Nippon AMR One Health Report (NAOR) 2019

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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
Lipopeptides	Daptomycin	DPT
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" positions efforts to ascertain the current status of antimicrobial-resistant bacteria and national antimicrobial use in the areas of human health, animals, food and the environment and trends therein as an important strategy for both evaluating current policy and examining future policy. For global monitoring and reporting, WHO has launched the Global Antimicrobial Resistance Surveillance System (GLASS) for the gathering and sharing of trends in resistant bacteria worldwide. Japan contributes to GLASS by providing our national data. In addition, Japan also submits data as part of our assistance with an initiative by 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 update both domestic and overseas stakeholders about the current status and progress of our AMR policy, in order both to reaffirm Japan's position in the global community and to accelerate and advance AMR policy at the international level.

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* has remained below 1% during the observed period, despite its global increase in humans. Likewise, the proportion of vancomycin-resistant enterococci in humans remains less than 1%. While the criteria for assessing carbapenem resistance in *Pseudomonas aeruginosa* changed in 2014, the resistance rate appears to be trending downward. The rate of resistance against the third-generation cephalosporins and fluoroquinolones among *Escherichia coli*, however, is increasing. Although the percentage of methicillin-resistant *Staphylococcus aureus* (MRSA) has been declining since 2011, levels remain 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 2018 fell by 10.6% from 2013 to a defined daily dose per 1,000 inhabitants per day (DID) of 13.3. Oral antimicrobial agents accounted for 90% of total sales, with cephalosporins, fluoroquinolones, and macrolides accounting for the highest shares. While the trend remained similar in 2018, a further decline in usage from FY2017 was observed, with the shares of each agent declining by

18.4%, 17.0%, and 18.0% respectively since 2013. However, use of parenteral antimicrobials saw a 10.0% increase from 2013.

In food-producing animals, monitoring of resistant bacteria in cattle, pigs and chickens is conducted. The proportion of antimicrobial-resistant *Escherichia coli* and *Salmonella* spp. derived from diseased animals tended to be higher than those derived from healthy animals. 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, while tetracycline resistance in the indicator bacteria, *Escherichia coli* derived from healthy food-producing animals, fell from 45.2% in 2014 to 39.9% in 2015, the rate has been increasing since then, reaching 40.1% in 2017. 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* (streptococcosis) 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, focusing on resistance of *Lactococcus garvieae* and *Vibrio* spp. In 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 among 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 Article 71-2 of 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 872.09 tons in 2017. This increase in the volume of sales 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 more than 40%. In contrast, third-generation cephalosporins and fluoroquinolones each accounted for less than 1% of the total. Total usage of antimicrobials in 2017 estimated from the volume of sales in each field was 1,804.3 tons, comprising 581.4 tons for human use, 694.2 tons for food-producing animals, 169.9 tons for aquatic animals, 6.9 tons for companion animals, 221.2 tons for antibiotic feed additives, and 142.7 tons for agrochemicals.

Observations:

Figures for 2018 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. This is principally attributed to a decline in the volume of antimicrobials prescribed within Japan for acute respiratory tract infections. 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 continue to climb, including fluoroquinolone resistance rates among *Escherichia coli* and penicillin-resistant *Streptococcus pneumoniae* in cerebrospinal fluid specimens.

The data in this report demonstrate that further promotion of measures against AMR will be required to achieve the targets for 2020. There are reports of a correlation between fluoroquinolone usage and the frequency of occurrence of fluoroquinolone-resistant *Escherichia coli*. There are also reports of a connection between MRSA and usage of third-generation cephalosporins, fluoroquinolones, and macrolides. Accordingly, unnecessary use of third-generation cephalosporins, fluoroquinolones, and macrolides must be reduced and the Manual of Antimicrobial Stewardship employed to promote the proper use of antimicrobials, primarily in respect of acute respiratory tract infections. As regional information about resistant bacteria is being put together, it would be desirable to select the type of antimicrobial to be prescribed with reference to the regional situation. Furthermore,

it will be necessary to continue using various techniques for education and awareness activities targeting the public and medical professionals, to achieve further progress in antimicrobial stewardship.

Total usage of veterinary antimicrobials estimated from the volume of sales shows increases mainly in macrolides (erythromycin used in aquatic animals and 16-membered macrolides used in food-producing animals) and penicillin derivatives for food-producing animals between 2013 and 2017. Accordingly, measures to curb the diseases thought to be the causes of these increases will be required. In terms of antimicrobial resistance rates among *Escherichia coli*, which have been set as 2020 targets, the rates of resistance to third-generation cephalosporins and fluoroquinolones among *Escherichia coli* have been kept at a low level. At the same time, while tetracycline resistance in *Escherichia coli* fell in 2015 from the year before, the decline has since halted. Accordingly, further efforts to ensure the prudent use of antimicrobials by encouraging a change in behavior among producers and veterinarians 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	2018	2020 (target value†)
Proportion of penicillin-non-susceptible *Streptococcus pneumoniae*, CSF specimens§	47.4	40.5	29.1	38.3	15% or lower
Proportion of penicillin-non-susceptible *Streptococcus pneumoniae*, non-CSF specimens§	3.2	2.7	2.1	2.2	
Proportion of fluoroquinolone-resistant *Escherichia coli*	35.5	38.0	40.1	40.9	25% or lower
Proportion of methicillin-resistant *Staphylococcus aureus*	51.1	48.5	47.7	47.5	20% or lower
Proportion of carbapenem-resistant *Pseudomonas aeruginosa* (Imipenem)	17.1	18.8	16.9	16.2	10% or lower
Proportion of carbapenem-resistant *Pseudomonas aeruginosa* (Meropenem)	10.7	13.1	11.4	10.9	10% or lower
Proportion of carbapenem-resistant *Escherichia coli* (Imipenem)	0.1	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	0.1	0.2% or lower (maintain at the same level)¶
Proportion of carbapenem-resistant *Klebsiella pneumoniae* (Imipenem)	0.3	0.3	0.2	0.3	0.2% or lower (maintain at the same level)¶
Proportion of carbapenem-resistant *Klebsiella pneumoniae* (Meropenem)	0.6	0.6	0.4	0.5	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: use of antimicrobials (DID) (based on volume of sales)

