)	(24,986)	(25,760)	(34,461)	(34,885)	(34,011)
EM	1	87.0	86.2	86.7	85.5	84.4	82.4
		(21,979)	(22,435)	(22,215)	(30,501)	(30,144)	(28,097)
CLDM	1	56.4	56.1	57.1	56.1	54.1	50.5
		(17,513)	(19,719)	(20,296)	(27,555)	(28,541)	(27,536)
LVFX	8	3.0	3.1	3.3	3.5	4.1	4.3
		(24,105)	(25,764)	(26,236)	(35,457)	(35,431)	(34,241)
VCM	2	0.0	0.0	0.0	0.0	0.0	0.0
		(24,085)	(25,425)	(25,775)	(33,530)	(33,670)	(32,681)

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 numbers of cases reported under NESID each year through 2016 are publicized as confirmed reported data. Cases reported since 2012 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 1,573 cases were reported in 2016. Surveillance for multidrug-resistant *Acinetobacter* (MDRA) infection was started in February 2011 and at first reporting of cases was limited to designated sentinel sites. Subsequently, it became a notifiable disease on September 19, 2014, and 33 cases were reported in 2016 (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

	2012	2013	2014	2015	2016
VRE	91	55	56	66	61
VRSA	0	0	0	0	0
CRE	-	-	314*	1673	1573
MDRA	-	-	15*	38	33

* 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

		2012	2013	2014	2015	2016
PRSP	Cases	3,564	3,161	2,292	2,057	2,017
	Cases per sentinel site	7.53	6.65	4.79	4.29	4.21
MRSA	Cases	22,129	20,155	18,082	17,057	16,338
	Cases per sentinel site	46.78	42.43	37.83	35.61	34.11
MDRA*	Cases	7	8	4	-	-
	Cases per sentinel site	0.01	0.02	0.01	-	-
MDRP	Cases	401	319	268	217	157
	Cases per sentinel site	0.85	0.67	0.56	0.45	0.33

* MDRA became reportable under notifiable disease surveillance on September 19, 2014.
-: Not under surveillance

4) Other antimicrobial-resistant bacteria

i. *Campylobacter jejuni/coli*.

Source: Tokyo Metropolitan Institute of Public Health

Tokyo Metropolitan Institute of Public Health has conducted trend surveillance concerning the proportion of antimicrobial-resistant *Campylobacter* spp. Among the 132 outbreaks of food-borne illness that occurred in Tokyo in 2017, 45 outbreaks (34.1%) were caused by *Campylobacter* spp., being the largest cause of bacterial food-borne illness.[4] Among the *Campylobacter jejuni* (*C. jejuni*) isolated from patients with diarrhea in 2016, the proportion of fluoroquinolone-resistant strains was 52.2%, higher than 2015. The proportion of fluoroquinolone-resistant *Campylobacter coli* (*C. coli*) strains was 35.7%, which was lower than the previous year. Note that, however, the number of tested strains was smaller for *C.coli* and this should be taken into consideration upon interpretation of the result.

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

	2011 (n=108)	2012 (n=83)	2013 (n=85)	2014 (n=125)	2015 (n=116)	2016 (n=113)
EM	3.7	2.4	1.2	0.8	0.9	0.9
NA	53.7	62.7	50.6	50.4	37.1	53.1
Fluoroquinolones†	53.7	62.7	50.6	50.4	37.1	52.2

* Strains isolated from diarrhea cases in Tokyo
†NFLX, OFLX, and CPFX were included.
Prepared from [4] with partial modification.

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

	2011 (n=8)	2012 (n=9)	2013 (n=12)	2014 (n=7)	2015 (n=8)	2016 (n=14)
EM	12.5	22.2	16.7	28.6	0.0	14.3
NA	87.5	66.7	75.0	57.1	50.0	50.0
Fluoroquinolones†	87.5	66.7	75.0	57.1	50.0	35.7

* Strains isolated from the stool of sporadic diarrhea cases in Tokyo Prefecture.
† NFLX, OFLX, and CPFX were included.
Prepared from [4] with partial modification.

ii. Non-typhoidal *Salmonella* spp.
Source: Public Health Institutes

The 21 Public Health Institutes across Japan conducted research on the multidrug-resistant status of the 1,536 *Salmonella* strains that were isolated between 2015 and 2017, using standardized methodology.[5] Table 18 lists the key serotypes of human-derived strains and food-derived strains.

In total, 41.1% of the 1,185 human-derived strains and 89.7% of the 351 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 that the investigation covered all regions of Japan and the proportion of resistant strains isolated between 2015 and 2017 was similar. Table 20 appears to show that resistance to cephalosporins (CTX, CAZ, CFX) rose in strains isolated in 2017, but the figures were the same as 2015 and 2016 or even lower when the focus was limited to domestic chicken meat (figures in parentheses). This suggested that the strains isolated in 2017 contained a high proportion of strains from foreign chicken meat. As for multidrug resistance, the proportion of three-drug resistance was large both among human-derived strains and among food-derived strains. Twenty-one among human-derived strains, and 30 among food-derived strains, indicated advanced resistance to as many as six to ten drugs.

Tables 21 and 22 show antimicrobial resistance in the top two serotypes of food-derived strains (*S.* Infantis and *S.* Schwarzengrund), while Tables 23 to 27 show antimicrobial resistance in the top five serotypes of human-derived strains (*S.* Infantis, *S.* Enteritidis, *S.* Saintpaul, *S.* 4:i:-, and *S.* Thompson). Among food-derived strains, trends in resistance by serotype have many aspects in common, but distinctive features were observed in serotype-specific resistance trends among human-derived strains.

In a comparison of antimicrobial resistance rates between human- and food-derived strains for the three serotypes (*S.* Infantis, *S.* Schwarzengrund, and *S.* Manhattan) appearing in both the top five serotypes among food-derived strains and the top 10 serotypes among human-derived strains (Table 28), clear similarities were observed in the overall trends in resistance rates for each serotype between human-derived strains and food-derived strains, suggesting a strong association between food-derived and human-derived antimicrobial-resistant bacteria.

Table 18. Serotypes of human- and food-derived non-typhoidal *Salmonella* spp

Human-derived strains (n=1,185)	%	Food-derived strains (n=351)	%
Infantis	12.2	Infantis	36.5
Enteritidis	10.6	Schwarzengrund	33.3
Saintpaul	8.0	Manhattan	8.3
O4:i:-	7.6	Agona	3.7

Thompson	7.3	Typhimurium	2.8
Typhimurium	4.7	Others	15.4
Schwarzengrund	4.4	Total	100.0
Manhattan	3.1		
Chester	2.6		
Stanley	2.5		
Others	36.9		
Total	100.0		

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

	2015 (n=388)	2016 (n=361)	2017 (n-436)	2015-2017 (n=1,185)
ABPC	17.3	17.7	15.4	16.7
GM	0.3	0.6	0.7	0.5
KM	5.9	11.6	7.6	8.3
SM	27.3	29.9	27.3	28.1
TC	32.5	29.1	28.0	29.8
ST	4.4	6.6	8.9	6.8
CP	2.3	6.4	5.0	4.6
CTX	0.3	2.8	3.0	2.0
CAZ	0.3	2.5	1.6	1.4
CFX	0.0	1.4	0.5	0.6
FOM	0.0	0.3	0.5	0.3
NA	7.0	8.0	9.4	8.2
CPFX	0.3	0.8	1.6	0.9
NFLX	0.3	0.8	0.5	0.5
AMK	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0
Number resistant to one or more antimicrobials	165	151	172	488
Proportion resistant to one or more antimicrobials	42.5	41.8	39.4	41.2

Table 20. The proportion (%) of antimicrobial-resistant food-derived non-typhoidal *Salmonella* spp.*

	2015 (n=156)	2016 (n=110)	2017 (n=85)	2015-2017 (n=351)
ABPC	17.9	13.6	11.8	15.1
GM	0.0	0.9	1.2	0.6
KM	48.1	47.3	44.7	47.0
SM	82.7	70.9	69.4	75.8
TC	85.9	76.4	72.9	79.8
ST	19.9	16.4	11.8	16.8
CP	7.1	10.0	2.4	6.8
CTX	5.1 (5.4)	5.5 (6.3)	8.2 (2.6)	6.0 (5.0)
CAZ	4.5 (4.8)	6.4 (7.3)	8.2 (2.6)	6.0 (5.0)
CFX	2.6 (2.7)	3.6 (4.2)	8.2 (2.6)	4.3 (3.1)
FOM	0.0	0.9	1.2	0.6
NA	18.6	18.2	14.1	17.4

CPFX	0.0	0.9	1.2	0.6
NFLX	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0
Number resistant to one or more antimicrobials	143	96	76	315
Proportion resistant to one or more antimicrobials	91.7	87.3	89.4	89.7

Figures in parentheses indicate resistance rate in strains isolated from domestic chicken meat.

Table 21. The proportion (%) of antimicrobial-resistant food-derived *S.* Infantis (2015-2017)

	2015 (n=65)	2016 (n=33)	2017 (n=19)	2015-2017 (n=117)
ABPC	10.8	12.1	5.3	10.3
GM	0.0	3.0	0.0	0.9
KM	46.2	42.4	15.8	40.2
SM	81.5	72.7	68.4	76.9
TC	89.2	81.8	68.4	83.8
ST	18.5	30.3	0.0	18.8
CP	3.1	3.0	0.0	2.6
CTX	4.6	6.1	5.3	5.1
CAZ	3.1	9.1	5.3	5.1
CFX	4.6	9.1	5.3	6.0
FOM	0.0	0.0	0.0	0.0
NA	3.1	9.1	0.0	4.3
CPFX	0.0	0.0	0.0	0.0
NFLX	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0

Table 22. The proportion (%) of antimicrobial-resistant food-derived *S.* Schwarzengrund (2015-2017)

	2015 (n=47)	2016 (n=37)	2017 (n=44)	2015-2017 (n=128)
ABPC	17.0	5.4	0.0	7.8
GM	0.0	0.0	0.0	0.0
KM	85.1	86.5	77.3	82.8
SM	93.6	78.4	81.8	85.2
TC	95.7	83.8	79.5	86.7
ST	36.2	16.2	22.7	25.8
CP	19.1	10.8	4.5	11.7
CTX	0.0	0.0	2.3	0.8
CAZ	0.0	0.0	2.3	0.8
CFX	0.0	0.0	2.3	0.8
FOM	0.0	0.0	2.3	0.8
NA	25.5	18.9	6.8	17.2
CPFX	0.0	0.0	0.0	0.0
NFLX	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0

IPM	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0

Table 23. The proportion (%) of antimicrobial-resistant human-derived *S.* Infantis (2015-2017)

	2015 (n=34)	2016 (n=48)	2017 (n=62)	2015-2017 (n=144)
ABPC	0	2.1	0	0.7
GM	0	0	0	0
KM	20.6	14.6	9.7	13.9
SM	29.4	33.3	22.6	27.8
TC	47.1	33.3	25.8	33.3
ST	14.7	14.6	6.5	11.1
CP	0	0	0	0
CTX	0	2.1	0	0.7
CAZ	0	2.1	0	0.7
CFX	0	2.1	0	0.7
FOM	0	0	0	0
NA	8.8	4.2	6.5	6.3
CPFX	0	0	0	0
NFLX	0	0	0	0
AMK	0	0	0	0
IPM	0	0	0	0
MEPM	0	0	0	0

Table 24. The proportion (%) of antimicrobial-resistant human-derived *S.* Enteritidis (2015-2017)

	2015 (n=39)	2016 (n=40)	2017 (n=47)	2015-2017 (n=126)
ABPC	5.1	17.5	4.3	8.7
GM	0.0	0.0	0.0	0.0
KM	2.6	2.5	0.0	1.6
SM	12.8	12.5	12.8	12.7
TC	10.3	2.5	4.3	5.6
ST	5.1	0.0	0.0	1.6
CP	2.6	0.0	0.0	0.8
CTX	0.0	2.5	0.0	0.8
CAZ	0.0	2.5	0.0	0.8
CFX	0.0	0.0	0.0	0.0
FOM	0.0	0.0	0.0	0.0
NA	10.3	25.0	12.8	15.9
CPFX	0.0	0.0	0.0	0.0
NFLX	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0

Table 25. The proportion (%) of antimicrobial-resistant human-derived *S.* Saintpaul (2015-2017)

	2015 (n=27)	2016 (n=26)	2017 (n=42)	2015-2017 (n=95)
ABPC	7.4	7.7	14.3	10.5
GM	0.0	0.0	2.4	1.1
KM	0.0	3.8	4.8	3.2
SM	3.7	3.8	11.9	7.4
TC	40.7	15.4	21.4	25.3

ST	0.0	11.5	16.7	10.5
CP	3.7	0.0	14.3	7.4
CTX	0.0	0.0	11.9	5.3
CAZ	0.0	0.0	2.4	1.1
CFX	0.0	3.8	0.0	1.1
FOM	0.0	0.0	2.4	1.1
NA	7.4	3.8	19.0	11.6
CPFX	3.7	0.0	9.5	5.3
NFLX	3.7	0.0	0.0	1.1
AMK	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0

Table 26. The proportion (%) of antimicrobial-resistant human-derived S. 4:i:- (2015-2017)

	2015 (n=42)	2016 (n=9)	2017 (n=39)	2015-2017 (n=90)
ABPC	83.3	77.8	79.5	81.1
GM	2.4	0.0	2.6	2.2
KM	4.8	0.0	2.6	3.3
SM	83.3	88.9	82.1	83.3
TC	81.0	66.7	76.9	77.8
ST	0.0	0.0	7.7	3.3
CP	0.0	0.0	7.7	3.3
CTX	0.0	0.0	2.6	1.1
CAZ	0.0	0.0	2.6	1.1
CFX	0.0	0.0	2.6	1.1
FOM	0.0	11.1	0.0	1.1
NA	0.0	0.0	5.1	2.2
CPFX	0.0	0.0	0.0	0.0
NFLX	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0

Table 27. The proportion (%) of antimicrobial-resistant human-derived *S.* Thompson (2015-2017)

	2015 (n=28)	2016 (n=28)	2017 (n=31)	2015-2017 (n=87)
ABPC	0.0	10.7	0.0	3.4
GM	0.0	0.0	0.0	0.0
KM	7.1	0.0	0.0	2.3
SM	7.1	7.1	3.2	5.7
TC	3.6	7.1	6.5	5.7
ST	0.0	7.1	0.0	2.3
CP	0.0	7.1	0.0	2.3
CTX	0.0	10.7	0.0	3.4
CAZ	0.0	7.1	0.0	2.3
CFX	0.0	7.1	0.0	2.3
FOM	0.0	0.0	0.0	0.0
NA	0.0	0.0	0.0	0.0
CPFX	0.0	7.1	0.0	2.3
NFLX	0.0	0.0	0.0	2.3
AMK	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0

MEPM	0.0	0.0	0.0	0.0

Table 28. Resistance rates among *S.* Infantis, *S.* Schwarzengrund, and *S.* Manhattan detected in humans and food (2015-2017) (%)

	Infantis		Schwarzengrund		Manhattan	
	Human (n=144)	Food (n=117)	Human (n=52)	Food (n=128)	Human (n=37)	Food (n=29)
ABPC	0.7	10.3	3.8	7.8	2.7	13.8
GM	0.0	0.9	0.0	0.0	0.0	0.0
KM	13.9	40.2	61.5	82.8	0.0	0.0
SM	27.8	76.9	75.0	85.2	89.2	96.6
TC	33.3	83.8	73.1	86.7	89.2	89.7
ST	11.1	18.8	21.2	25.8	2.7	3.4
CP	0.0	2.6	0.0	11.7	0.0	0.0
CTX	0.7	5.1	3.8	0.8	0.0	13.8
CAZ	0.7	5.1	3.8	0.8	0.0	13.8
CFX	0.7	6.0	0.0	0.8	0.0	0.0
FOM	0.0	0.0	0.0	0.8	0.0	0.0
NA	6.3	4.3	21.2	17.2	10.8	20.7
CPFX	0.0	0.0	0.0	0.0	0.0	0.0
NFLX	0.0	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0

iii. *Neisseria gonorrhoeae*

Source: National Institute of Infectious Diseases

The 618, 675, and 982 *Neisseria gonorrhoeae* strains that were respectively isolated in 2015, 2016, and 2017 were tested for antimicrobial susceptibility (based on EUCAST breakpoints; Table 29). Ceftriaxone (CTRX)-resistant strains respectively accounted for 6.2%, 4.3%, and 4.3%. Strains assessed as resistant based on the CLSI Criteria (MIC ≥ 0.5 μg/mL) accounted for 0.6%, 0.4%, and 0.5%. 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 and 42.6% in 2017.

The CLSI Criteria do not provide a resistance breakpoint for azithromycin, but, using the azithromycin MIC distribution of strains with the 23S rRNA gene mutation as the basis, strains with a MIC of 2 μg/mL or higher are referred to as "non-wild-type." The resistance rate was investigated for reference purposes (see Appendix (8)) and a MIC of 2 μg/mL or higher was found in 3.2%, 4.0%, and 4.0% of strains respectively between 2015 and 2017. According to clinical assessments in Japan, strains indicating an azithromycin MIC of 1 μg/mL or higher can reasonably be regarded as resistant. Under this criterion (R ≥ 1 μg/mL), azithromycin-resistant strains accounted for 11%, 9.3%, and 11.2% of strains respectively between 2015 and 2017. 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 a therapeutic effect on more than 90% of strains.

Table 29. The proportion (%) of antimicrobial-resistant *Neisseria gonorrhoeae*

	2015 (618 strains)	2016 (675 strains)	2017 (982 strains)
CTRX	6.2	4.3	4.3
SPCM	0.0	0.0	0.0
AZM	13.0	33.5	42.6
PCG	38.4 (96.6)*	36.3 (96.9)*	37.8(99.0) *
CFIX	36.2	43.2	31.0
CPFX	79.5	78.0	75.8

The EUCAST (Appendix 8) standards were used for susceptibility and resistance assessment.

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

The EUCAST resistance breakpoints are as follows. CTRX (>0.125 μg/mL), SPCM (> 64 μg/mL), AZM (>0.5 μg/mL), PCR (> 1 μg/mL), CFIX (>0.125 μg/mL), CPFX (> 0.06 μg/mL)

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

The 32, 46, and 31 *Salmonella* Typhi strains that were respectively isolated in 2015, 2016, and 2017 were tested for antimicrobial susceptibility (Table 30). Ciprofloxacin (CPFX)-non-susceptible strains respectively accounted for 68.8%, 63.0%, and 83.9%. Strains with advanced resistance (MIC ≥ 4) to ciprofloxacin accounted for 12.5%, 23.9%, and 16.1%, respectively. Multidrug-resistant *Salmonella* Typhi that indicated resistance to ampicillin (ABPC), chloramphenicol (CP) and ST were isolated in all years (two strains in 2015, one strain in 2016, and four strains in 2017), including six strains (one each in 2015 and 2016, and four in 2017) that were non-susceptible to ciprofloxacin (CPFX).

The 30, 20, and 13 *Salmonella* Paratyphi A strains that were respectively isolated in 2015, 2016, and 2017 were tested for antimicrobial susceptibility (Table 31). Ciprofloxacin (CPFX)-non-susceptible strains respectively accounted for 83.3%, 85.0%, and 76.9%. No cefotaxime (CTX)-resistant strains were isolated among the *Salmonella* Typhi and *Salmonella* Paratyphi A.

The 105, 73, and 91 *Shigella* spp. strains that were respectively isolated in 2015, 2016, and 2017 were tested for antimicrobial susceptibility (Table 32). ST-resistant strains respectively accounted for 81.0%, 80.8%, and 73.6%; ciprofloxacin-non-susceptible strains for 45.7%, 35.6%, and 35.2%; and cefotaxime-resistant strains for 5.7%, 16.4%, and 13.2%.

Table 30. The proportion (%) of antimicrobial-resistant *Salmonella* Typhi

	2015 (32 strains)	2016 (46 strains)	2017 (31 strains)
ABPC	5.7	2.2	12.9
CP	5.7	2.2	12.9
ST	5.7	2.2	12.9
NA	68.8	63.0	83.9
CPFX	68.8 (12.5)*	63.0 (23.9)*	83.9 (16.1*)
CTX	0.0	0.0	0.0

* Advanced resistance to fluoroquinolone

Table 31. The proportion (%) of antimicrobial-resistant *Salmonella* Paratyphi A

	2015 (30 strains)	2016 (20 strains)	2017 (13 strains)
ABPC	0.0	0.0	0.0
CP	0.0	0.0	0.0
ST	0.0	0.0	0.0
NA	80.0	80.0	76.9
CPFX	83.3	83.3	76.9
CTX	0.0	0.0	0.0

Table 32. The proportion (%) of antimicrobial-resistant *Shigella* spp.

	2015 (105 strains)	2016 (73 strains)	2017 (91 strains)
ABPC	21.9	42.5	31.9
CP	11.4	24.7	26.4
ST	81.0	80.8	73.6
NA	63.8	52.1	52.8
CPFX	45.7	35.6	35.2
CTX	5.7	16.4	13.2

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 2017, the proportion of resistance to major antituberculosis antibiotics—isoniazid (INH), rifampicin (RFP), streptomycin (SM), and ethambutol (EB)—remained mostly at the same level, but there was a rise of up to 1.1 percentage points in streptomycin (SM) resistance in 2017 compared with the levels between 2012 and 2016. The number of newly reported cases with multidrug-resistant tuberculosis that are resistant at least to both INH and RFP remained in the range of 50 to 60 (0.5-0.7%) per year (Table 33).

Table 33. Newly Notified Patients with Culture-positive Pulmonary Tuberculosis: Trends in Drug Susceptibility at the Time of Notification

	2011	2012	2013	2014	2015	2016	2017
Culture-positive patients, N	10,915	11,261	10,523	10,259	10,035	9878	9,580
INH-resistant, n (%)*	386 (4.8)	380 (4.6)	369 (4.8)	349 (4.6)	372 (4.9)	369 (4.8)	383 (4.9)
RFP-resistant, n (%)*	86 (1.1)	73 (0.9)	64 (0.8)	76 (1.0)	77 (1.0)	74 (1.0)	80 (1.0)
INH & RFP-resistant†, n (%)*	60 (0.7)	60 (0.7)	47 (0.4)	56 (0.5)	48 (0.5)	49 (0.6)	52 (0.7)
SM-resistant, n (%)§	-	509 (6.1)	475 (6.2)	469 (6.2)	476 (6.3)	461 (6.0)	557 (7.1)
EB-resistant, n (%)¶	-	151 (1.8)	106 (1.4)	130 (1.7)	129 (1.7)	100 (1.3)	106 (1.3)

* The denominator was defined as the number of patients with recorded INH- and RFP-susceptibility testing results among all culture-positive patients: 8,046 (73.7%) patients in 2011, 8,347 (74.1%) patients in 2012, 7,701 (73.2%) patients in 2013, 7,645 (74.5%) patients in 2014, 7,630 (76.0%) patients in 2015, 7,732 (78.3%) patients in 2016, and 7,891 (82.4%) patients in 2017.

-: Not under surveillance

† 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, 48 patients in 2015, 47 patients in 2016 and 51 patients in 2017.

¶ 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, 19 in 2015, 17 in 2016 and 14 in 2017).

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 34). In 2016, among 274,132 surgical operations undertaken at 730 institutions, SSI were reported in 15,674 (5.7%) 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 1.3-1.5 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 2016 (Table 35). 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 occurred between 48 hours after admission to ICU and discharge from ICU.

i. Surgical site infection

Table 34. The trend of reported SSI cases

	2011	2012	2013	2014	2015	2016
Total SSI cases per total surgical operations (%)*	**6.0**	**6.8**	**6.5**	**6.0**	**5.8**	**5.7**
Participated medical institutions	333	363	442	552	671	730
Total surgical operations	127,731	129,825	161,077	207,244	251,832	274,132
Total SSI cases	7,719	8,771	10,445	12,508	14,701	15,674

* Total SSI cases per total surgical 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.[6]

ii. Infections at ICU

Table 35. Incidence rates of infection at ICU

		2011	2012	2013	2014	2015	2016
Ventilator-associated pneumonia	**Total infection incidence rate***	**1.7**	**1.4**	**1.3**	**1.4**	**1.5**	**1.5**
	Total infections at monitored medical institutions	382	327	324	395	522	499

Urinary tract infection	**Total infection incidence rate***	**0.5**	**0.5**	**0.6**	**0.5**	**0.5**	**0.6**
	Total infections at monitored medical institutions	111	124	143	148	190	219
Catheter-related bloodstream infection	**Total infection incidence rate***	**0.7**	**0.7**	**0.8**	**0.7**	**0.7**	**0.8**
	Total infections at monitored medical institutions	168	162	204	205	240	263

* 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.[7]

7) *Clostridioides (Clostridium) difficile* infection

Clostridioides (Clostridium) difficile is a spore-forming gram-positive anaerobic bacillus that colonizes the intestines of about 10% of healthy adults.[8] *Clostridioides (Clostridium) 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.[9]

The CDI incidence rate in Japan is 0.8-4.7 cases per 10,000 patient days, while prevalence is 0.3-5.5 cases per 1,000 admissions.[10] However, consideration must be given to the impact of such factors as the lack of both uniform testing methods and a standardized definition of recurrence, and differences in the average length of admission compared with other countries. The CDI incidence rate among patients with diarrhea is reported to be 7.9 cases per 10,000 patient days.[11] No surveillance of CDI is carried out in Japan. CDI surveillance is due to be launched in 2019 via Japan Surveillance for Infection Prevention and Health-care Epidemiology (J-SIPHE).

(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 used EUCAST values or were determined microbiologically (midpoint of a bimodal MIC distribution).

Bacteria derived from diseased animals

i. *Salmonella* spp.

Monitoring of antimicrobial resistance on 11 agents was carried out between 2011 and 2016. While resistance to ampicillin (ABPC) and tetracycline (TC) was observed in more than 40% of strains in 2016, resistance rates to cefotaxime (CTX), ciprofloxacin (CPFX), and colistin (CL)—critically important antimicrobials for human medicine—were below 5%. It must be noted that the BPs of cefazolin (CEZ), CPFX, and CL were lowered between 2015 and 2016 to bring them into line with the values established by CLSI (Table 36). The most common *Salmonella* serotypes isolated from diseased food-producing animals were Typhimurium and its monophasic variant 4:i:- among cattle; Typhimurium, 4:i:-, and Choleraesuis among pigs; and Schwarzengrund and Infantis among chickens (Table 37).

Table 36. The proportion (%) of antimicrobial-resistant *Salmonella* spp. isolated from diseased animals

Agent	BP	Animal	2011	2012	2013	2014	2015	2016
ABPC	32*	Cattle	28.0	32.9	60.7	61.9	56.6	50.0
		Pigs	25.4	25.3	45.0	41.4	46.9	41.1
		Chickens	12.0	9.4	4.0	3.9	14.3	-
CEZ	32 (8* in 2016)	Cattle	10.0	1.2	8.9	7.9	7.9	22.9
		Pigs	0.0	0.0	0.0	0.0	6.1	23.2
		Chickens	0.0	3.1	4.0	0.0	0.0	-
CTX	4*	Cattle	10.0	1.2	8.9	7.9	7.9	4.3
		Pigs	0.0	0.0	0.0	0.0	4.1	0.0
		Chickens	0.0	0.0	4.0	0.0	0.0	-
GM	16*	Cattle	0.0	0.0	0.0	3.2	7.9	4.3
		Pigs	6.3	3.6	15.0	15.5	8.2	17.9
		Chickens	0.0	0.0	2.0	0.0	0.0	-
KM	64*	Cattle	12.0	3.7	25.0	14.3	21.1	25.7
		Pigs	9.5	12.0	6.7	8.6	6.1	10.7
		Chickens	24.0	15.6	22.0	29.4	42.9	-
TC	16*	Cattle	30.0	32.9	66.1	50.8	55.3	42.9
		Pigs	61.9	53.0	66.7	60.3	61.2	58.9
		Chickens	36.0	34.4	30.0	39.2	42.9	-
NA	32*	Cattle	2.0	7.3	1.8	3.2	11.8	5.7
		Pigs	15.9	21.7	5.0	15.5	6.1	7.1
		Chickens	8.0	6.3	8.0	3.9	28.6	-
CPFX	4 (1* in 2016)	Cattle	0.0	0.0	0.0	0.0	0.0	0.0
		Pigs	0.0	0.0	0.0	0.0	0.0	3.6
		Chickens	0.0	0.0	0.0	0.0	0.0	-
CL	16 (4 in 2016)	Cattle	0.0	0.0	0.0	0.0	0.0	1.4
		Pigs	0.0	0.0	1.7	0.0	0.0	3.6
		Chickens	0.0	3.1	2.0	0.0	0.0	-
CP	32*	Cattle	14.0	12.2	10.7	17.5	22.4	12.9
		Pigs	12.7	13.3	11.7	25.9	12.2	8.9
		Chickens	0.0	6.3	6.0	3.9	14.3	-
TMP (SMX/TMP in 2011)	16* (SMX/TMP 76/4*)	Cattle	2.0	1.2	1.8	6.3	13.2	4.3
		Pigs	25.4	21.7	36.7	32.8	22.4	21.4
		Chickens	20.0	15.6	14.0	29.4	42.9	-
Strains tested (n)		Cattle	50	82	56	63	76	70
		Pigs	63	83	60	58	49	56
		Chickens	25	32	50	51	7	-

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

Table 37. Number of strains of *Salmonella enterica* isolated from diseased food-producing animals by serotype (FY2014-15)

Serotypes	Cattle	Pigs	Chickens	Total	(%)
Typhimurium	41	43	1	85	28.0
4:i:-	50	18	0	68	22.4
Choleraesuis	0	14	0	14	4.6
Schwarzengrund	0	0	14	14	4.6
Derby	2	9	0	11	3.6
Infantis	1	1	8	10	3.3
Braenderup	1	3	5	9	3.0
Newport	5	2	1	8	2.6
Mbandaka	3	0	5	8	2.6
Thompson	4	1	2	7	2.3
Enteritidis	0	0	6	6	2.0
Dublin	5	0	0	5	1.6
Rissen	2	2	0	4	1.3
Stanley	2	0	0	2	0.7
Tennessee	0	0	2	2	0.7
Others	23	14	14	51	16.8
Total	139	107	58	304	100.0

ii *Staphylococcus aureus*

Monitoring of antimicrobial resistance on 8 agents was carried out between 2011 and 2016. Ampicillin (ABPC) and tetracycline (TC) resistance in pig-derived strains was observed to exceed 50% in 2016. Resistance rates to all antimicrobials other than gentamicin (GM) were observed to be higher in strains isolated from pigs than in those derived from cattle and chickens. Resistance to ciprofloxacin (CPFX), which is a critically important antimicrobial for human medicine, was 11.1% in pig-derived strains, but less than 4% in strains isolated from cattle and chickens (Table 38).

Table 38. The proportion (%) of antimicrobial-resistant *Staphylococcus aureus* isolated from diseased animal

Agent*	BP	Animal	2011	2012	2013	2014	2015	2016
ABPC	0.5	Cattle	5.5	13.6	11.0	11.1	21.3	7.8
		Pigs	-	-	-	-	-	75.6
		Chickens	0.0	25.0	0.0	15.4	50.0	3.7
SM	64	Cattle	6.4	2.3	2.8	1.1	2.7	1.4
		Pigs	-	-	-	-	-	33.3
		Chickens	0.0	10.0	0.0	7.7	16.7	3.7
GM	16†	Cattle	0.9	2.3	1.8	0.0	1.3	0.0
		Pigs	-	-	-	-	-	2.2
		Chickens	0.0	15.0	0.0	0.0	0.0	3.7
EM	8†	Cattle	1.8	3.4	5.5	0.0	6.7	2.8
		Pigs	-	-	-	-	-	37.8
		Chickens	50.0	55.0	0.0	15.4	16.7	22.2
TC	16†	Cattle	0.0	2.3	8.3	5.5	6.7	0.0
		Pigs	-	-	-	-	-	57.8
		Chickens	37.5	5.0	0.0	16.7	16.7	33.3
CP	32†	Cattle	0.0	0.0	0.9	0.0	1.3	0.0
		Pigs	-	-	-	-	-	22.2
		Chickens	0.0	0.0	0.0	15.4	33.3	3.7
CPFX	4†	Cattle	0.0	0.0	0.9	0.0	1.3	0.7
		Pigs	-	-	-	-	-	11.1

	Chickens	25.0	0.0	4.2	15.4	33.3	3.7
Strains tested (n)	Cattle	109	88	109	91	75	141
	Pigs	-	-	-	-	-	45
	Chickens	8	20	24	12	6	27

The unit of BP is μg/mL.

-: No data for pigs was listed before 2016, because the number of strains was less than five each year.