	2013†	2018	Change from 2013	2020 (target value*)
All antimicrobials	14.90	13.31	10.6%↓	33%↓
Oral cephalosporins	3.91	3.19	18.4%↓	50%↓
Oral fluoroquinolones	2.82	2.34	17.0%↓	50%↓
Oral macrolides	4.83	3.96	18.0%↓	50%↓
Intravenous antimicrobials	0.96	1.06	10.0%↑	20%↓

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

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

	2014*	2015*	2017	2020 (target value**)
Proportion of tetracycline-resistant *Escherichia coli* (farms)	45.2	39.9		33% or lower
(Animal slaughterhouses)		39.8	40.8	
Proportion of third-generation cephalosporin-resistant *Escherichia coli* (farms)	1.5	0.9		The same level as in other G7 nations
(Animal slaughterhouses)		0.7	2.1	
Proportion of fluoroquinolone-resistant *Escherichia coli* (farms)	4.7	3.8		The same level as in other G7 nations
(Animal slaughterhouses)		2.7	4.0	

* Prepared from [3] with partial modification
JVARM "Results of Monitoring of Antimicrobial Resistant Bacteria Isolated from Food-producing Animals on Farms"
** Target values were quoted from [1].

References

1. Ministerial Conference for the Control of Globally Threatening Infectious Diseases. "The National Action Plan on Antimicrobial Resistance (AMR)2016-2020." 2016.

2. Muraki Y, *et al.*"Japanese antimicrobial consumption surveillance: first report on oral and parenteral antimicrobial consumption in Japan (2009–2013)" J Glob Antimicrob Resist. 2016 Aug 6;7:19-23.
3. National Veterinary Assay Laboratory, Ministry of Agriculture, Forestry and Fisheries. "Monitoring of AMR." Accessed on Apr. 30th, 2020, from https://www.maff.go.jp/nval/yakuzai/yakuzai_p3.html

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%, as in Tables 1 and 2. However, as the rate of resistance against third-generation cephalosporins such as cefotaxime (CTX) and fluoroquinolones such as levofloxacin (LVFX) among *Escherichia coli* continues to increase, measures targeted at these areas in particular appear to be required.

The proportion of carbapenem-resistant *Enterobacter cloacae* (Table 3) and *Klebsiella (Enterobacter) aerogenes* (Table 4) remained between around 1% and 2%; 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	2018
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)	52.2 (325,553)
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)	46.0 (342,066)
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)	1.7 (263,131)
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)	38.7 (347,491)
CMZ	64	64	-	-	-	1.0 (163,342)	0.9 (260,844)	1.0 (300,089)	0.9 (325,296)	0.9 (348,832)
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)	27.5 (251,068)
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)	12.4 (352,819)
CFPM	32	32	-	-	10.9 (81,456)	12.8 (129,606)	15.0 (236,705)	15.8 (273,587)	16.1 (296,143)	16.7 (321,745)
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)	19.3 (273,064)
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)	0.1 (321,043)
MEPM*	16	4	-	-	0.1 (95,180)	0.2 (144,913)	0.2 (269,893)	0.2 (317,987)	0.1 (340,687)	0.1 (365,600)
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)	0.1 (362,591)
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)	40.9 (360,329)

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	2018
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)	79.4 (158,654)
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)	22.9 (165,430)
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)	2.6 (127,778)

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)	14.3 (166,906)
CMZ	64	64	-	-	-	1.9 (85,749)	1.9 (132,163)	1.7 (152,086)	1.5 (159,375)	1.6 (168,787)
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)	9.4 (122,459)
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)	5.7 (169,097)
CFPM	32	32	-	-	3.0 (41,143)	3.5 (66,399)	4.0 (119,563)	4.8 (138,737)	5.1 (145,745)	5.8 (156,485)
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)	6.7 (133,009)
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)	0.3 (154,879)
MEPM*	16	4	-	-	0.2 (48,190)	0.6 (73,903)	0.6 (135,930)	0.5 (159.623)	0.4 (166,298)	0.5 (175,408)
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)	0.1 (174,259)
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)	3.1 (172,010)