* While NA was also included in the scope of monitoring, its proportion of NA-resistant strains was not listed because BP could not be established. † BP follows CLSI Criteria.

iii. *Escherichia coli*

Monitoring of antimicrobial resistance on 12 agents was carried out between 2012 and 2016. In 2016, antimicrobial resistance in excess of 40% was observed among strains isolated from food-producing animals as follows: ampicillin (ABPC), kanamycin (KM), and nalidixic acid (NA) resistance among cattle and chickens; streptomycin (SM) and tetracycline (TC) resistance among cattle, pigs, and chickens; and colistin (CL), chloramphenicol (CP), and trimethoprim (TMP) resistance among pigs. Resistance rates to all antimicrobials other than cefotaxime (CTX), KM, and NA were observed to be higher in strains isolated from pigs than in those derived from cattle and chickens. Resistance to CTX, ciprofloxacin (CPFX), and CL, which are critically important antimicrobials for human medicine, was in the ranges 2.9-7.8%, 8.7-24.5%, and 8.7-56.9, respectively. It must be noted that the BPs of cefazolin (CEZ) and CL were lowered between 2015 and 2016 to bring them into line with the values established by CLSI (Table 39).

Table 39. The proportion (%) of antimicrobial-resistant *Escherichia coli* isolated from diseased animals

Agent	BP	Animal	2012†	2013†	2014†	2015	2016
ABPC	32*	Cattle	-	61.4	57.8	63.8	37.7
		Pigs	-	65.2	50.4	57.4	74.5
		Chickens	75.6	54.2	-	60.4	43.5
CEZ	32 (8* in 2016)	Cattle	-	21.1	6.7	14.9	15.6
		Pigs	-	10.1	6.1	9.3	34.3
		Chickens	40.2	16.7	-	14.6	15.2
CTX	4*	Cattle	-	10.5	6.7	8.5	7.8
		Pigs	-	2.5	0.0	3.7	2.9
		Chickens	37.8	14.6	-	10.4	6.5
SM	32	Cattle	-	-	68.9	78.7	49.4
		Pigs	-	-	64.3	66.7	74.5
		Chickens	-	-	-	60.4	56.5
GM	16*	Cattle	-	17.5	6.7	12.8	10.4
		Pigs	-	24.1	8.7	19.4	21.6
		Chickens	6.1	3.1	-	2.1	10.9
KM	64*	Cattle	-	38.6	26.7	29.8	16.9
		Pigs	-	34.2	33.9	31.5	46.1
		Chickens	51.2	35.4	-	39.6	50.0
TC	16*	Cattle	-	50.9	66.7	66.0	54.5
		Pigs	-	79.1	75.7	75.9	87.3
		Chickens	74.4	61.5	-	70.8	78.3
NA	32*	Cattle	-	29.8	33.3	36.2	18.2
		Pigs	-	60.1	52.2	50.0	48.0
		Chickens	73.2	59.4	-	52.1	56.5
CPFX	4*	Cattle	-	19.3	24.4	34.0	11.7
		Pigs	-	36.1	23.5	32.4	24.5
		Chickens	22.0	25.0	-	8.3	8.7
CL	16 (4* in 2016)	Cattle	-	5.3	6.7	0.0	10.4
		Pigs	-	3.2	0.0	2.8	56.9§
		Chickens	2.4	1.0	-	0.0	8.7
CP	32*	Cattle	-	21.1	28.9	46.8	19.5
		Pigs	-	64.6	64.3	61.1	69.6
		Chickens	22	25	-	16.7	21.7
TMP	16	Cattle	-	22.8	33.3	44.7	23.4
		Pigs	-	49.4	59.1	64.8	62.7
		Chickens	31.7	33.3	-	33.3	23.9
Strains tested (n)		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.
§If the microbiological BP of 16 used by JVARM is applied, CL resistance in pig-derived strains was 2.9% in 2016.

Bacteria derived from healthy animals in farms

i. *Campylobacter jejuni*

Monitoring of antimicrobial resistance on 8 agents was carried out between 2011 and 2015. Ampicillin (ABPC) resistance in strains isolated from layers was observed to exceed 40% in 2015, as was tetracycline (TC) resistance in cattle- and broiler-derived strains. On the other hand, streptomycin (SM) resistance was less than 5% and no resistance to erythromycin (EM) or chloramphenicol (CP) was observed. Resistance to ciprofloxacin (CPFX), which is a critically important antimicrobial for human medicine, ranged between 16.1% and 35.6% (Table 40).

Table 40. 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 tested (n)		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 was not listed because BP could not be established.
† BP follows CLSI Criteria.

ii. *Campylobacter coli*

Monitoring of antimicrobial resistance on 8 agents was carried out between 2011 and 2015. Resistance to streptomycin (SM), tetracycline (TC), nalidixic acid (NA), and ciprofloxacin (CPFX) exceeding 50% was observed in pig-derived strains in 2015. On the other hand, ampicillin (ABPC) resistance was less than 10% and no resistance to chloramphenicol (CP) was observed. Resistance to CPFX, which is a critically important antimicrobial for human medicine, was 57.9% (Table 41).

Table 41. 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 tested (n)	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.

Monitoring of antimicrobial resistance on 13 agents was carried out between 2011 and 2015. Resistance to dihydrostreptomycin (DSM), kanamycin (KM), erythromycin (EM), and tylosin (TS) in strains isolated from broilers was observed to exceed 40% in 2015, as was oxytetracycline (OTC) and lincomycin (LCM) resistance in pig- and broiler-derived strains. On the other hand, no ampicillin (ABPC) resistance was observed, while gentamicin (GM) resistance was below 10%. Resistance to enrofloxacin (ERFX), which is a critically important antimicrobial for human medicine, ranged between 6.8% and 20.2% (Table 42).

Among *Enterococcus* spp. in 2015, resistant strains accounted for between 2.3% (5 out of 220 cattle-derived strains) and 61.0% (89 out of 146 broiler-derived strains) of *Enterococcus faecalis*, and for between 7.5% (11 out of 146 broiler-derived strains) and 11.4% (25 out of 220 cattle-derived strains and 13 out of 114 layer-derived strains) of *Enterococcus faecium*. Resistance to enrofloxacin (ERFX), which is a critically important antimicrobial for human medicine, ranged between 6.8% and 20.2% among *Enterococcus* spp., but whereas the figures for *Enterococcus faecalis* ranged between 0.0% and 6.3%, those for *Enterococcus faecium* varied from 28.0% to as high as 92.3% (Table 43, 44).

Table 42. 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 tested (n)	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 proportion 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 was calculated using cut-off of 64 μg/mL.

Table 43. The proportion (%) of antimicrobial-resistant *Enterococcus faecalis* derived from healthy animals

Agent*	BP	Animal	2011	2012	2013	2014	2015
ABPC	16†	Cattle	0.0	0.0	-	0.0	0.0
		Pigs	0.0	2.6	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
DSM	128	Cattle	25.0	35.7	-	33.3	20.0
		Pigs	92.3	51.3	68.2	37.5	62.5
		Broilers	61.1	40.0	80.0	58.1	62.7
		Layers	47.7	34.2	62.7	42.9	36.0
GM	32	Cattle	12.5	0.0	-	0.0	0.0
		Pigs	23.1	12.8	13.6	0.0	0.0
		Broilers	1.9	16.7	16.4	9.7	11.9
		Layers	13.8	6.6	13.4	3.6	3.4
KM	128	Cattle	12.5	0.0	-	16.7	0.0
		Pigs	61.5	35.9	27.3	12.5	31.3
		Broilers	35.2	37.8	50.9	41.9	46.3
		Layers	26.2	31.6	22.4	14.3	21.3
OTC	16	Cattle	50.0	0.0	-	83.3	20.0
		Pigs	100.0	61.5	77.3	100.0	68.8
		Broilers	64.8	68.9	85.5	64.5	68.7
		Layers	36.9	57.9	49.3	39.3	48.3
CP	32†	Cattle	0.0	0.0	-	33.3	20.0
		Pigs	61.5	48.7	31.8	87.5	31.3
		Broilers	5.6	10.0	21.8	6.5	19.4
		Layers	0.0	5.3	7.5	1.8	1.1
EM	8†	Cattle	0.0	0.0	-	50.0	0.0
		Pigs	76.9	53.8	59.1	62.5	56.3
		Broilers	50.0	53.3	49.1	48.4	44.8
		Layers	21.5	27.6	23.9	17.9	14.6
LCM	128	Cattle	0.0	0.0	-	50.0	0.0
		Pigs	76.9	56.4	63.6	62.5	62.5
		Broilers	51.9	54.4	50.9	48.4	44.8
		Layers	23.1	27.6	22.4	17.9	14.6
ERFX	4	Cattle	0.0	0.0	-	0.0	0.0
		Pigs	15.4	0.0	0.0	0.0	6.3
		Broilers	11.1	0.0	5.5	6.5	1.5
		Layers	1.5	2.6	1.5	3.6	4.5
TS§	64	Cattle	0.0	0.0	-	50.0	0.0
		Pigs	76.9	51.3	54.5	62.5	50.0
		Broilers	50.0	55.6	49.1	48.4	44.8
		Layers	21.5	27.6	22.4	17.9	14.6
Strains tested (n)		Cattle	8	14	-	6	5
		Pigs	13	39	22	8	16
		Broilers	54	90	55	31	67
		Layers	65	76	67	56	89

The unit of BP is μg/mL.

-: No data for cattle was listed in 2013, because the number of strains was less than five.

* While BC, SNM and VGM were also included in the scope of survey, the proportion of BC-, SNM- and VM-resistant strains was 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 was calculated using cut-off of 64 μg/mL.

Table 44. The proportion (%) of antimicrobial-resistant *Enterococcus faecium* derived from healthy animals

Agent*	BP	Animal	2011	2012	2013	2014	2015
ABPC	16†	Cattle	0.0	0.0	0.0	0.0	0.0
		Pigs	0.0	0.0	0.0	0.0	0.0
		Broilers	4.1	2.4	2.2	1.9	0.0
		Layers	0.0	0.0	0.0	0.0	0.0
DSM	128	Cattle	10.5	22.7	20.0	7.4	16.0
		Pigs	43.3	30.3	22.2	40.4	31.3
		Broilers	18.4	28.6	23.9	23.4	23.1
		Layers	7.1	6.3	0.0	10.1	9.1
GM	32	Cattle	0.0	2.3	0.0	7.4	0.0
		Pigs	3.3	0.0	0.0	0.0	6.3
		Broilers	6.1	3.6	2.2	0.9	0.0
		Layers	0.0	1.6	0.0	0.0	0.0
KM	128	Cattle	36.8	34.1	60.0	29.6	24.0
		Pigs	53.3	30.3	61.1	59.6	43.8
		Broilers	40.8	34.5	73.9	45.8	15.4
		Layers	47.6	35.9	54.5	43.5	45.5
OTC	16	Cattle	23.7	9.1	0.0	14.8	16.0
		Pigs	56.7	42.4	50.0	53.2	50.0
		Broilers	65.3	63.1	67.4	61.7	61.5
		Layers	11.9	7.8	22.7	20.3	9.1
CP	32†	Cattle	2.6	0.0	0.0	0.0	0.0
		Pigs	3.3	0.0	16.7	12.8	12.5
		Broilers	2.0	4.8	2.2	12.1	7.7
		Layers	0.0	0.0	0.0	1.4	0.0
EM	8†	Cattle	28.9	11.4	30.0	11.1	8.0
		Pigs	33.3	15.2	50.0	27.7	37.5
		Broilers	24.5	32.1	23.9	22.4	38.5
		Layers	19.0	6.3	9.1	8.7	9.1
LCM	128	Cattle	10.5	9.1	0.0	11.1	4.0
		Pigs	43.3	39.4	38.9	40.4	37.5
		Broilers	18.4	31.0	28.3	24.3	30.8
		Layers	2.4	0.0	0.0	11.6	0.0
ERFX	4	Cattle	34.2	36.4	30.0	33.3	28.0
		Pigs	40.0	45.5	38.9	40.4	56.3
		Broilers	65.3	65.5	87.0	61.7	92.3
		Layers	40.5	56.3	54.5	52.2	63.6
TS§	64	Cattle	7.9	9.1	0.0	7.4	0.0
		Pigs	30.0	12.1	33.3	27.7	31.3
		Broilers	8.2	26.2	15.2	15.0	30.8
		Layers	0.0	1.6	0.0	5.8	0.0
Strains tested (n)		Cattle	38	44	10	27	25
		Pigs	30	33	18	47	16
		Broilers	49	84	46	107	13
		Layers	42	64	22	69	11

The unit of BP is μg/mL.

* While BC, SNM and VGM were also included in the scope of survey, the proportion of BC-, SNM- and VM-resistant strains was 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 was calculated using cut-off of 64 μg/mL.

iv. Escherichia coli

Monitoring of antimicrobial resistance on 12 agents was carried out between 2011 and 2015. Ampicillin (ABPC) resistance in strains isolated from broilers was observed to exceed 40% in 2015, as was tetracycline (TC) resistance in pig- and broiler-derived strains. On the other hand, cefazolin (CEZ) and gentamicin (GM) resistance was less than 5%. In the realm of critically important antimicrobials for human medicine, resistance rates to cefotaxime

(CTX) and ciprofloxacin (CPFX) were respectively less than 3% and less than 10%, while no resistance to colistin (CL) was observed. The proportion of cefazolin (CEZ)- and cefotaxime (CTX)-resistant strains in broilers had declined from 2012 (Table 45). 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.[38]

Table 45. 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 tested (n)		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*

Monitoring of antimicrobial resistance on 12 agents was carried out between 2012 and 2015. Ampicillin (ABPC) and streptomycin (SM) resistance in strains isolated from chickens was observed to exceed 40% in 2015, as was tetracycline (TC) resistance in pig- and chicken-derived strains. On the other hand, cefazolin (CEZ) and gentamicin (GM) resistance was less than 4%. In the realm of critically important antimicrobials for human medicine, resistance rates to cefotaxime (CTX), ciprofloxacin (CPFX), and colistin (CL) were respectively less than 3%, less than 5%, and less than 1% (Table 46).

Table 46. 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 tested (n)		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*

Monitoring of antimicrobial resistance on 8 agents was carried out between 2012 and 2015. Resistance to tetracycline (TC), nalidixic acid (NA), and ciprofloxacin (CPFX) exceeding 40% was observed in cattle-derived strains in 2015. On the other hand, rates of resistance to streptomycin (SM), erythromycin (EM), and chloramphenicol (CP) were less than 4%, less than 2%, and less than 2%, respectively. Resistance to CPFX, which is a critically important antimicrobial for human medicine, was 40.8% in cattle-derived strains and 26.6% in chicken-derived strains (Table 47).

Table 47. 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 tested (n)		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*

Monitoring of antimicrobial resistance on 8 agents was carried out between 2012 and 2015. Resistance to streptomycin (SM), tetracycline (TC), nalidixic acid (NA), and ciprofloxacin (CPFX) exceeding 40% was observed in pig-derived strains in 2015. On the other hand, chloramphenicol (CP) resistance was less than 10%. Resistance to CPFX, which is a critically important antimicrobial for human medicine, was 47.7% (Table 48).

Table 48. 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 tested (n)		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.

Monitoring of antimicrobial resistance on 13 agents was carried out between 2012 and 2014, but VCM was added in 2015, bringing the number monitored to 14. Resistance to dihydrostreptomycin (DSM), kanamycin (KM), erythromycin (EM), and lincomycin (LCM) in strains isolated from chickens was observed to exceed 40% in 2015, as was oxytetracycline (OTC) resistance in pig- and chicken-derived strains. On the other hand, gentamicin (GM) resistance was less than 10% and no resistance to ampicillin (ABPC) was observed. In the realm of critically important antimicrobials for human medicine, resistance to enrofloxacin (ERFX) ranged between 0.4% and 13.3%, but no resistance to vancomycin (VCM) was observed (Table 49).

Among *Enterococcus* spp. in 2015, resistant strains accounted for between 5.2% (14 out of 269 cattle-derived strains) and 54.1% (91 out of 181 chicken-derived strains) of *Enterococcus faecalis*, and for between 2.2% (6 out of 269 cattle-derived strains) and 17.1% (31 out of 181 chicken-derived strains) of *Enterococcus faecium*. Resistance to enrofloxacin (ERFX), which is a critically important antimicrobial for human medicine, was 0.4% in cattle-derived and 13.3% in chicken-derived strains of *Enterococcus* spp., but whereas the figure for *Enterococcus faecalis* was 0.0%, the figures for *Enterococcus faecium* were 16.7% and as high as 71.0%, respectively. No vancomycin (VCM) resistance was observed (Table 50, 51).