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	2018
ABPC	32	32	80.9 (35,849)	79.0 (39,344)	80.2 (55,960)	79.3 (61,667)	79.8 (61,970)	81.2 (64,820)
PIPC	128	128	20.6 (36,988)	20.0 (39,636)	19.8 (58,039)	20.1 (63,580)	20.8 (64,217)	21.2 (66,020)
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)	9.8 (52,186)
CEZ*	32	8	97.2 (37,359)	98.2 (41,422)	98.3 (58,637)	98.3 (64,634)	98.3 (64,693)	98.3 (68,017)
CMZ**	-	64	-	83.4 (37,492)	85.4 (56,647)	85.5 (63,331)	86.1 (64,158)	88.0 (68,013)
CTX*	64	4	19.2 (30,106)	31.1 (32,718)	31.6 (46,727)	31.2 (50,311)	32.4 (50,022)	32.9 (51,470)
CAZ*	32	16	20.6 (37,202)	24.7 (41,456)	25.0 (59,533)	24.9 (65,317)	25.8 (65,027)	26.3 (68,737)
CFPM	32	32	4.2 (17,900)	4.2 (29,836)	4.2 (52,218)	4.0 (58,298)	4.0 (59,398)	3.9 (64,337)
AZT*	32	16	16.8 (29,460)	23.8 (33,551)	24.0 (48,570)	23.9 (52,951)	24.3 (53,374)	24.9 (55,988)
IPM*	16	4	0.4 (34,403)	1.6 (37,396)	1.3 (54,926)	1.2 (60,602)	1.1 (60,689)	1.1 (63,611)
MEPM*	16	4	0.6 (21,164)	1.3 (32,589)	1.4 (59,009)	1.2 (67,250)	1.1 (67,392)	1.1 (71,119)
AMK	64	64	0.4 (37,947)	0.2 (42,005)	0.2 (61,086)	0.1 (67,133)	0.1 (67,125)	0.1 (70,659)
LVFX	8	8	4.2 (37,274)	3.5 (40,942)	3.7 (59,393)	3.4 (65,161)	3.5 (65,690)	3.2 (69,392)

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	2018
ABPC	32	32	76.5 (17,362)	77.1 (18,385)	78.9 (26,680)	77.9 (29,228)	79.1 (30,844)	80.3 (32,746)
PIPC	128	128	14.5 (18,029)	14.5 (18,550)	14.2 (27,189)	15.8 (29,852)	17.1 (31,802)	17.4 (33,048)
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)	6.9 (26,272)
CEZ**	32	8	90.8 (17,945)	94.0 (19,173)	93.7 (27,526)	94.2 (30,088)	94.5 (31,800)	95.0 (33,996)
CMZ	64	64	-	84.8 (17,587)	86.8 (26,739)	87.1 (29,681)	88.0 (31,915)	89.1 (34,051)
CTX**	64	4	5.2 (14,452)	28.3 (15,173)	30.7 (21,985)	31.1 (23,572)	32.9 (24,195)	33.4 (25,493)
CAZ**	32	16	17.3 (17,992)	24.3 (19,439)	25.2 (27,886)	25.7 (30,388)	26.7 (32,030)	27.8 (34,142)
CFPM	32	32	1.0	1.2	1.1	1.1	1.3	1.4

			(8,909)	(13,499)	(24,302)	(27,146)	(29.464)	(32,216)
AZT**	32	16	7.5 (14,639)	15.8 (15,846)	17.5 (23,225)	17.5 (25,023)	18.0 (26,772)	19.2 (28,281)
IPM**	16	4	0.4 (16,881)	1.7 (17,463)	1.9 (25,690)	1.9 (28,307)	1.9 (29,869)	2.6 (31,288)
MEPM**	16	4	0.2 (10,249)	0.9 (15,003)	0.8 (27,560)	0.8 (31,311)	0.8 (33,150)	0.8 (35,448)
AMK	64	64	0.2 (18,369)	0.2 (19,492)	0.1 (28,627)	0.1 (31,338)	0.1 (33,074)	0.1 (35,214)
LVFX	8	8	1.1 (18,111)	1.0 (19,068)	0.9 (28,012)	1.0 (30,451)	0.9 (32,503)	0.9 (34,383)

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	2018
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)	10.0 (206,858)
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)	8.1 (172,748)
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)	8.4 (203,554)
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)	13.1 (162,365)
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)	6.0 (194,385)
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)	16.2 (188,778)
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)	10.9 (209,149)
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)	2.9 (184,135)
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)	0.9 (209,413)
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)	10.2 (199,760)

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. *Acintobacter* spp.

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

	BP	2011	2012	2013	2014	2015	2016	2017	2018
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)	10.3 (27,905)
TAZ/ PIPC	4/128	-	-	7.8 (4,953)	7.8 (5,215)	8.1 (9,058)	8.6 (10,551)	9.0 (10,983)	9.4 (12,171)
SBT/ ABPC	16/32	6.5 (2,942)	7.2 (3,601)	5.8 (4,498)	5.2 (6,462)	4.8 (11,356)	5,4 (12,831)	4.7 (12,241)	4.4 (13,111)
CAZ	32	10.3 (19,672)	10.6 (20,067)	10.0 (20,856)	9.3 (20,852)	8.0 (28,166)	7.6 (29,844)	7.9 (27,308)	7.6 (28,077)
CFPM	32	10.4 (13,013)	10.5 (14,093)	9.2 (15,394)	7.6 (17,424)	7.2 (25,412)	7.4 (27,386)	7.6 (25,631)	6.8 (26,616)
IPM	16	2.2 (18,048)	2.0 (18,238)	2.3 (16,947)	3.6 (11,147)	3.2 (13,942)	3.1 (15,147)	2.5 (14,383)	2.0 (16,995)
MEPM	16	2.9 (15,485)	2.4 (15,880)	2.3 (17,027)	2.0 (18,859)	1.8 (28,227)	1.9 (30,489)	1.3 (28,064)	1.5 (29,024)
GM	16	9.6 (18,276)	10.2 (18,842)	9.5 (19,422)	8.9 (18,832)	8.5 (25,689)	8.5 (27,313)	8.2 (24,887)	7.8 (25,465)
AMK	64	4.5 (19,348)	4.5 (19,793)	3.5 (20,863)	3.6 (20,851)	3.1 (28,568)	2.3 (30,279)	2.3 (27,835)	2.0 (28,437)
LVFX	8	9.5 (18,732)	9.8 (19,484)	8.3 (20,040)	8.5 (20,047)	7.7 (27,858)	8.2 (29,702)	8.0 (27,360)	7.0 (28,209)

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 10), 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 11, 12). 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 13). The proportion of PRSP was low for non-CSF samples at below 1% (Table 14), and below 5% even adding penicillin intermediate resistant bacteria.

i. *Staphylococcus aureus*

Table 7. Trends in the proportion (%) of all antimicrobial-resistant *Staphylococcus aureus strains**

	BP	2018
PCG	0.25	75.4 (287,805)
MPIPC	4	47.8 (266,047)
CFX	8	46.1 (57,604)
CEZ	32	20.7 (360,772)
GM	16	30.4 (345,964)
EM	8	51.7 (325,918)
CLDM	4	22.0 (340,953)
MINO	16	12.2 (377,507)
VCM	16	0.0 (374,982)
TEIC	32	<0.05 (336,502)
LVFX	4	50.4 (358,941)
LZD	8	<0.05 (286,366)
DPTF	2	0.3 (72,401)

The unit of BP is μg/mL.
Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.
*Data collection began in 2018.
-: Not under surveillance

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

	BP	2011	2012	2013	2014	2015	2016	2017	2018
PCG	0.25	61.1 (68,839)	60.1 (75,025)	59.0 (82,477)	57.7 (86,314)	56.2 (119,343)	55.0 (126,394)	53.9 (129,943)	52.9 (135,360)
CEZ	32	0.3 (77,483)	<0.05 (84,520)	0.2 (93,945)	0.2 (103,603)	0.1 (146,254)	<0.05 (157,917)	<0.05 (161,831)	<0.05 (164,909)
CVA/ AMPC	4/8	0.3 (11,696)	0.1 (9,466)	0.2 (11,230)	0.2 (11,666)	0.1 (19,163)	0.1 (21,783)	0.1 (24,713)	0.1 (26,376)
IPM	16	0.3 (74,636)	<0.05 (80,472)	0.2 (88,422)	0.2 (95,951)	<0.05 (136,878)	<0.05 (146,433)	<0.05 (149,014)	<0.05 (149,454)
EM	8	22.7 (72,738)	23.4 (79,683)	24.0 (88,528)	23.8 (96,829)	22.9 (136,763)	23.3 (146,280)	23.5 (148,795)	23.1 (150,809)
CLDM	4	3.4 (67,523)	3.1 (74,387)	3.2 (83,914)	2.8 (93,467)	2.8 (136,292)	2.9 (148,439)	2.9 (151,841)	2.7 (155,141)

MINO	16	0.7	0.6	0.5	0.6	0.6	0.5	0.6	0.6
		(77,872)	(84,595)	(94,425)	(104,145)	(151,493)	(163,214)	(167,178)	(169,953)
LVFX	4	9.3	10.2	10.6	10.7	11.6	12.3	13.1	13.8
		(73,163)	(79,857)	(89,641)	(99,898)	(144,083)	(154,868)	(159,066)	(161,691)

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

Table 9. Trends in the proportion (%) of methicillin-resistant *Staphylococcus aureus* (MRSA)

	BP (2014-)	2011	2012	2013	2014	2015	2016	2017	2018
EM	8	91.3	90.6	88.4	86.0	84.1	83.8	82.9	81.7
		(105,936)	(109,521)	(108,607)	(107,836)	(149,851)	(155,587)	(157,708)	(159,215)
CLDM	4	76.8	73.5	67.3	60.3	56.0	51.6	46.3	41.7
		(102,895)	(106,124)	(105,503)	(106,910)	(153,329)	(160,500)	(164,301)	(169,049)
MINO	16	48.2	43.7	37.1	35.1	31.7	29.1	27.1	23.7
		(117,325)	(120,321)	(120,300)	(121,258)	(173,983)	(182,306)	(185,770)	(189,813)
VCM	16	0.0	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)	(189,853)
TEIC	32	<0.05	<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)	(169,651)
LVFX	4	89.0	88.3	86.8	85.4	85.2	85.8	86.5	86.8
		(111,598)	(114,381)	(114,551)	(115,586)	(164,734)	(172,494)	(176,790)	(179,731)
LZD*	8	0.1	<0.05	<0.05	<0.05	0.1	<0.05	<0.05	<0.05
		(76,632)	(84,550)	(85,223)	(88,255)	(127,278)	(136,468)	(139,785)	(144,332)
Daptomycin*	2	-	-	-	1.1	0.9	0,8	0.7	0.5
					(3,078)	(16,648)	(23,217)	(26,874)	(35,618)

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 2018, 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 10. The proportion of (%) of patients with MRSA among all patients with *Staphylococcus aureus* (*S. aureus*)

Table 10-1. All participating medical institutions

	2011	2012	2013	2014	2015	2016	2017	2018
Number of participating medical institutions	594	660	745	883	1435	1653	1795	1947
The number of patients with MRSA	114,933	117,209	118,539	120,702	169,528	177,768	182,619	185,709
The number of patients with *S. aureus*	210,382	221,239	231,909	246,030	349,743	372,787	383,006	391,316
The proportion of MRSA (%)*	54.6	53.0	51.1	49.1	48.5	47.7	47.7	47.5

Table 10-2. Participating medical institutions with 200 or more beds

	2011	2012	2013	2014	2015	2016	2017	2018
Number of participating medical institutions	-	-	-	791	1177	1269	1312	1334
The number of patients with MRSA	-	-	-	115,757	157,419	160,060	160,714	159,054
The number of patients with *S. aureus*	-	-	-	237,343	328,540	341,822	344,543	344,156
The proportion of MRSA (%)*	-	-	-	48.8	47.9	46.8	46.6	46.2