Table 49. 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 tested (n)		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 proportion of BC-, SNM- and VGM-resistant 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.

Table 50. The proportion (%) of antimicrobial-resistant *Enterococcus faecalis* 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	90.6	36.4	35.7
		Pigs	88.2	62.5	100.0
		Chickens	76.9	53.8	72.4
GM	32	Cattle	68.8	27.3	0.0
		Pigs	76.5	12.5	15.4
		Chickens	35.6	9.9	14.3
KM	128	Cattle	71.9	9.1	14.3
		Pigs	72.9	12.5	69.2
		Chickens	71.2	57.1	66.3
OTC	16	Cattle	31.3	27.3	28.6
		Pigs	64.7	87.5	92.3

		Chickens	75.0	67.0	70.4
CP	32§	Cattle	9.4	0.0	0.0
		Pigs	30.6	62.5	53.8
		Chickens	17.3	13.2	9.2
EM	8§	Cattle	21.9	9.1	0.0
		Pigs	51.8	62.5	69.2
		Chickens	58.7	64.8	60.2
LCM	128	Cattle	34.4	9.1	0.0
		Pigs	76.5	75.0	92.3
		Chickens	57.7	45.1	54.1
ERFX	4	Cattle	3.1	0.0	0.0
		Pigs	5.9	0.0	7.7
		Chickens	2.9	1.1	0.0
TS	64	Cattle	6.3	0.0	0.0
		Pigs	50.6	62.4	69.2
		Chickens	57.7	65.9	53.1
VCM	32	Cattle	-	-	0.0
		Pigs	-	-	0.0
		Chickens	-	-	0.0
Strains tested (n)		Cattle	32	11	14
		Pigs	85	8	13
		Chickens	104	91	98

The unit of BP is μg/mL.
* While BC, SNM, and VGM were also included in the scope of monitoring, the proportion of BC-, SNM- and VGM-resistant 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.

Table 51. The proportion (%) of antimicrobial-resistant *Enterococcus faecium* 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	2.4	0.0	0.0
DSM	128	Cattle	22.7	33.3	0.0
		Pigs	30.3	58.3	0.0
		Chickens	28.6	13.9	16.1
GM	32	Cattle	2.3	0.0	0.0
		Pigs	0.0	0.0	0.0
		Chickens	3.6	2.8	3.2
KM	128	Cattle	34.1	33.3	16.7
		Pigs	30.3	25.0	72.7
		Chickens	34.5	33.3	35.5
OTC	16	Cattle	9.1	0.0	16.7
		Pigs	42.4	41.7	9.1
		Chickens	63.1	58.3	64.5
CP	32§	Cattle	0.0	0.0	0.0
		Pigs	0.0	25.0	0.0
		Chickens	4.8	8.3	6.5
EM	8§	Cattle	11.4	0.0	33.3
		Pigs	15.2	58.3	54.5
		Chickens	32.1	30.6	35.5
LCM	128	Cattle	9.1	0.0	0.0
		Pigs	39.4	50.0	9.1
		Chickens	31.0	19.4	29.0
ERFX	4	Cattle	36.4	0.0	16.7
		Pigs	45.5	25.0	0.0
		Chickens	65.5	13.9	71.0
TS	64	Cattle	9.1	0.0	0.0
		Pigs	12.1	16.7	0.0
		Chickens	26.2	19.4	22.6
VCM	32	Cattle	-	-	0.0

	Pigs	-	-	0.0
	Chickens	-	-	0.0
Strains tested (n)	Cattle	44	6	6
	Pigs	84	12	11
	Chickens	64	36	31

The unit of BP is μg/mL.
* While BC, SNM, and VGM were also included in the scope of monitoring, the proportion of BC-, SNM- and VGM-resistant 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.

Monitoring of antimicrobial resistance on 12 agents was carried out between 2012 and 2015 in respect of strains derived from chicken. Resistance to streptomycin (SM), kanamycin (KM), tetracycline (TC), and sulfamethoxazole-trimethoprim (SMX/TMP) exceeding 40% was observed in chicken-derived strains in 2015. On the other hand, cefazolin (CTX) and chloramphenicol (CP) resistance was less than 2% and no resistance to gentamicin (GM) was observed. In the realm of critically important antimicrobials for human medicine, the rate of resistance to cefotaxime (CTX) was 1.6%, but no resistance to colistin (CL) or ciprofloxacin (CPFX) was observed (Table 52). The *Salmonella* serotypes most commonly isolated from poultry slaughterhouses in FY2014-15 were Schwarzengrund, Infantis, Manhattan, and Typhimurium (Table 53).

Table 52. 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 tested		Chickens	94	118	128	123

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

Table 53. Serotypes of *Salmonella enterica* derived from poultry slaughterhouses (FY2014-15)

Serotypes	Number of strains isolated	(%)
Schwarzengrund	115	45.8
Infantis	66	26.3
Manhattan	24	9.6
Typhimurium	23	9.2
Others	23	9.2
Total	251	100.0

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 environment. 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 surveillance of trends in antimicrobial resistance in aquaculture, the scope of surveillance was expanded to all farmed fish species in FY2017. The results of antimicrobial susceptibility monitoring of *Lactococcus garvieae* and *Vibrio* spp. are due to be published once available.

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

The monitoring of antimicrobial resistance was conducted on 4 agents that had efficacy on the streptococcal diseases from 2011 to 2014. Antimicrobial resistance was 0.0-92.6%, 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 54).

Table 54. 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 tested (n)		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.*piscicida* derived from diseased fish (Seriola)

The monitoring of antimicrobial resistance was conducted on 5 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 55).

Table 55. The proportion (%) of antimicrobial-resistant pseudotuberculosis-causing bacteria (*Photobacterium damselae* subsp. *piscicida*)

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 tested (n)		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 was resistant to those agents was 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" (hereinafter referred to as "Working Group"), in order to collect inputs from experts concerning monitoring methods for antimicrobial-resistant bacteria in companion animals, and to conduct a pilot surveillance. Informed by their input, routine monitoring of antimicrobial-resistant bacteria derived from diseased dogs and cats was launched in FY2017. Antimicrobial susceptibility tests measured the MIC values of antimicrobials in respect of the bacterial strains collected, using a

broth microdilution method compliant with the CLSI Criteria. For agents with a BP indicated by the CLSI, susceptibility was interpreted using the CLSI Criteria. The BPs of the other antimicrobial agents used EUCAST values or were determined microbiologically (midpoint of a bimodal MIC distribution).

It must be noted that monitoring of antimicrobial resistance in bacteria derived from diseased animals has the potential to be affected by the use of antimicrobials in treatment or by the incidence of diseases. As with food-producing animals, obtaining information about antimicrobial resistance trends in healthy companion animals to serve as a baseline is considered important. Accordingly, as well as ongoing monitoring of diseased animals, there are plans to move forward with a study of healthy companion animals, taking into account the deliberations by the Working Group.

i. *Escherichia coli*

Monitoring of antimicrobial resistance on 15 agents was carried out in 2017. Ampicillin (ABPC) and nalidixic acid (NA) resistance in dog- and cat-derived strains was observed to exceed 40%, as was ciprofloxacin (CPFX) resistance in dog-derived and cephalexin (CEX) resistance in cat-derived strains. On the other hand, the rate of resistance to kanamycin (KM), colistin (CL), and fosfomycin (FOM) in strains isolated from dogs and cats was less than 10%. The rates of resistance to critically important antimicrobials for human medicine in dog- and cat-derived strains respectively were as follows: 26.1% and 33.8% to cefotaxime (CTX); 1.0% and 0.0% to CL; and 43.2% and 39.0% to ciprofloxacin (CPFX). No resistance to meropenem (MEPM) was observed (Table 56).

Table 56. Resistance rates of *Escherichia coli* derived from diseased dogs and cats (%)

Agent	BP	Animal	2017
ABPC	32*	Dogs	55.3
		Cats	64.0
CEZ	32*	Dogs	31.2
		Cats	37.5
CEX	32†	Dogs	31.7
		Cats	41.9
CTX	4*	Dogs	26.1
		Cats	33.8
MEPM	4*	Dogs	0.0
		Cats	0.0
SM	32†	Dogs	29.6
		Cats	32.4
GM	16*	Dogs	14.1
		Cats	12.5
KM	64*	Dogs	6.5
		Cats	8.1
TC	16*	Dogs	28.1
		Cats	24.3
CP	32*	Dogs	12.6
		Cats	13.2
CL	4†	Dogs	1.0
		Cats	0.0
NA	32*	Dogs	61.8
		Cats	58.8
CPFX	4*	Dogs	43.2
		Cats	39.0
FOM	256*	Dogs	0.5
		Cats	1.5
ST	76/4*	Dogs	24.6
		Cats	22.1
Strains tested (n)		Dogs	199
		Cats	136

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

ii. *Klebsiella* spp.

Monitoring of antimicrobial resistance on 15 agents was carried out in 2017. Resistance to ampicillin (ABPC), cefazolin (CEZ), cephalexin (CEX), cefotaxime (CTX), nalidixic acid (NA), and sulfamethoxazole-trimethoprim (ST) in dog- and cat-derived strains was observed to exceed 40%, as was resistance to streptomycin (SM), gentamicin (GM), and tetracycline (TC) in cat-derived strains. On the other hand, resistance to colistin (CL) in

dog- and cat-derived strains was less than 10%, as was resistance to kanamycin (KM) in strains isolated from dogs and fosfomycin (FOM) in those isolated from cats. The rates of resistance to critically important antimicrobials for human medicine in dog- and cat-derived strains respectively were as follows: 41.7% and 80.8% to CTX; 1.4% and 3.8% to colistin (CL); and 44.4% and 84.6% to ciprofloxacin (CPFX). No resistance to meropenem (MEPM) was observed (Table 57).

Table 57. Resistance rates of *Klebsiella* spp. derived from diseased dogs and cats (%)

Agent	BP	Animal	2017 年
ABPC	32*	Dogs	90.3
		Cats	96.2
CEZ	32*	Dogs	47.2
		Cats	84.6
CEX	32†	Dogs	44.4
		Cats	84.6
CTX	4*	Dogs	41.7
		Cats	80.8
MEPM	4*	Dogs	0.0
		Cats	0.0
SM	32†	Dogs	26.4
		Cats	57.7
GM	16*	Dogs	26.4
		Cats	61.5
KM	64*	Dogs	8.3
		Cats	23.1
TC	16*	Dogs	33.3
		Cats	57.7
CP	32*	Dogs	25.0
		Cats	26.9
CL	4†	Dogs	1.4
		Cats	3.8
NA	32*	Dogs	51.4
		Cats	84.6
CPFX	4*	Dogs	44.4
		Cats	84.6
FOM	256†	Dogs	15.3
		Cats	7.7
ST	76/4*	Dogs	41.7
		Cats	76.9
Strains tested (n)		Dogs	72
		Cats	26

The unit of BP is μg/mL.

* BP follows CLSI Criteria.

†BP for FOM uses values for *E. coli*, while EUCAST values were used as the BP for CEX and CL. As EUCAST has not set a BP for SM, the JVARM value (midpoint of a bimodal MIC distribution obtained in FY2001) was used.

iii. Coagulase-positive *Staphylococcus* spp.

Monitoring of antimicrobial resistance on 15 agents was carried out in 2017. The most common coagulase-positive *Staphylococcus* spp. in both dogs and cats was *S. pseudintermedius* (91.7% of dogs and 70.8% of cats), followed by *S. aureus* (4.5% of dogs and 29.2% of cats). In addition, *S. schleiferi* subsp. *Coagulans* was collected from dogs (3.0%) and *S. intermedius* (0.8%) from cats.

In *S. pseudintermedius*, resistance to tetracycline (TC), chloramphenicol (CP), erythromycin (EM), azithromycin (AZM), and ciprofloxacin (CPFX) in dog- and cat-derived strains was observed to exceed 40%, as was oxacillin (MPIPC) resistance in strains isolated from cats. On the other hand, gentamicin (GM) resistance was below 10% in strains isolated from dogs. The rates of resistance to critically important antimicrobials for human medicine in dog- and cat-derived strains respectively were as follows: 53.3% and 66.7% to AZM, and 58.2% and 88.2% to CPFX (Table 58).

In *S. aureus* isolated from cats resistance to MPIPC, cefazolin (CEZ), cephalexin (CEX), cefoxitin (CFX), cefotaxime (CTX), GM, EM, AZM, and CPFX was observed to exceed 40%. On the other hand, the SM resistance rate was less than 10% and no CP resistance was observed. In the realm of critically important antimicrobials for

human medicine, the rate of CTX resistance was 61.9%, AZM resistance 66.7%, and CPFX resistance 61.9% (Table 59).

Table 58. Resistance rates of *Staphylococcus pseudintermedius* derived from diseased dogs and cats (%)

Agent*	BP	Animal	2017
MPIPC	0.5†	Dogs	38.5
		Cats	68.6
GM	16†	Dogs	6.6
		Cats	13.7
TC	16†	Dogs	44.3
		Cats	52.9
CP	32†	Dogs	41.8
		Cats	64.7
EM	8†	Dogs	54.9
		Cats	70.6
AZM	8†	Dogs	53.3
		Cats	66.7
CPFX	4†	Dogs	58.2
		Cats	88.2
Strains tested (n)		Dogs	122
		Cats	51

The unit of BP is μg/mL.
† BP follows CLSI Criteria.
While ABPC, CEZ, CEX, CFX, CMZ, CTX, SM, and NA were also included in the scope of monitoring, the proportion of ABPC-, CEZ-, CEX-, CFX-, CMZ-, CTX-, SM- and NA-resistant strains were not listed because BP could not be established.

Table 59. Resistance rates of *Staphylococcus aureus* derived from diseased dogs and cats (%)

Agent	BP	Animal	2017
MPIPC	4†	Cats	61.9
CEZ	4$	Cats	61.9
CEX	16$	Cats	61.9
CFX	8$	Cats	61.9
CTX	8$	Cats	61.9
SM	32$	Cats	4.8
GM	16†	Cats	47.6
TC	16†	Cats	14.3
CP	32†	Cats	0.0
EM	8†	Cats	66.7
AZM	8†	Cats	66.7
CPFX	4†	Cats	61.9
Strains tested (n)		Cats	21

The unit of BP is μg/mL.
† BP follows CLSI Criteria.
$ Uses EUCAST's ECOFF value
* While ABPC, CMZ, and NA were also included in the scope of monitoring, the proportion of ABPC-, CMZ- and NA-resistant strains were not listed because BP could not be established.

iv. *Enterococcus* spp.

Monitoring of antimicrobial resistance on 13 agents was carried out in 2017. Tetracycline (TC) and erythromycin (EM) resistance in dog- and cat-derived strains was observed to exceed 40%, as was resistance to ciprofloxacin (CPFX) in strains isolated from dogs. In the realm of critically important antimicrobials for human medicine, 42.7% of strains isolated from dogs and 34.7% of those isolated from cats were observed to be CPFX-resistant (Table 60).

Table 60. Resistance rates of *Enterococcus* spp. derived from diseased dogs and cats (%)

Agent*	BP	Animal	2017
ABPC	16†	Dogs	26.7
		Cats	17.3
GM	32§	Dogs	22.9

		Cats	19.4
TC	16†	Dogs	65.6
		Cats	70.4
CP	32†	Dogs	20.6
		Cats	20.4
EM	8†	Dogs	61.8
		Cats	41.8
CPFX	4†	Dogs	42.7
		Cats	34.7
Strains tested (n)		Dogs	131
		Cats	98

The unit of BP is μg/mL.

* While CEZ, CEX, CMZ, CTX, SM, AZM, and NA were also included in the scope of monitoring, the proportion of CEZ-, CEX-, CMZ-, CTX-, SM-, AZM- and NA-resistant strains were not listed because BP could not be established.

† BP follows CLSI Criteria.

§ As EUCAST has not set a BP for GM, the JVARM value (midpoint of a bimodal MIC distribution obtained in FY2002) was used.

(3) Food

Shinomiya et. al. conducted research regarding antimicrobial-resistant bacteria in food.[5] An outline of this research was presented under (1)-4)-ii, "Non-typhoidal *Salmonella* spp." in this report. The resistance rate among *Escherichia coli* isolated from chicken meat was reported in a study conducted as a Ministry of Health, Labour and Welfare research project between 2015 and 2017.[4] Resistance tests were conducted on between one and three strains of *Escherichia coli* isolated from a single chicken specimen and the resistance rate was calculated as a proportion of the total number of *Escherichia coli* strains included in the study. In a study using strains isolated in FY2015, NA and CPFX resistance rates in domestic chicken meat were 23.1% and 6.5% respectively, while those in imported chicken meat were 51.4% and 29.7% respectively. CTX-resistant *Escherichia coli* strains accounted for 14.9% of *Escherichia coli* isolated from domestic chicken meat (ESBL strains accounted for 4.3% and AmpC strains for 0.7%) and for 42.5% isolated from imported chicken meat (with ESBL strains accounting for 27.0% and AmpC strains for 2.7%). Tests of resistance to colistin (strains with a MIC of 4μg/ml or more) among *Escherichia coli* isolated from commercially available meat (chicken and pork) conducted between 2015 and 2016 found resistance in 22 out of a total 310 strains (7.1%) of *Escherichia coli* derived from domestic and imported chicken meat and in 2 out of 117 strains (1.7%) derived from pork. Investigation of these resistant strains using the PCR method to check for the presence of the *mcr-1* gene found that 21 of the chicken-derived strains and 2 of the pork-derived strains were positive for the gene. No significant difference was found between strains from domestic and imported meat in the rate of isolation of colistin-resistant strains.

(4) Environment

Attention to environmental AMR in the context of measures to combat AMR based on the One Health approach should focus on the risks posed by environmental water deemed to have been contaminated with antimicrobial-resistant bacteria and on the assessment of those risks. It is currently difficult to set concrete benchmarks for discussing these risks, because only a very few studies have, to date, quantitatively evaluated the risks thus posed and the Japanese government has not conducted ongoing assessment. However, countries around the world have reported a series of cases in which antimicrobial-resistant factors have been detected not only in hospitals, communities and food-producing animals, but also in the environment (e.g. soil and rivers).[12][13][14][15] For instance, marked contamination of the environment by antimicrobials has occurred in an area on the outskirts of an Indian city that is home to plants that manufacture generic for the global market, with concerns reported about environmental pollution and the emergence of antimicrobial-resistant bacteria due to selective pressure caused by the antimicrobials discharged.[16] The contamination of vegetables believed to result from the use of river water for irrigation [17] and assessments of the risk of exposure through water-based recreation [18] are starting to be reported, albeit only little by little. Given reports such as the isolation of carbapenem-resistant *Enterobacteriaceae* at one of the aquatic venues for the Rio de Janeiro Olympics,[19] the situation appears to have reached a stage at which the risks of exposure should be accurately evaluated.

With the support of the WHO, the Global Sewage Surveillance Project [20] is being conducted with the involvement of 90 countries. Japan has already provided samples and the results are awaited. A research group funded by a Ministry of Health, Labour and Welfare research grant has been formed to conduct a more detailed evaluation of the situation in Japan in parallel with this project. Led by Hajime Kanamori, the research group will conduct a study entitled "Research to Establish Methods of Surveying Antimicrobial-resistant Bacteria and Antimicrobials in the Environment" from 2018 to 2020. Prior to the formation of the research group, next-generation sequencers were used to establish a comprehensive technique for sequencing antimicrobial resistance genes (metagenomic analysis) in environmental water (Pathogen Genomics Center, National Institute of Infectious

Diseases). During the first year of the study (FY2018), the group plans to obtain and analyze samples of wastewater from 27 local governments to identify characteristics of AMR based on population, as well as local and industrial features.

Information on the situation within Japan is starting to emerge, such as a report on the isolation of carbapenemase-producing *Enterobacteriaceae* at sewage treatment plants in both Japan and Taiwan and the clarification of its genomic information,[21] as well as a report on the isolation from a site in Tokyo Bay of a KPC-2-positive *Klebsiella pneumoniae* strain, which is rarely found in Japan, even in clinical isolates.[22] As in the case of the contamination situation overseas, a more extensive field survey would appear to be required in Japan, at least to ascertain the true extent of the isolation of antimicrobial-resistant bacteria in environmental water. Global efforts to link field surveys into risk assessment are expected to be accelerated globally, through such initiatives as the workshop for the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) [23] held in September 2017 to assess the risk posed to human health by such antimicrobial-resistant bacteria in the environment.

In the area of health care associated infections, field epidemiology and molecular epidemiological analysis of isolated strains have, thus far, been used for identifying modes of transmission and quantifying the risk of health effects. However, as described above, research findings indicating that antimicrobial-resistant bacteria derived from the environment affect human and animal health are scarce. Accordingly, there are no established opinions on whether the extent of antimicrobial resistance in the environment may pose health risks, so challenges for the future include not only undertaking systematic reviews of the main body of literature and building up studies that enable the health risks to be evaluated, but also enhancing testing by local governments via local public health institutes and the like.

7. Current Volume of Use of Antimicrobials in Japan

(1) Antimicrobials for humans

Source: IQVIA Solutions Japan K.K.

Tables 61 and 62 show the usage of antimicrobials in Japan between 2013 and 2017, based on the amount of sales. Overall use of antimicrobials in Japan in 2017 amounted to 13.8 DID (DDDs/1,000 inhabitants/day). A comparison with DID in major countries in 2015 [25] shows that this was lower than France (35.7), South Korea (29.8), the U.S.A. (28.2), and Germany (18.2), but higher than Sweden (12.9) and the Netherlands (11.3). No major changes in the use of antimicrobials were observed between 2013 and 2016, but usage in 2017 declined by 7.3% from the 2013 level.

Oral antimicrobial use in 2017 (Table 61) was 12.8 DID, accounting for 92.4% of all antimicrobials. Antimicrobials subject to a reduction target of 50% under Japan's National Action Plan on AMR, namely oral macrolides (4.2 DID), oral cephalosporins (3.4 DID), and oral fluoroquinolones (2.6 DID) together accounted for 73.7% of all oral antimicrobials (the figure for oral cephalosporins is the total for first- (0.1 DID), second- (0.3 DID), and third-generation (3.1 DID) oral cephalosporins). While this trend has not changed since 2013, use of oral macrolides, oral cephalosporins, and oral fluoroquinolones fell by 13.5%, 12.2%, and 9.1% respectively over that period. On the other hand, use of parenteral antimicrobials increased by 9.3% between 2013 and 2017 (Table 62).

A survey of oral and parenteral antimicrobial use in terms of potency by weight from a One Health perspective (Table 63) showed no change in overall use. One of the main reasons for the discrepancy between this and the standardized figures expressed as DID is believed to be the effect of the increased parenteral usage of ampicillin/sulbactam, which has a high-potency daily dosage and is used to treat aspiration pneumonia in elderly people. While factors such as the increasing number of elderly people make it difficult to reduce the use of parenteral antimicrobials in Japan, the effects of the National Action Plan on AMR are believed to be influencing the proper use of oral antimicrobials. Continued efforts to ascertain the extent of antimicrobial use are required.

Table 61. Trends in oral antimicrobial use in Japan based on the volume of sales

	2013	2014	2015	2016	2017
Tetracyclines	0.76	0.75	0.77	0.80	0.81
Amphenicols	<0.01	<0.01	<0.01	<0.01	<0.01
Penicillins with extended spectrum	0.88	0.89	0.99	0.97	0.95
Beta Lactamase-sensitive penicillins	<0.01	<0.01	<0.01	<0.01	<0.01
Combinations of penicillins, including beta lactamase inhibitors	0.21	0.22	0.24	0.25	0.26
1st generation cephalosporins	0.07	0.07	0.07	0.07	0.07
2nd generation cephalosporins	0.30	0.29	0.29	0.29	0.28
3rd generation cephalosporins	3.53	3.41	3.46	3.32	3.08
Carbapenems	0.01	0.02	0.02	0.02	0.01
Other cephalosporins and penems	0.14	0.14	0.13	0.12	0.12
Combinations of sulfonamides and trimethoprim, including derivatives	0.25	0.27	0.29	0.31	0.33
Macrolides	4.83	4.50	4.59	4.56	4.18
Lincosamides	0.01	0.01	0.02	0.01	0.02
Fluoroquinolones	2.82	2.83	2.71	2.75	2.57
Other quinolones	0.01	<0.01	<0.01	<0.01	<0.01
Other antibacterials	0.10	0.10	0.10	0.10	0.09
Total	13.93	13.50	13.67	13.57	12.76

* As a unit, defined daily doses (DDDs) per 1,000 inhabitants per day (DID) is used.
* Figures shown here for antimicrobial use in 2013 differ from those shown in last year's report, because of differences in the DDD values defined by the World Health Organization at the time of calculation. Figures do not include antifungal agents.

Table 62. Trends in parenteral antimicrobial use in Japan based on the volume of sales

	2013	2014	2015	2016	2017
Tetracyclines	0.02	0.02	0.02	0.02	0.02
Amphenicols	<0.01	<0.01	<0.01	<0.01	<0.01
Penicillins with extended spectrum	0.04	0.04	0.04	0.04	0.04
Beta Lactamase-sensitive penicillins	<0.01	<0.01	<0.01	<0.01	<0.01
Combinations of penicillins, including beta lactamase inhibitors	0.13	0.15	0.16	0.18	0.19
1st generation cephalosporins	0.13	0.13	0.14	0.14	0.15

2nd generation cephalosporins	0.11	0.11	0.10	0.10	0.10
3rd generation cephalosporins	0.18	0.19	0.21	0.22	0.23
4th generation cephalosporins	0.06	0.05	0.05	0.05	0.05
Monobactams	<0.01	<0.01	<0.01	<0.01	<0.01
Carbapenems	0.11	0.11	0.11	0.11	0.11
Combinations of sulfonamides and trimethoprim, including derivatives	<0.01	<0.01	<0.01	<0.01	<0.01
Macrolides	<0.01	<0.01	<0.01	<0.01	<0.01
Lincosamides	0.02	0.02	0.02	0.02	0.02
Streptogramins	<0.01	<0.01	<0.01	<0.01	<0.01
Other aminoglycosides	0.05	0.05	0.05	0.04	0.04
Fluoroquinolones	0.04	0.04	0.04	0.04	0.04
Glycopeptides	0.03	0.03	0.03	0.03	0.03
Polymyxins	<0.01	<0.01	<0.01	<0.01	<0.01
Metronidazole	<0.01	<0.01	<0.01	<0.01	<0.01
Other antibacterials	0.02	0.02	0.02	0.02	0.02
Total	0.96	0.96	1.00	1.03	1.05

* As a unit, defined daily doses (DDDs) per 1,000 inhabitants per day (DID) is used.
* Figures shown here for antimicrobial use in 2013 differ from those shown in last year's report, because of differences in the DDD values defined by the World Health Organization at the time of calculation. Figures do not include antifungal agents.

Table 63. Trends in oral antimicrobial consumption in Japan in terms of potency by weight based on the volume of sales (t)

	2013	2014	2015	2016	2017
Tetracyclines	7.1	6.9	7.1	7.2	7.0
Amphenicols	0.2	0.1	0.1	0.1	0.1
Penicillins with extended spectrum	53.7	53.6	57.6	56.3	54.5
Beta Lactamase-sensitive penicillins	1.7	1.8	1.7	1.5	1.4
Combinations of penicillins, including beta lactamase inhibitors	88.1	95.4	105.8	114.6	124.1
1st generation cephalosporins	25.0	24.9	25.2	26.3	27.2
2nd generation cephalosporins	28.5	27.4	27.0	26.7	25.9
3rd generation cephalosporins	97.7	95.1	97.8	95.9	91.2
4th generation cephalosporins	6.6	6.1	6.0	5.7	5.5
Monobactams	0.1	0.1	0.1	0.1	0.1
Carbapenems	9.9	9.9	10.1	10.2	10.1
Combinations of sulfonamides and trimethoprim including derivatives	45.8	49.9	53.7	58.6	62.1
Macrolides	108.0	101.4	103.4	102.9	94.5
Lincosamides	2.8	2.7	2.6	2.5	2.4
Streptogramins	<0.1	<0.1	<0.1	<0.1	<0.1
Other aminoglycosides	1.0	0.9	0.9	0.8	0.8
Fluoroquinolones	61.3	60.2	56.6	57.4	53.2
Other quinolones	0.5	0.4	0.3	0.3	0.2
Glycopeptides	2.2	2.1	2.3	2.4	2.5
Polymyxins	<0.1	<0.1	<0.1	<0.1	<0.1
Metronidazole (parenteral)	<0.1	<0.1	0.2	0.2	0.2
Other antibacterials	17.5	16.5	16.6	16.7	14.3
TOTAL	562.6	560.2	579.7	591.0	581.4

* Unit: tons (t). Figures do not include antifungal agents.

(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). In the period from 2013 to 2016, the volume of sales of veterinary antimicrobials ranged between 749.47 t and 832.56 t. The approximately 52 t increase in sales over this period was mainly accounted for by increases in macrolides (approximately 56 t) and penicillins (approximately 22 t). Tetracyclines took up largest share in the overall volume of sales, accounting for 39.8 to 43.6%.

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 64).

Table 64. Amounts of veterinary antimicrobials in terms of active ingredients (unit: tons)

	2013	2014	2015	2016
Penicillins	78.17	77.96	83.73	99.75
Cephalosporins (total)	5.58	5.50	5.89	6.45
1st generation cephalosporins	(4.71)	(4.58)	(4.98)	(5.41)
2nd generation cephalosporins	(0.19)	(0.20)	(0.12)	(0.16)
3rd generation cephalosporins	(0.68)	(0.71)	(0.79)	(0.88)
Aminoglycosides	39.52	40.64	35.47	47.86
Macrolides	77.70	70.43	98.41	134.12
Lincosamides	38.99	43.26	28.66	21.87
Tetracyclines	340.52	324.85	333.86	331.55
Peptides	11.78	9.98	14.54	14.02
Other antibacterials	25.98	28.85	32.39	31.97
Sulfonamides	103.90	97.57	96.67	95.85
Quinolones	1.01	1.91	1.71	1.74
Fluoroquinolones	5.53	5.63	7.35	6.08
Thiamphenicols and derivatives	21.53	26.15	29.73	26.49
Furan and derivatives	14.46	1.76	1.24	1.57
Other synthetic antibacterials	15.02	13.97	13.35	12.12
Antifungal antibiotics	1.18	1.03	1.08	1.12
Total	780.88	749.47	784.06	832.56

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

1) Food-producing animals

The estimated volumes of veterinary antimicrobials sold for food-producing animals (cattle, pigs, horses, chickens, and others) in terms of active ingredients are listed in Table 58. During the period 2013 to 2016, the estimated volume of sales ranged between 640.25 t and 669.68 t. The approximately 18 t increase in sales over this period was mainly accounted for by increases in penicillins (approximately 24 t), aminoglycosides (approximately 10 t), and 16-membered macrolides such as tylosin (approximately 17 t). Tetracyclines (275.83 tons to 286.74 tons) took up the largest share in the overall volume of sales of antimicrobials for food-producing animals, accounting for 41.9 to 44.0%. 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 less than 1% of total volume of sales in food-producing animals (Table 65).

Table 65. 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)

	2013	2014	2015	2016
Penicillins	59.50	61.96	67.25	83.56
Cephalosporins (total)	3.12	3.06	3.22	3.34
1st generation cephalosporins	(2.45)	(2.34)	(2.52)	(2.52)
2nd generation cephalosporins	(0.19)	(0.20)	(0.12)	(0.16)
3rd generation cephalosporins	(0.49)	(0.51)	(0.58)	(0.65)
Aminoglycosides	37.40	38.66	34.07	47.46
Macrolides	56.00	53.30	60.36	72.68
Lincosamides	35.88	36.61	23.65	15.62
Tetracyclines	286.74	275.83	276.24	280.66
Peptides	11.77	9.97	14.54	14.01
Other antibacterials	25.71	28.43	32.23	31.55
Sulfonamides	95.62	88.43	84.40	78.57
Quinolones	0.22	0.20	0.20	0.16
Fluoroquinolones	4.64	4.73	6.41	5.19
Thiamphenicols and derivatives	19.66	25.14	27.39	24.82

Furan and derivatives	0.00	0.00	0.00	0.00
Other synthetic antibacterials	14.98	13.92	13.32	12.07
Antifungal antibiotics	0.00	0.00	0.00	0.00
Total	651.24	640.25	643.28	669.68

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

2) Aquatic animals

The estimated volumes of veterinary antimicrobials sold for aquatic animals (saltwater fish, freshwater fish, and ornamental fish) in terms of active ingredients are summarized in Table 59. In the period from 2013 to 2016, the estimated volume of sales ranged between 100.09 t and 155.08 t, accounting for between 13.4% and 18.6% of the total volume of veterinary antimicrobial sales. Tetracyclines (ranging between 49.01 t and 57.62 t) took up the largest share in the overall volume of sales of aquatic antimicrobials until 2015, accounting for 43.7% to 49.0%, but the top spot was taken by a macrolide (erythromycin) in 2016, with sales totaling 61.44 t and accounting for 39.6% of the overall volume of sales. The approximately 35 t increase in the volume of sales between 2013 and 2016 was due to a rise in sales of a macrolide (erythromycin), which was attributed to an outbreak of *Lactococcus garvieae* infection.