Table 10-3. Participating medical institutions with fewer than 200 beds

	2011	2012	2013	2014	2015	2016	2017	2018
Number of participating medical institutions	-	-	-	92	258	384	483	613
The number of patients with MRSA	-	-	-	4,945	12,109	17,708	21,905	26,655
The number of patients with *S. aureus*	-	-	-	8,687	21,203	30,965	38,463	47,160
The proportion of MRSA (%)*	-	-	-	56.9	57.1	57.2	57.0	56.5

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

	BP	2011	2012	2013	2014	2015	2016	2017	2018
PCG	16	2.2	2.1	1.8	1.6	1.4	1.1	1.0	0.9
		(53,290)	(60,342)	(65,220)	(67,324)	(92,132)	(98,465)	(98,478)	(104,023)
ABPC	16	0.4	0.4	0.3	0.3	0.3	0.2	0.2	0.2
		(60,686)	(68,440)	(72,587)	(77,997)	(107,733)	(115,548)	(116,493)	(119,014)
EM	8	57.8	58.0	57.1	55.5	54.8	54.3	53.8	52.7
		(53,222)	(60,825)	(64,465)	(69,171)	(95,409)	(101,036)	(101,379)	(102,496)
MINO	16	47.8	47.7	47.7	52.1	49.7	48.9	50.3	50.9
		(61,549)	(69,421)	(74,880)	(81,925)	(115,648)	(123,860)	(125,728)	(128,160)
VCM	32	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
		(61,747)	(69,719)	(75,162)	(81,867)	(115,100)	(124,305)	(126,510)	(129,545)
TEIC	32	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05
		(56,591)	(63,747)	(69,500)	(76,160)	(105,403)	(112,636)	(113,501)	(115,397)
LVFX	8	19.3	18.0	15.5	13.7	12.5	11.9	11.2	10.4
		(58,877)	(65,934)	(70,895)	(77,563)	(109,160)	(117,297)	(120,136)	(122,551)

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

Table 12. Trends in the proportion (%) of antimicrobial-resistant *Enterococcus faecium*

	BP	2011	2012	2013	2014	2015	2016	2017	2018
PCG	16	86.9	87.4	87.7	86.9	87.6	88.2	87.8	87.5
		(17,642)	(21,139)	(23,466)	(24,534)	(34,752)	(38,060)	(39,478)	(42,178)
ABPC	16	86.0	86.2	86.9	86.9	87.6	88.0	87.9	87.6
		(19,780)	(23,885)	(26,199)	(28,564)	(41,459)	(45,069)	(47,046)	(49,207)
EM	8	87.2	88.1	85.9	84.5	84.5	84.0	83.1	83.0
		(17,668)	(21,498)	(23,594)	(25,922)	(37,536)	(40,509)	(42,259)	(43,555)
MINO	16	26.9	28.8	29.3	32.2	35.1	34.7	36.2	38.3
		(21,877)	(25,961)	(28,387)	(31,550)	(46,351)	(50,325)	(52,494)	(54,540)
VCM	32	1.0	0.4	0.7	0.7	0.7	0.9	0.8	0.9
		(21,782)	(25,787)	(28,334)	(30,996)	(45,514)	(49,618)	(52,127)	(54,279)
TEIC	32	0.4	0.3	0.2	0.2	0.3	0.6	0.4	0.6
		(20,163)	(23,855)	(26,282)	(29,151)	(41,905)	(45,388)	(47,321)	(48,991)
LVFX	8	82.9	83.4	84.5	84.7	85.8	86.6	86.5	86.7
		(19,417)	(23,032)	(25,629)	(28,448)	(42,068)	(45,834)	(48.995)	(51,003)
LZD	8	0.0	0.1	<0.05	0.1	0.1	0.1	<0.05	0.1
		(12,877)	(16,296)	(18,561)	(22,044)	(33,382)	(37,099)	(39,584)	(41.596)

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

	BP	2012	2013	2014	2015	2016	2017	2018
PCG	0.125	38.6	47.4	47.0	40.5	36.4	29.1	38.3
		(101)	(97)	(83)	(126)	(140)	(117)	(94)
CTX	2	3.7	1.2	2.9	2.0	1.0	2.1	4.5
		(82)	(84)	(69)	(100)	(105)	(97)	(88)
MEPM	1	4.2	2.2	1.2	4.2	0.7	5.0	2.1
		(95)	(92)	(83)	(119)	(134)	(120)	(95)
EM	1	82.5	82.7	92.5	84.9	75.5	82.4	75.0
		(80)	(81)	(67)	(86)	(98)	(91)	(76)
CLDM	1	53.8	68.7	65.1	62.7	61.2	49.5	43.7
		(65)	(67)	(63)	83)	(98)	(91)	(71)
LVFX	8	0.0	0.0	1.3	0.0	0.0	0.9	2.3
		(88)	(91)	(76)	(105)	(123)	(111)	(88)
VCM	2	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		(91)	(90)	(82)	(119)	(134)	(116)	(98)

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 14. Trends in the proportion (%) of antimicrobial-resistant *Streptococcus pneumoniae* (nonCSF specimens)

	BP	2012	2013	2014	2015	2016	2017	2018
PCG*	4	3.2	2.7	2.5	2.7	2.1	2.1	2.2
		(24,980)	(26,932)	(27,206)	(36,475)	(35,960)	(34,415)	(33,483)
CTX	4	2.4	2.0	1.8	1.6	1.4	1.6	1.4
		(21,654)	(23,096)	(23,002)	(30,734)	(29,405)	(27,773)	(27,004)
MEPM	1	6.9	5.1	5.4	5.0	5.7	6.0	6.3
		(22,989)	(24,986)	(25,760)	(34,461)	(34,885)	(34,011)	(33,115)
EM	1	87.0	86.2	86.7	85.5	84.4	82.4	81.3
		(21,979)	(22,435)	(22,215)	(30,501)	(30,144)	(28,097)	(27,154)
CLDM	1	56.4	56.1	57.1	56.1	54.1	50.5	49.9
		(17,513)	(19,719)	(20,296)	(27,555)	(28,541)	(27,536)	(26,459)

LVFX	8	3.0 (24,105)	3.1 (25,764)	3.3 (26,236)	3.5 (35,457)	4.1 (35,431)	4.3 (34,241)	4.4 (33,551)
VCM	2	0.0 (24,085)	0.0 (25,425)	0.0 (25,775)	0.0 (33,530)	0.0 (33,670)	0.0 (32,681)	0.0 (31,741)

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 2017 are publicized as confirmed reported data. Cases reported since 2013 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.

Among notifiable diseases (diseases that must be reported to the authorities in all cases), although the annual number of reports of vancomycin-resistant enterococcal (VRE) infection remained under a hundred during the observed period, no sign of a downward trend was observed and the number of reports in 2017 was the highest of this five-year 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 the annual number of reports has remained more or less at the same level since figures became available in 2015, with 1,660 cases reported in 2017. 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 28 cases were reported in 2017.

Under a March 2017 notification issued by the Director of the Tuberculosis and Infectious Diseases Control Division, Health Service Bureau, MHLW, local public health institutes and other organizations are required to use the PCR method to test strains isolated from notified cases of CRE infection for carbapenemase genes and other information. In 2017, results for 865 strains derived from 865 people thought to be cases notified via the surveillance program were reported. A carbapenemase gene of some kind was detected in 239 strains (28%), with IMP variants—the most prevalent carbapenemase genes in Japan—accounting for the majority (227 strains).

Looking at antimicrobial-resistant infections notified by Japan's approximately 500 designated sentinel sites (medical institutions that have 300 or more beds), 16,551 cases of MRSA infection were reported in 2017. Although the number of reports of MRSA infection and number of reports per site had been declining since 2011, the figures began to increase slightly in 2017. On the other hand, both the total number of reports of penicillin-resistant *Streptococcus pneumoniae* infection (PRSP) and multidrug-resistant *Pseudomonas aeruginosa* infection (MDRP) and the number of reports per site are continuing to trend downward.

i. Diseases subject to notifiable disease surveillance

Table 15. Number of cases reported for diseases subject to notifiable disease surveillance

	2013	2014	2015	2016	2017
VRE	55	56	66	61	83
VRSA	0	0	0	0	0
CRE	-	314*	1,673	1,573	1,660
MDRA	-	15*	38	33	28

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

ii. Diseases reportable from designated sentinel sites

Table 16. Number of cases reported for diseases reportable from designated sentinel sites

		2013	2014	2015	2016	2017
PRSP	Cases	3,161	2,292	2,057	2,017	2,001

	Cases per sentinel site	6.65	4.79	4.29	4.21	4.18
MRSA	Cases	20,155	18,082	17,057	16,338	16,551
	Cases per sentinel site	42.43	37.83	35.61	34.11	34.55
MDRA*	Cases	8	4	-	-	-
	Cases per sentinel site	0.02	0.01	-	-	-
MDRP	Cases	319	268	217	157	128
	Cases per sentinel site	0.67	0.56	0.45	0.33	0.27

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

4) Other antimicrobial-resistant bacteria

i. *Campylobacter* spp.

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 185 outbreaks of food-borne illness that occurred in Tokyo in 2018, 41 outbreaks (22.2%) were caused by *Campylobacter* spp., being the largest cause of bacterial food-borne illness.[1] Among the *Campylobacter jejuni* (*C. jejuni*) isolated from patients with diarrhea in 2017, the proportion of fluoroquinolone-resistant strains was 43.5%, lower than 2016. The proportion of fluoroquinolone-resistant *Campylobacter coli* (*C. coli*) strains was 62.5%, which was higher 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 17. 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)	2017 (n=115)
EM	3.7	2.4	1.2	0.8	0.9	0.9	1.7
NA	53.7	62.7	50.6	50.4	37.1	53.1	46.1
Fluoroquinolones†	53.7	62.7	50.6	50.4	37.1	52.2	43.5

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

Table 18. 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)	2017 (n=8)
EM	12.5	22.2	16.7	28.6	0.0	14.3	25.0
NA	87.5	66.7	75.0	57.1	50.0	50.0	62.5
Fluoroquinolones†	87.5	66.7	75.0	57.1	50.0	35.7	62.5

* 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.

Public Health Institutes

The 21 Public Health Institutes across Japan conducted research on the multidrug-resistant status of the 1,962 *Salmonella* strains that were isolated between 2015 and 2018, using standardized methodology.[2] Table 19 lists the key serotypes of human-derived strains and food-derived strains.

In total, 42.9% of the 1,502 human-derived strains and 90.0% of the 460 food-derived strains indicated resistance to one or more antimicrobials (Tables 20 and 21). 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

2018 was similar. Table 20 appears to show that rates of resistance to cephalosporins (CTX, CAZ, CFX) rose in strains isolated in 2017 and 2018, but the same trend was seen in 2015 and 2016 when the focus was limited to domestic chicken meat (figures in parentheses), suggesting that the strains isolated in 2017 and 2018 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-seven among human-derived strains, and 44 among food-derived strains, indicated advanced resistance to as many as six to 11 drugs.