Third-generation cephalosporins and fluoroquinolones that are important for human health are not approved for aquatic animal use (Table 66).

Table 66. The estimated volumes of sales of veterinary antimicrobials used for aquatic animals (saltwater fish, freshwater fish, and ornamental fish) in terms of active ingredients (unit: tons)

	2013	2014	2015	2016
Penicillins	16.31	13.87	14.38	14.62
Cephalosporins (total)	0.00	0.00	0.00	0.00
1st generation cephalosporins	0.00	0.00	0.00	0.00
2nd generation cephalosporins	0.00	0.00	0.00	0.00
3rd generation cephalosporins	0.00	0.00	0.00	0.00
Aminoglycosides	0.00	0.00	0.00	0.00
Macrolides	21.70	17.13	38.05	61.44
Lincosamides	3.02	6.56	4.90	6.12
Tetracyclines	53.78	49.01	57.62	50.89
Peptides	0.00	0.00	0.00	0.00
Other antibacterials	0.27	0.42	0.16	0.42
Sulfonamides	7.68	8.59	11.71	16.74
Quinolones	0.79	1.71	1.51	1.58
Fluoroquinolones	0.00	0.00	0.00	0.00
Thiamphenicols and derivatives	1.87	1.01	2.33	1.67
Furan and derivatives	14.46	1.76	1.24	1.57
Other synthetic antibacterials	0.02	0.04	0.02	0.04
Antifungal antibiotics	0.00	0.00	0.00	0.00
Total	119.91	100.09	131.91	155.08

3) Companion animals

The estimated volumes of veterinary antimicrobials sold for companion animals (dogs and cats) in terms of active ingredients are summarized in Table 67. In the period from 2013 to 2016, the estimated volume of sales ranged between 7.79 t and 9.67 t, accounting for between 0.9% and 1.2 % of the total volume of veterinary antimicrobial sales. Use of human antimicrobials in companion animals is not monitored under JVARM and is therefore excluded from the values in the table, but monitoring of the extent of their use has recently begun.

Table 67. The estimated volumes of sales of veterinary antimicrobials used for companion animals (cats and dogs) in terms of active ingredients (unit: tons)

	2013	2014	2015	2016
Penicillins	2.36	2.13	2.08	1.57
Cephalosporins (total)	2.45	2.44	2.67	3.12
1st generation cephalosporins	(2.26)	(2.23)	(2.46)	(2.89)
2nd generation cephalosporins	(0.00)	(0.00)	(0.00)	(0.00)
3rd generation cephalosporins	(0.20)	(0.20)	(0.21)	(0.23)
Aminoglycosides	2.07	1.97	1.40	0.41
Macrolides	0.00	0.00	0.00	0.00
Lincosamides	0.09	0.09	0.11	0.13
Tetracyclines	0.00	0.00	0.00	0.00
Peptides	0.01	0.01	0.01	0.01
Other antibacterials	0.00	0.00	0.00	0.00
Sulfonamides	0.60	0.55	0.56	0.53
Quinolones	0.00	0.00	0.00	0.00
Fluoroquinolones	0.90	0.90	0.94	0.89
Thiamphenicols and derivatives	0.00	0.00	0.00	0.00
Furan and derivatives	0.00	0.00	0.00	0.00
Other synthetic antibacterials	0.02	0.01	0.01	0.01
Antifungal antibiotics	1.18	1.03	1.08	1.12
Total	9.67	9.13	8.86	7.79

* 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 68. While the volume of such additives distributed remained at more or less the same level in the period 2013 to 2016, ranging between 216.4 t and 235.1 t, comparisons among the different types of antimicrobials showed an upward trend in the distribution of polyethers.

Table 68. Volume of distribution of antibiotic feed additives in terms of effective value (unit: tons)

	2013	2014	2015	2016
Aminoglycosides	0.0	0.0	0.0	0.0
Polypeptides	35.0	28.3	29.6	32.1
Tetracyclines	1.6	2.2	2.6	2.0
Macrolides	5.6	5.3	5.5	1.4
Polysaccharides	0.2	0.0	0.1	0.1
Polyethers	136.0	142.5	141.7	159.9
Other antimicrobials	20.8	18.3	12.5	14.6
Synthetic antimicrobials	35.9	29.3	24.4	18.1
Total	235.1	225.9	216.4	228.2

Figures do not include antifungal agents.

(4) Agrochemicals

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

Table 69 indicates the volume of shipment in Japan of antimicrobials that are used as agrochemicals, in terms of active ingredients (unit: tons). In the period from 2013 to 2016, the volume of shipments of antimicrobials used as agrochemicals remained at around the 150 t mark, ranging between 146.59 t and 153.63 t.

Table 69. The volume of shipment in Japan of antimicrobials that are used as agrochemicals, in terms of active ingredients (unit: tons).

	2013	2014	2015	2016
Streptomycin	36.12	36.21	35.49	39.80
Oxytetracycline	10.52	12.00	12.54	10.50
Kasugamycin	20.53	20.96	21.24	20.56
Validamycin	23.11	25.50	24.97	24.80
Oxolinic acid	40.08	40.79	41.16	42.17
Polyoxins	16.24	15.49	15.25	15.80
Total	146.59	150.94	150.66	153.63

Figures shown are for the agrochemical year (the 2013 agrochemical year ran from October 2012 to September 2013). Figures do not include antifungal agents.

(5) Current status of antimicrobial use in Japan

Tables 70 and 71 show the total use of antimicrobials in humans, food producing animals, aquatic animals, companion animals, antimicrobial feed additives, and agrochemicals. Antimicrobial selection pressure in Japan from a One Health perspective is highest among tetracyclines at 19-21%, followed by penicillins at 13-15%, and macrolides at 11-13% (Table 70). Use of both penicillins and macrolides has been growing over recent years, so caution regarding future trends will be required. On the other hand, the fact that barely any changes in cephalosporins and fluoroquinolones were observed is attributed to differences in the antimicrobials that can be used in humans and in non-humans (Table 71). Cephalosporins and fluoroquinolones are not used as drugs for aquatic animals or as antimicrobial feed additives or agrochemicals. As third-generation cephalosporins and fluoroquinolones are critically important antimicrobials for human medicine, they are positioned as a second-line drug for food-producing animals and used with great caution, based on assessments by the Food Safety Commission of Japan of their impact on human health via food. Accordingly, they account for only a small proportion of antimicrobials used in animals. Third-generation cephalosporins and fluoroquinolones also are positioned as second-line drugs for companion animals and are consequently used with caution.

Table 70. Current volume of antimicrobial use in Japan (t)

	2013	2014	2015	2016
Penicillins	221.7	228.7	248.7	272.2
Cephalosporins	168.3	163.7	166.5	165.6
Monobactams	0.1	0.1	0.1	0.1
Carbapenems	9.9	9.9	10.1	10.2
Aminoglycosides	97.1	98.7	93.1	109.1
Macrolides	191.3	177.2	207.3	238.5
Lincosamides	41.8	45.9	31.3	24.4
Tetracyclines	359.7	346.0	356.1	351.2
Peptides and glycopeptides	49.0	40.4	46.5	48.5
Sulfonamides*	149.7	147.5	150.4	154.4
Fluoroquinolones	66.8	65.8	63.9	63.5
Other quinolones	41.5	43.1	43.2	44.2
Amphenicols, thiamphenicols and derivatives	21.7	26.3	29.8	26.6
Furan and derivatives	14.5	1.8	1.2	1.6
Polysaccharides	0.2	0.0	0.1	0.1
Polyethers	136.0	142.5	141.7	159.9
Polyoxins	16.2	15.5	15.3	15.8
Others*	138.3	132.4	124.4	118.5
Total	1723.9	1685.5	1729.7	1804.3

*Sulfonamides used as antimicrobial feed additives and the agrochemical validamycin are included in "Others." Figures do not include antifungal agents.

Table 71. Changes in the volume of antimicrobial use in Japan by year (t)

	2013						2014						2015						2016					
	Humans	Food-producing animals	Aquatic animals	Companion animals	Antimicrobial feed additives	Agrochemicals	Humans	Food-producing animals	Aquatic animals	Companion animals	Antimicrobial feed additives	Agrochemicals	Humans	Food-producing animals	Aquatic animals	Companion animals	Antimicrobial feed additives	Agrochemicals	Humans	Food-producing animals	Aquatic animals	Companion animals	Antimicrobial feed additives	Agrochemicals
Penicillins	143.5	59.5	16.3	2.4	0.0	0.0	150.8	62.0	13.9	2.1	0.0	0.0	165.0	67.3	14.4	2.1	0.0	0.0	172.5	83.6	14.6	1.6	0.0	0.0
Cephalosporins	162.7	3.1	0.0	2.5	0.0	0.0	158.2	3.1	0.0	2.4	0.0	0.0	160.6	3.2	0.0	2.7	0.0	0.0	159.1	3.3	0.0	3.1	0.0	0.0
Monobactams	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0
Carbapenems	9.9	0.0	0.0	0.0	0.0	0.0	9.9	0.0	0.0	0.0	0.0	0.0	10.1	0.0	0.0	0.0	0.0	0.0	10.2	0.0	0.0	0.0	0.0	0.0
Aminoglycosides	1.0	37.4	0.0	2.1	0.0	56.7	0.9	38.7	0.0	2.0	0.0	57.2	0.9	34.1	0.0	1.4	0.0	56.7	0.8	47.5	0.0	0.4	0.0	60.4
Macrolides	108.0	56.0	21.7	0.0	5.6	0.0	101.4	53.3	17.1	0.0	5.3	0.0	103.4	60.4	38.1	0.0	5.5	0.0	102.9	72.7	61.4	0.0	1.4	0.0
Lincosamides	2.8	35.9	3.0	0.1	0.0	0.0	2.7	36.6	6.6	0.1	0.0	0.0	2.6	23.7	4.9	0.1	0.0	0.0	2.5	15.6	6.1	0.1	0.0	0.0
Tetracyclines	7.1	286.7	53.8	0.0	1.6	10.5	6.9	275.8	49.0	0.0	2.2	12.0	7.1	276.2	57.6	0.0	2.6	12.5	7.2	280.7	50.9	0.0	2.0	10.5
Peptides and glycopeptides	2.2	11.8	0.0	0.0	35.0	0.0	2.1	10.0	0.0	0.0	28.3	0.0	2.3	14.5	0.0	0.0	29.6	0.0	2.4	14.0	0.0	0.0	32.1	0.0
Sulfonamides	45.8	95.6	7.7	0.6	0.0	0.0	49.9	88.4	8.6	0.6	0.0	0.0	53.7	84.4	11.7	0.6	0.0	0.0	58.6	78.6	16.7	0.5	0.0	0.0
Fluoroquinolones	61.3	4.6	0.0	0.9	0.0	0.0	60.2	4.7	0.0	0.9	0.0	0.0	56.6	6.4	0.0	0.9	0.0	0.0	57.4	5.2	0.0	0.9	0.0	0.0
Other quinolones	0.5	0.2	0.8	0.0	0.0	40.1	0.4	0.2	1.7	0.0	0.0	40.8	0.3	0.2	1.5	0.0	0.0	41.2	0.3	0.2	1.6	0.0	0.0	42.2
Amphenicols, thiamphenicols and derivatives	0.2	19.7	1.9	0.0	0.0	0.0	0.1	25.1	1.0	0.0	0.0	0.0	0.1	27.4	2.3	0.0	0.0	0.0	0.1	24.8	1.7	0.0	0.0	0.0
Furan and derivatives	0.0	0.0	14.5	0.0	0.0	0.0	0.0	0.0	1.8	0.0	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	1.6	0.0	0.0	0.0
Polysaccharides	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0
Polyethers	0.0	0.0	0.0	0.0	136.0	0.0	0.0	0.0	0.0	0.0	142.5	0.0	0.0	0.0	0.0	0.0	141.7	0.0	0.0	0.0	0.0	0.0	159.9	0.0
Polyoxins	0.0	0.0	0.0	0.0	0.0	16.2	0.0	0.0	0.0	0.0	0.0	15.5	0.0	0.0	0.0	0.0	0.0	15.3	0.0	0.0	0.0	0.0	0.0	15.8
Others*	17.5	40.7	0.3	0.0	56.7	23.1	16.5	42.4	0.5	0.0	47.6	25.5	16.8	45.6	0.2	0.0	36.9	25.0	16.9	43.6	0.5	0.0	32.7	24.8
Total	562.6	651.2	119.9	8.5	235.1	146.6	560.2	640.2	100.1	8.1	225.9	151.0	579.7	643.3	131.9	7.8	216.4	150.7	591.0	669.7	155.1	6.7	228.2	153.6
Total for year						1,723.9						1,685.5						1729.7						1,804.3

*Sulfonamides used as antimicrobial feed additives and the agrochemical validamycin are included in "Others." Antifungal antibiotics used as veterinary drugs are not included in "Others." Figures do not include antifungal agents.

(6) 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.[25] 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).[26]

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.[27] 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 bioreactor.[25] 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.[26]

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.[28] 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 1,866 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.

A research group funded by a Ministry of Health, Labour and Welfare research grant began work in the current fiscal year on a study entitled "Research to Establish Methods of Surveying Antimicrobial-resistant Bacteria and Antimicrobials in the Environment," which will run from 2018 to 2020 and be led by Hajime Kanamori. One of the objectives of the study is to establish a method of evaluating antimicrobial resistance in environmental water and it will incorporate surveillance aimed at studying the true extent of antimicrobial-resistant bacteria and residual antimicrobials in environmental water in Japan. Hopes are high that this study will help to advance research in this area.

8. Public Awareness regarding Antimicrobial Resistance in Japan

(1) Survey of the general public

Ohmagari et al. conducted surveys of public awareness concerning antimicrobial resistance in March 2017 and February 2018, funded by a Ministry of Health, Labour and Welfare research grant.[29, 30] In both studies, consumers (excluding medical professionals) who had registered with INTAGE Research Inc. to participate in various market research surveys completed an online questionnaire. The 2017 survey had 3,390 respondents and the 2018 survey 3,192. Women comprised 48.8% of respondents in 2017 and 49.7% in 2018, while the average age of respondents was 45.5 years and 45.9 years in 2017 and 2018 respectively. About half of all respondents experienced taking antibiotics because of cold. Similarly, approximately 40% of respondents thought that antibiotics were effective for cold and influenza. Approximately 20% discontinued taking antibiotics based on their own judgment; and approximately 10% kept the remaining antibiotics at home. Among the respondents who kept antibiotics at home, approximately 80% used them based on their own judgment. The trends in responses to the 2017 and 2018 surveys were more or less the same, so ongoing efforts to raise public awareness using a variety of measures are required in order to change attitudes among the public (Table 72-75).

Table 72. Reasons for taking oral antibiotics (%)

n=3,390 (2017), 3,192 (2018) (select all that applied)	2017 (%)	2018 (%)
Cold	45.5	44.7
Others/unknown	24.3	21.2
Influenza	11.6	12.4
Fever	10.7	11.3
Nasopharyngitis	9.5	10.8
Cough	9.0	10.8
Sore throat	7.7	7.8
Skin or wound infection	6.5	7.0
Bronchitis	5.4	6.6
Headache	4.3	5.0
Diarrhea	3.1	3.2
Urinary tract infection	2.3	2.5
Pneumonia	1.4	1.7

Table 73. Do you think each of the following statement is correct or incorrect? (%)

		2017 (n=3,390)	2018 (n=3,192)
Antibiotics beat viruses	Correct	46.8	46.6
	Incorrect	21.9	20.3
	Do not know	31.3	33.0
Antibiotics have effect on cold and influenza	Correct	40.6	43.8
	Incorrect	24.6	22.1
	Do not know	34.8	34.1
Unnecessary use of antibiotics may result in the loss of their effect	Correct	67.5	68.8
	Incorrect	3.1	3.7
	Do not know	29.4	27.5
Adverse effects are involved in the use of antibiotics	Correct	38.8	41.5
	Incorrect	12.7	13.4
	Do not know	48.6	45.0

Table 74. Does each statement below apply to you? (%)

		2017 (n=3,390)	2018 (n=3,192)
I have discontinued taking antibiotics, or adjusted a dose or frequency based on my own judgment	Yes	23.6	24.0
	No	76.4	76.0
I keep antibiotics in my house	Yes	11.7	11.9
	No	88.3	88.1

Table 75. Does each statement below apply to you? (%)

		2017 (n=396*)	2018 (n=426*)
I have used antibiotics that I kept at home for myself	Yes	75.8	77.5
	No	24.2	22.5
I have given antibiotics that I kept at home to my family or friend	Yes	26.5	27.2
	No	73.5	72.8

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

(2) Survey of healthcare providers

1) Survey of attitudes among clinicians

Nakahama et al. conducted a survey of awareness among clinicians.[31] The survey was conducted between January and February 2017, with questionnaires distributed to physicians known to the research team and via primary care mailing lists. Physicians who responded were also able to distribute the questionnaire to others in their circle of professional acquaintances. In total, 612 physicians responded to the questionnaire: 40% answered as self-employed physicians and 60% answered as employed physicians. By specialty, the share of internal medicine was the largest at 69%, followed by pediatrics at 16%.