Tables 22 and 23 show antimicrobial resistance in the top two serotypes of food-derived strains (*S*. Infantis and *S*. Schwarzengrund), while Tables 24 to 28 show antimicrobial resistance in the top five serotypes of human-derived strains (*S*. Infantis, *S.* Enteritidis, *S.* Thompson, *S*. 4:i:-, and *S*. Saintpaul). Among food-derived strains, trends in resistance by serotype have many aspects in common, but distinctive features were observed in serotypespecific resistance trends among human-derived strains.

In a comparison of antimicrobial resistance rates between human- and food-derived strains for the three serotypes (*S.* Schwarzengrund, *S.* Infantis, and *S.* Manhattan) appearing in both the top five serotypes among food-derived strains and the top 10 serotypes among human-derived strains (Table 29), 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 19. Serotypes of human- and food-derived non-typhoidal *Salmonella* spp. (2015-2018)

Human-derived strains (n=1,502)	%	Food-derived strains (n=460)	%
Enteritidis	11.5	Schwarzengrund	31.3
Infantis	11.0	Infantis	38.7
4:i:-	8.4	Manhattan	9.1
Thompson	7.9	Agona	2.8
Saintpaul	6.5	Typhimurium	2.4
Typhimurium	5.7	Others	15.7
Schwarzengrund	4.7	Total	100.0
Chester	3.0		
Manhattan	2.8		
Newport	2.7		
Others	35.8		
Total	100.0		

Table 20. The proportion of antimicrobial-resistant human-derived non-typhoidal *Salmonella* spp. (2015-2018)

	2015 (n=388)	2016 (n=361)	2017 (n-436)	2018 (n-317)	2015-2018 (n=1,502)
ABPC	17.3	17.7	15.4	25.4	17.2
GM	0.3	0.6	0.7	0.8	0.5
KM	5.9	11.6	7.6	10.4	8.2
SM	27.3	29.9	27.3	37.5	28.2
TC	32.5	29.1	28.0	32.9	28.8
ST	4.4	6.6	8.9	7.9	6.6
CP	2.3	6.4	5.0	7.5	4.8
CTX	0.3	2.8	3.0	3.8	2.2
CAZ	0.3	2.5	1.6	2.1	1.5
CFX	0.0	1.4	0.5	0.8	0.6
FOM	0.0	0.3	0.5	0.4	0.3

NA	7.0	8.0	9.4	8.3	7.8
CPFX	0.3	0.8	1.6	0.4	0.8
NFLX	0.3	0.8	0.5	0.0	0.4
AMK	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0
Number resistant to one or more antimicrobials	165	151	172	124	612
Proportion resistant to one or more antimicrobials	42.5	41.8	39.4	39.1	42.9

Table 21. The proportion (%) of antimicrobial-resistant food-derived non-typhoidal *Salmonella* spp.* (2015-2018)

	2015 (n=156)	2016 (n=110)	2017 (n=85)	2018 (n=109)	2015-2018 (n=460)
ABPC	17.9	13.6	11.8	13.8	14.8
GM	0.0	0.9	1.2	0.0	0.4
KM	47.4	47.3	44.7	47.7	47.0
SM	82.7	70.9	68.2	75.2	75.4
TC	85.9	76.4	72.9	78.9	79.6
ST	19.9	16.4	11.8	36.7	21.5
CP	7.1	10.0	2.4	7.3	7.0
CTX	5.1(5.4)	5.5(6.3)	8.2(2.6)	8.3(4.4)	6.5(4.9)
CAZ	4.5(4.8)	6.4(7.3)	8.2(2.6)	8.3(4.4)	6.5(4.9)
CFX	2.6(2.7)	3.6(4.2)	7.1(2.6)	7.3(3.3)	4.8(3.2)
FOM	0.0	0.9	1.2	0.0	0.4
NA	18.6	18.2	14.1	18.3	17.6
CPFX	0.0	0.9	1.2	0.0	0.4
NFLX	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0
Number resistant to one or more antimicrobials	143	96	76	99	414
Proportion resistant to one or more antimicrobials	91.7	87.3	89.4	90.8	90.0

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

Table 22. The proportion (%) of antimicrobial-resistant food-derived *S.* Infantis (2015-2018)

	2015 (n=65)	2016 (n=33)	2017 (n=19)	2018 (n=27)	2015-2018 (n=144)
ABPC	10.8	12.1	5.3	14.8	11.1
GM	0.0	3.0	0.0	0.0	0.7
KM	46.2	42.4	15.8	33.3	38.9
SM	81.5	72.7	68.4	85.2	78.5
TC	89.2	81.8	68.4	85.2	84.0
ST	18.5	30.3	0.0	44.4	23.6
CP	3.1	3.0	0.0	0.0	2.1
CTX	4.6	6.1	5.3	11.1	6.3
CAZ	3.1	9.1	5.3	11.1	6.3
CFX	4.6	9.1	5.3	14.8	7.6
FOM	0.0	0.0	0.0	0.0	0.0
NA	3.1	9.1	0.0	3.7	4.2
CPFX	0.0	0.0	0.0	0.0	0.0
NFLX	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0

IPM	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0

Table 23. The proportion (%) of antimicrobial-resistant food-derived *S.* Schwarzengrund (2015-2018)