With respect to the administration of antimicrobials for the common cold syndrome, the most frequent response was "0 to less than 10%" at around 60%. 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%. 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 76-79).

Table 76. 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

Table 77. 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
Cephalosporins	14.5	18.0	12.2
Macrolides	35.0	38.9	32.3
Fluoroquinolones	7.5	9.0	6.5
Others	8.5	5.3	11.1

Table 78. 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 79. 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

2) Survey of attitudes among clinicians

Gu et al. conducted a survey of awareness among outpatient physicians between October and December 2017, funded by a Ministry of Health, Labour and Welfare research grant.[32] Questionnaires were distributed via 10 local medical associations across Japan to 2,416 association members, with valid responses received from 524 respondents (a response rate of 21.7%). In terms of the main medical institutions where respondents practiced, 90.6% provided medical care at clinics and 8.0% at hospitals. Among those practicing at clinics, internal medicine was the most common specialism of those clinics, accounting for 63.2%, followed by pediatrics at 10.1% and otolaryngology at 5.3%.

When asked about the percentage of cases for which, having diagnosed the common cold, they prescribed antimicrobials, the majority of respondents (about 60%) replied “0-20%.” The most commonly prescribed antimicrobials were macrolides at 33.4%, followed by third-generation cephalosporins at 32.2%, penicillins at 20.0%, and new quinolones at 9.8%. The most commonly cited reason for administering antimicrobials was “To prevent aggravation of infection,” accounting for more than 30% of responses, followed by “At the patient’s request,” which accounted for 7.8%.

Almost all respondents reported having consciously considered the proper use of antimicrobials within the last year, although the extent to which they had done so varied (always, quite often, sometimes). About 60% of respondents stated that they thought the proper use of antimicrobials by individual clinicians to be “Highly effective” in curbing antimicrobial-resistant bacteria (Table 80-84).

Table 80. Percentage of cases of the common cold in which antimicrobials were administered (%)

n=478	Percentage
0-20%	59.4
21-40%	19.7
41-60%	12.3
61-80%	5.0
>=81%	3.6

Table 81. Antimicrobials most commonly prescribed for the common cold (%)

n=410	Percentage
Penicillins	20.0
β-lactamase inhibitor combinations with penicillins	2.9
3rd generation cephalosporins	32.2
Macrolides	33.4
New quinolones	9.8
Others	1.7

Table 82. Reasons for administering antimicrobials for the common cold (%)

n=410	Percentage
To prevent secondary bacterial infection	18.8
To prevent worsening of infection	33.4
Difficult to distinguish whether the cause is viral or bacterial	27.1
Patients' requests	7.8
Habitual administration	2.7
Other	10.2

Table 83. Conscious consideration of the proper use of antimicrobials in the last year (%)

n=524	Percentage
Always consciously considered it	31.3
Quite often consciously considered it	29.6
Sometimes consciously considered it	36.3
Never consciously considered it	1.9
No response/unclear	1.0

Table 84. Effectiveness of the proper use of antimicrobials by individual clinicians in curbing antimicrobial-resistant bacteria (%)

n=524	Percentage
Highly effective	63.2
Somewhat, but not highly effective	22.5
Not effective	1.0
Can't say either way	4.4
Don't know	8.0
No response/unclear	1.0

(3) Surveys of animal producers and clinical veterinarians

The Japan Livestock Industry Association conducted surveys of antimicrobial resistance awareness among animal producers and livestock veterinarians. These surveys were funded under the Japan Racing Association's FY2017 Livestock Industry Promotion Project (Project to Promote Greater Awareness and Application of Measures to Combat Antimicrobial Resistance). The online questionnaires were conducted among animal producers and livestock veterinarians nationwide via prefectures and livestock-focused organizations between September 25 and October 20, 2017.

It must be noted that the results below summarize only the situation among those animal producers who responded to the questionnaire. The Japan Livestock Industry Association plans to conduct another online questionnaire in FY2018 to obtain responses from a larger number of animal producers and veterinarians.

1) Survey of animal producers

Responses were received from 320 individuals, 141 (44%) of whom were involved in handling cattle, with 94 (29%) handling pigs and 85 (27%) handling chickens. Looking at each topic considered in the questionnaire, approximately 30% of respondents were aware of Japan's National Action Plan on Antimicrobial Resistance (AMR), while the proportion aware that "Antimicrobial-resistant bacteria make it harder to treat bacterial infections in both humans and livestock" and that "Using antimicrobials causes antimicrobial-resistant bacteria to increase" was about 80% in both cases. Around 70% of respondents were aware of "Concerns about the transmission of antimicrobial-resistant bacteria to humans via livestock." By livestock type, awareness of all topics was highest among pig producers.

Approximately 80% reported being aware that "There is feed which contains antimicrobial feed additives and feed which does not," while about 80% of respondents who reported being aware of this fact were also aware of "What kind of

antimicrobial feed additives the feed contains." By livestock type, awareness of all these topics was highest among pig producers, but cattle producers accounted for the largest percentage of those responding that they "Have taken steps to reduce the use of antimicrobials by using feed which does not contain antimicrobial feed additives, wherever possible," at around 50%.

Approximately 90% of respondents reported being aware that "Preventing outbreaks of disease through improvements in the rearing environment and the use of vaccines reduces the use of antimicrobials," while about 80% of respondents who were aware of this fact had actually taken steps to put such measures into practice. By livestock type, awareness of these topics was highest among pig producers (Table 85).

Table 85. Awareness of topics among animal producers (%)

	Total (n=320)	Cattle (n=141)	Pigs (n=94)	Chickens (n=85)
Japan's National Action Plan on Antimicrobial Resistance	29.4	22.7	44.7	23.5
Antimicrobial-resistant bacteria make it harder to treat bacterial infections in both humans and livestock	77.8	73.8	89.4	71.8
Using antimicrobials causes antimicrobial-resistant bacteria to increase	80.6	77.3	88.3	77.6
Concerns about the transmission of antimicrobial-resistant bacteria to humans via livestock	68.8	63.8	80.9	63.5
There is feed which contains antimicrobial feed additives and feed which does not*	80.3	76.6	86.2	80.0
(*Of whom) What kind of antimicrobial feed additives the feed contains	75.1	68.5	84.0	75.0
(*Of whom) Have taken steps to reduce the use of antimicrobials by using feed which does not contain antimicrobial feed additives, wherever possible	51.8	57.4	45.7	50.0
Preventing outbreaks of disease through improvements in the rearing environment and the use of vaccines reduces the use of antimicrobials	86.3	80.1	95.7	85.9
(Of whom) Have actually put these measures into practice	79.7	75.2	87.8	76.7

2) Survey of livestock veterinarians

Responses were received from 534 respondents, 362 (68%) of whom were veterinarians involved in treating and providing hygiene guidance concerning dairy cows, while 346 (65%) dealt with beef cows, 131 (25%) with pigs, 57 (11%) with chickens, and 47 (9%) with other livestock (multiple answers to the question about the type of livestock dealt with were permitted, so there is some overlap).

Approximately 40% were aware of Japan's National Action Plan on Antimicrobial Resistance, with awareness as high as 60% or more among veterinarians dealing with pigs, chickens, and other livestock. About 80% of respondents were aware of the "Basic concept of the prudent use of veterinary antimicrobial products for the production of animal products" (http://www.maff.go.jp/j/syouan/tikusui/yakuzi/koukinzai.html#prudent_use), in which Japan's Ministry of Agriculture, Forestry and Fisheries summarizes basic approaches to ensuring the responsible and prudent use of antimicrobials in the livestock sector. By livestock type, awareness was as high as around 90% or more among veterinarians dealing with pigs and chickens.

Approximately 90% reported that they "Take care in routine practice to restrict the use of antimicrobials to those cases in which they are truly necessary, based on an appropriate diagnosis," with awareness high among all livestock types. Around 90% stated that they "Have provided guidance on preventing infectious disease through vaccines and improvements in rearing hygiene management, with the objective of reducing opportunities for antimicrobial use," with awareness highest among veterinarians dealing with pigs and chickens. About 70% of respondents reported that they "Conduct antimicrobial susceptibility tests in routine practice when using antimicrobials," with awareness highest among veterinarians dealing with pigs. Approximately 60% stated that they are "Aware of what kinds of antimicrobial feed additives are found in feed in the context of treatment using antimicrobials," with awareness highest among veterinarians dealing with pigs and chickens (Table 86).

Table 86. Awareness of topics among livestock veterinarians (%)

	Total (n=534)	Dairy cattle (n=362)	Beef cattle (n=346)	Pigs (n=131)	Chickens (n=57)	Other (n=47)
Japan's National Action Plan on Antimicrobial Resistance	44.4	34.8	35.3	61.1	64.9	66.0
Basic concept of the prudent use of veterinary antimicrobial products for the production of animal products	77.0	73.2	76.0	87.8	91.2	78.7
Take care in routine practice to restrict the use of antimicrobials to those cases in which they are truly necessary, based on an appropriate diagnosis, and, where their use is necessary, make an appropriate choice of effective antimicrobial and keep the amount used to the minimum necessary	90.8	89.0	90.5	95.4	98.2	93.6
Have provided guidance on preventing infectious disease through vaccines and improvements in rearing hygiene management, with the objective of reducing opportunities for antimicrobial use	87.8	86.5	87.3	96.2	100.0	76.6
Conduct antimicrobial susceptibility tests in routine practice when using antimicrobials	66.3	69.3	65.6	75.6	61.4	61.7
Aware of what kinds of antimicrobial feed additives are found in feed in the context of treatment using antimicrobials	58.4	50.3	56.1	74.8	84.2	66.0

9. Way Forward

This document follows on from last year's report in presenting 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 sales) of human and veterinary antimicrobials. 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. Part of this report includes data obtained after Japan's "National Action Plan on Antimicrobial Resistance (AMR) 2016-2020" was published. Figures for 2017 show that usage of oral antimicrobials, including oral cephalosporins, oral macrolides, and oral fluoroquinolones is trending downward compared with the data for 2013. However, further promotion of measures against AMR will be required to achieve the 2020 targets.

While an increase in the volume of sales of veterinary antimicrobials was observed between 2013 and 2016, primarily among macrolides and penicillins, resistance among *Escherichia coli* to third-generation cephalosporins and fluoroquinolones—which are both critically important antimicrobials for human medicine—remained low. In addition, a fall in resistance to tetracycline was observed between 2014 and 2015. Further efforts to ensure thorough adherence to the prudent use of antimicrobials will be required to achieve the targets for 2020.

Comparisons between the volume of antimicrobial use (or sales) in the fields of human medical care, veterinary care, and agriculture were possible for the first time in this report. Major progress was thus seen in such areas as the highlighting of differences in the volume of antimicrobial use in each field by type of antimicrobial, the reporting of antimicrobial resistance rates in diseased companion animals, and the enhancement of data on trends in antimicrobial-resistant bacteria in the area of food. Hopes are high that progress in the surveillance of trends in each field will continue next year and beyond. Furthermore, it is hoped that initiatives of the kind spotlighted by the National Action Plan on Antimicrobial Resistance, focusing on linking data from antimicrobial resistance trend surveillance and monitoring in such areas as human health, animals, and food, will contribute to combating antimicrobial resistance in Japan in the future.

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 patriated 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 institution 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 2,000 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 2018, 1,988 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. Since 2014, figures have also been compiled on the basis of hospital scale, divided into hospitals with 200 or more beds and those with fewer than 200 beds. Only bacteria that are isolated from specimens from hospitalized 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 interpreted 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 Surveillance, 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.[33] Japan has provided necessary data from JANIS and other pertinent monitoring systems to GLASS. Of note, data for 2014 to 2017 have already been submitted. GLASS is calling for the same set of antimicrobials to be used in antimicrobial susceptibility tests at medical institutions subject to monitoring in each country. As JANIS is a voluntary surveillance program, it collects whatever data can be supplied by the participating medical institutions, in whatever form that data emerges from the institutions' routine testing operations. Standardizing the types of antimicrobials tested is therefore difficult. Techniques for compiling data are being considered as part of the JANIS program, to facilitate international cooperation in surveillance. Under GLASS, the expansion of the scope of surveillance to food-producing animal and other areas are discussed.[33] 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-Resistant 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) Prospects

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 July 2018, 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 cases where it was detected from specimens that normally should be aseptic. Carriers 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.

3) 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.

4) Prospects

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 healthcare-associated 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.

(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 tuberculosis 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 calendar 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 tuberoses, 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 tuberculosis 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) Prospects

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 80% 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 monitoring systems in "Antimicrobial resistance: global report on surveillance 2014," published by WHO.

Figure 1. Overview of veterinary antimicrobial resistance monitoring

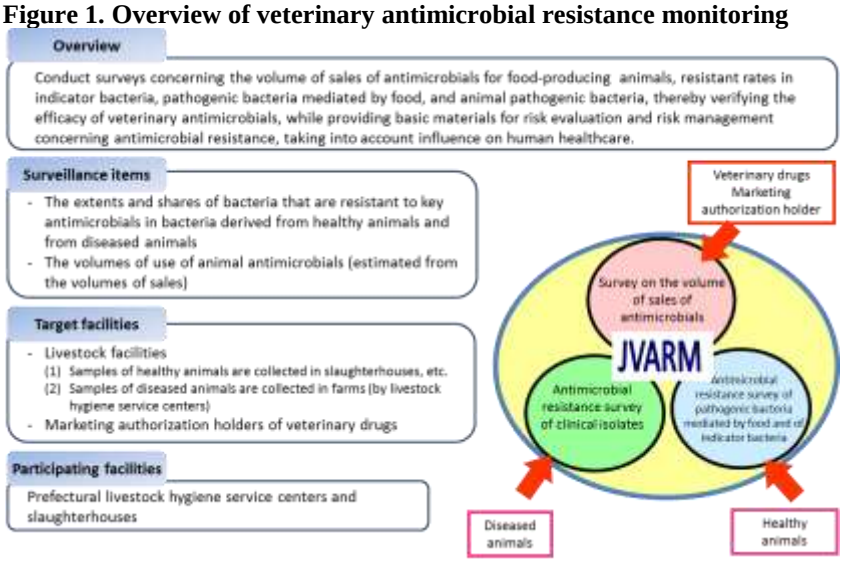


Figure 2. System for antimicrobial resistance monitoring in healthy food-producing animals at animal and poultry slaughterhouses

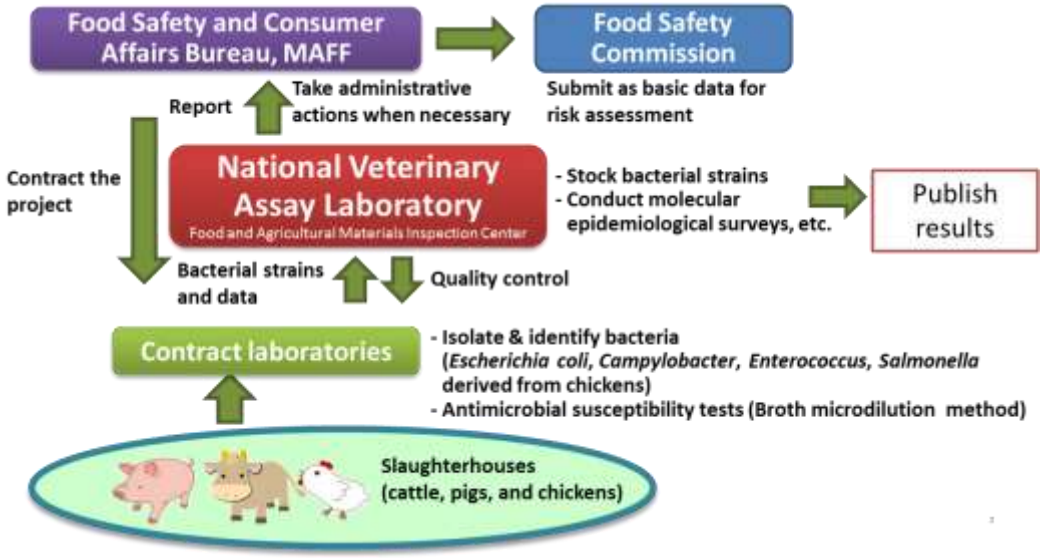
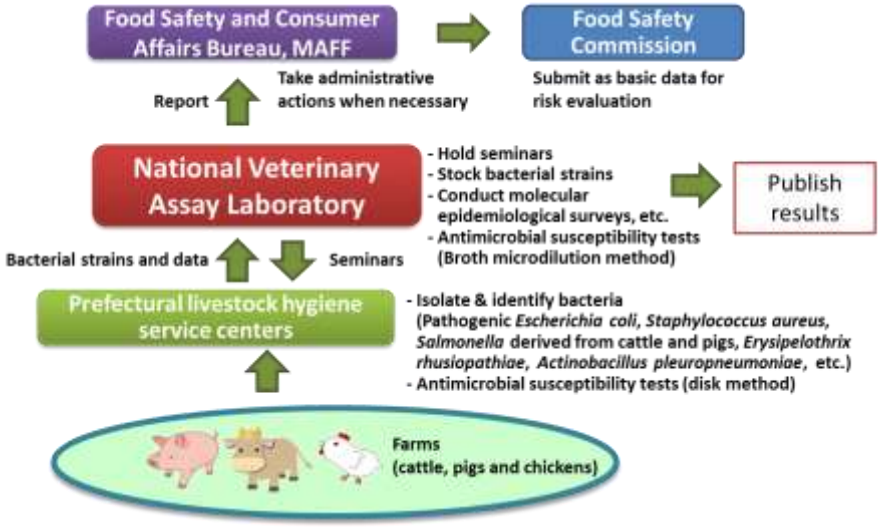
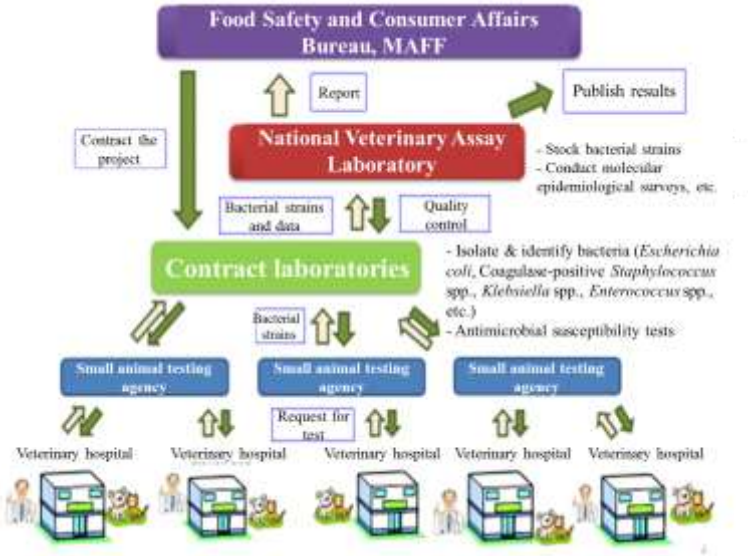


Figure 3. System for antimicrobial resistance monitoring in diseased food-producing animals



Under JVARM, three types of monitoring 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.[34] In FY2016, reviews were carried out to consider how to strengthen antimicrobial resistance surveillance in aquatic animals, and how to conduct antimicrobial resistance surveillance in companion animals, in accordance with the strategies of the National Action Plan on Antimicrobial Resistance (AMR). Antimicrobial resistance surveillance in diseased dogs and cats was launched in FY2017 (Figure 4).

Figure 4. System for antimicrobial resistance monitoring in diseased dogs and cats (from FY2017)



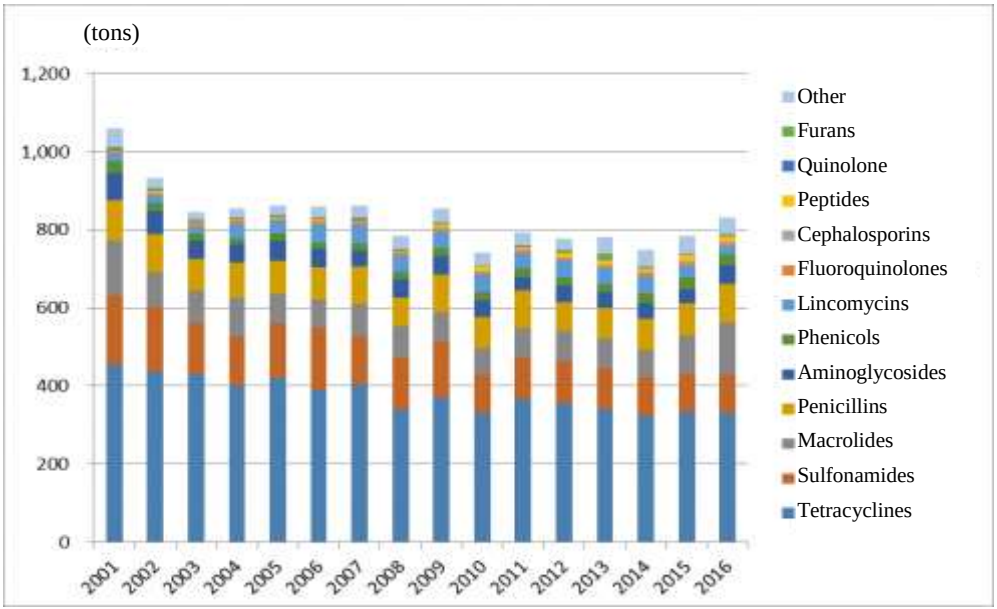
3) Monitoring details on the volumes of sales of antimicrobials

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 2001, 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,[35] 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.

When monitoring began, the volume of sales was in excess of 1,000 tons, but the figure progressively decreased thereafter, with average sales over the last ten years amounting to 795.94 t, while the average for the last five years is 784.79 t (Figure 5).

Figure 5. Changes in veterinary antimicrobial sales by antimicrobial type (2001-2016)



Usage volumes (sales volumes) by weight (tons) are indicated in all fields (including human) from the report. Whereas usage of cephalosporins and fluoroquinolones was higher among humans than in other fields, usage of tetracyclines and aminoglycosides was higher among animals than elsewhere. The total weight of antimicrobial use in agrochemicals was less than in humans or animals, with oxolinic acid and streptomycin accounting for more than half of this.

When evaluating antimicrobial use, it is helpful to compare on the basis not only of gross weight, but also of quantities that take into account the weight of the subject to which they are administered. In the case of humans, the WHO has set a defined daily dose (DDD) and comparisons between humans often use DID (DDDs/1,000 inhabitants/day). However, animal weights vary considerably between one species and another, from chicks weighing just a few dozen grams to dairy cows in excess of 600 kg, so no standardized DDD has been set. Animal weights are therefore evaluated as biomass weight and usage per unit of biomass weight is often used, but the method of calculation is set by each individual country or region, so it is not standardized. However, the OIE has proposed a method of calculating biomass weight for use in collating data on the volume of veterinary antimicrobial use, while the EU has set DDD for some food-producing animals (cattle, pigs, and broilers), so it would appear to move forward the harmonized method for evaluation of antimicrobial consumption.

4) 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 is 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 2017, 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.[36]

The survey method used for the 2017 surveillance of companion animals was informed by the results of deliberations by the Working Group for the Surveillance of Antimicrobial Resistance (AMR) in Companion Animals. Gram-negative (*Escherichia coli*, *Klebsiella* spp., and others) and gram-positive (coagulase-positive *Staphylococcus* spp., *Enterococcus*) bacterial strains isolated from the urine, reproductive organs, skin, and ears of diseased dogs and cats were gathered from clinical laboratories and sent to a contracted laboratory, which used a CLSI-based method of broth microdilution to measure the MIC. The survey focused on both the antimicrobials included in the surveillance of food-producing animals and other antimicrobials used on companion animals in clinical settings, namely the following: ampicillin, oxacillin (*Staphylococcus* spp. only), cefazolin, cephalexin, cefoxitin (*Staphylococcus* spp. only), cefmetazole (gram-positive bacteria only), cefotaxime, meropenem (gram-negative bacteria only), streptomycin, gentamicin, kanamycin (gram-negative bacteria only), tetracycline, chloramphenicol, erythromycin (gram-positive bacteria only), azithromycin (gram-positive bacteria only), colistin (gram-negative bacteria only), nalidixic acid, ciprofloxacin, fosfomycin (gram-negative bacteria only), and sulfamethoxazole-trimethoprim (gram-negative bacteria only).

5) 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 3). From 2000 to 2015, 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. The Food Safety Commission of Japan's Food Safety Risk Assessment of Resistance to Fluoroquinolone Antimicrobials Used in Cattle and Pigs (March 2010) called for the establishment of a comprehensive antimicrobial resistance monitoring system capable of offering epidemiological assessment and testing. Accordingly, sampling of feces from healthy animals commenced in animal and poultry slaughterhouses in FY2012 (Figure 2); when the results were compared with those from feces sampling on farms, no major differences were found in antibacterial resistance rates, MIC_{50}, or MIC_{90} among *Escherichia coli* and *Campylobacter strains* isolated in FY2012 and FY2013. Sampling of feces on farms was therefore discontinued in FY2016 and efforts to monitor food-borne pathogenic bacteria and indicator bacteria from healthy animals switched to sampling at 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.

6) Monitoring on the sales volumes of antimicrobials

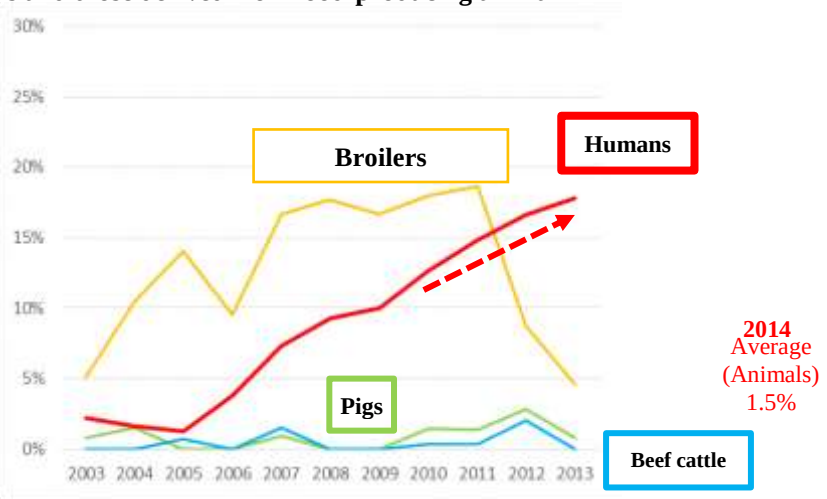
Each marketing authorization holder of veterinary drugs annually submit, to the National Veterinary Assay Laboratory, the sales volume of antimicrobials from January 1 to December 31, using a designated reporting form. The data are aggregated and published on the website of the National Veterinary Assay Laboratory as "Annual Report of Sales Amount and Sales Volume of Veterinary drugs, Quasi-drugs and Medical Devices." (Figure 6)

Figure 6

7) Collaboration with JANIS

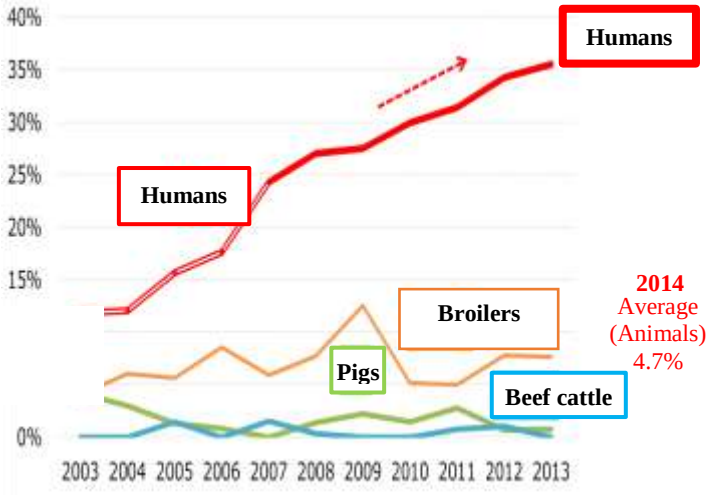
Since FY2012, collaboration has been promoted between JVARM and JANIS (Japan Nosocomial Infections Surveillance). The data of *Escherichia coli* derived from healthy animals collected under JVARM are converted into a format comparable with JANIS data, and the results are published as antibiograms on the website of the National Veterinary Assay Laboratory.[37] These data enable the comparison of trends in antimicrobial-resistant bacteria between humans and animals.

Figure 7 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. [38] On the other hand, the proportion still continues to rise in humans, indicating different trends between humans and broilers.

Figure 8 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.

8) Prospects

JVARM still faces three key tasks: 1) monitoring resistance in strains derived from healthy companion animals; 2) conducting more advanced surveillance and analysis of antimicrobial resistance genes (ARG) by such means as whole genome analysis; and 3) monitoring the usage of human antimicrobials in companion animals. While continuing to carry out monitoring in existing veterinary fields, JVARM will move forward with monitoring focused on these tasks in 2018. To further promote One Health monitoring, further collaboration with JANIS will continue to be pursued through comparisons of 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 their 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 was 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 online data collection by pharmacists, 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 interchangeably used in overseas journals. Although AUD used in Europe is relatively easy to handle and can be utilized for cost calculation 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 proportion of resistance is improved, compared to when the total patient-days is used as the denominator.

5) Prospects

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 Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE), which is installed in the AMR Clinical Reference Center (AMRCRC) established in April 2017 at the National Center for Global Health and Medicine (NCGM). J-SIPHE allows 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 information 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 113 *C. jejuni* strains and 14 *C. coli* strains that were isolated from the stool of diarrhea cases at hospitals in Tokyo in 2016 were tested using imicrobials such as tetracycline (TC), nalidixic acid (NA), ciprofloxacin (CPFX), norfloxacin (NFLX), ofloxacin (OFLX), and erythromycin (EM).

3) Prospects

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.[5] 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) Prospects

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 these 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) is 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) Prospects

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 isolated in Japan 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. Reports of the isolation of strains with the same resistance gene as the resistant strain isolated in Osaka in 2015 [39] have been received from across the globe since 2017.[40]

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	2017
CTRX[$]	0.6	0.4	0.5
SPCM	0	0	0
AZM*	3.2	4.0	4.0
PCG[†]	36.0 (96.1)	35.8 (96.7)	37.8(99.0) [†]
CFIX[$]	16.1	11.0	10.0
CPFX[†]	79.0 (79.4)	77.9 (78.3)	74.2(75.8)

[$] Non-susceptibility rate

* 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 is no routine antimicrobial resistance monitoring 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) Prospects

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/

National Epidemiological Surveillance of Infectious Disease (NESID)
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/

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

The Antimicrobial Resistance One health Surveillance Committee: Terms of References

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 establishing systems for such one health AMR surveillance.

Under these circumstances, the Antimicrobial Resistance One health Surveillance Committee (hereinafter referred to as "Committee") 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 Committee

(1) The Committee should consist of experienced experts and other stakeholders.
(2) The Chair should be elected from members by mutual voting.
(3) The Committee should be presided over by the Chair.
(4) The Director-General of the Health Service Bureau may request non-member experts to participate at Committee 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 Committee should be held by the Director-General of the Health Service Bureau, MHLW.
(2) Clerical affairs for the Committee 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 Committee should be held openly in principle.
(4) Necessary matters concerning the operation of the Committee, other than those specified in this Overview, should be determined at the Committee.

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 additional experts and cooperating governmental agencies:1st meeting on 2/3/2017, 2nd meeting on 3/8/2017, 3rd meeting on 8/21/2017, 4th meeting on 10/2/2017, 5th meeting on 9/5/2018, and 6th meeting on 10/22/2018.

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