	2015 (n=47)	2016 (n=37)	2017 (n=44)	2018 (n=50)	2015-2018 (n=178)
ABPC	17.0	5.4	0.0	8.0	7.9
GM	0.0	0.0	0.0	0.0	0.0
KM	85.1	86.5	77.3	80.0	82.0
SM	93.6	78.4	81.8	76.0	82.6
TC	95.7	83.8	79.5	86.0	86.5
ST	36.2	16.2	22.7	56.0	34.3
CP	19.1	10.8	4.5	10.0	11.2
CTX	0.0	0.0	2.3	0.0	0.6
CAZ	0.0	0.0	2.3	0.0	0.6
CFX	0.0	0.0	2.3	0.0	0.6
FOM	0.0	0.0	2.3	0.0	0.6
NA	25.5	18.9	6.8	22.0	18.5
CPFX	0.0	0.0	0.0	0.0	0.0
NFLX	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0

Table 24. The proportion (%) of antimicrobial-resistant human-derived *S.* Infantis (2015-2018)

	2015 (n=34)	2016 (n=48)	2017 (n=62)	2018 (n=21)	2015-2018 (n=165)
ABPC	0.0	2.1	0.0	9.5	1.8
GM	0.0	0.0	0.0	0.0	0.0
KM	20.6	14.6	9.7	23.8	15.2
SM	29.4	33.3	22.6	47.6	30.3
TC	47.1	33.3	25.8	52.4	35.8
ST	14.7	14.6	6.5	14.3	11.5
CP	0.0	0.0	0.0	9.5	1.2
CTX	0.0	2.1	0.0	4.8	1.2
CAZ	0.0	2.1	0.0	0.0	0.6
CFX	0.0	2.1	0.0	0.0	0.6
FOM	0.0	0.0	0.0	0.0	0.0
NA	8.8	4.2	6.5	0.0	5.5
CPFX	0.0	0.0	0.0	0.0	0.0
NFLX	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0

Table 25. The proportion (%) of antimicrobial-resistant human-derived *S.* Enteritidis (2015-2018)

	2015 (n=39)	2016 (n=40)	2017 (n=47)	2018 (n=46)	2015-2018 (n=172)
ABPC	5.1	17.5	4.3	8.7	8.7
GM	0.0	0.0	0.0	0.0	0.0
KM	2.6	2.5	0.0	0.0	1.2
SM	12.8	12.5	12.8	15.2	13.4
TC	10.3	2.5	4.3	10.9	7.0
ST	5.1	0.0	0.0	0.0	1.2

CP	2.6	0.0	0.0	0.0	0.6
CTX	0.0	2.5	0.0	0.0	0.6
CAZ	0.0	2.5	0.0	0.0	0.6
CFX	0.0	0.0	0.0	0.0	0.0
FOM	0.0	0.0	0.0	2.2	0.6
NA	10.3	25.0	12.8	26.1	18.6
CPFX	0.0	0.0	0.0	0.0	0.0
NFLX	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0

Table 26. The proportion (%) of antimicrobial-resistant human-derived *S.* Saintpaul (2015-2018)

	2015 (n=27)	2016 (n=26)	2017 (n=42)	2018 (n=10)	2015-2018 (n=105)
ABPC	7.4	7.7	14.3	10.0	10.5
GM	0.0	0.0	2.4	0.0	1.0
KM	0.0	3.8	4.8	0.0	2.9
SM	3.7	3.8	11.9	0.0	6.7
TC	40.7	15.4	21.4	10.0	23.8
ST	0.0	11.5	16.7	10.0	10.5
CP	3.7	0.0	14.3	0.0	6.7
CTX	0.0	0.0	11.9	0.0	4.8
CAZ	0.0	0.0	2.4	0.0	1.0
CFX	0.0	3.8	0.0	0.0	1.0
FOM	0.0	0.0	2.4	0.0	1.0
NA	7.4	3.8	19.0	0.0	10.5
CPFX	3.7	0.0	9.5	0.0	4.8
NFLX	3.7	0.0	0.0	0.0	1.0
AMK	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0

Table 27. The proportion (%) of antimicrobial-resistant human-derived *S.* 4:i:- (2015-2018)

	2015 (n=42)	2016 (n=9)	2017 (n=39)	2018 (n=36)	2015-2018 (n=126)
ABPC	83.3	77.8	79.5	86.1	82.5
GM	2.4	0.0	2.6	0.0	1.6
KM	4.8	0.0	2.6	8.3	4.8
SM	83.3	88.9	82.1	91.7	85.7
TC	81.0	66.7	76.9	80.6	78.6
ST	0.0	0.0	7.7	8.3	4.8
CP	0.0	0.0	7.7	13.9	6.3
CTX	0.0	0.0	2.6	2.8	1.6
CAZ	0.0	0.0	2.6	0.0	0.8
CFX	0.0	0.0	2.6	0.0	0.8
FOM	0.0	11.1	0.0	0.0	0.8
NA	0.0	0.0	5.1	0.0	1.6
CPFX	0.0	0.0	0.0	0.0	0.0
NFLX	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0

MEPM	0.0	0.0	0.0	0.0	0.0

Table 28. The proportion (%) of antimicrobial-resistant human-derived *S*. Thompson (2015-2018)

	2015 (n=28)	2016 (n=28)	2017 (n=31)	2018 (n=24)	2015-2018 (n=111)
ABPC	0.0	10.7	0.0	0.0	2.7
GM	0.0	0.0	0.0	0.0	0.0
KM	7.1	0.0	0.0	0.0	1.8
SM	7.1	7.1	3.2	0.0	4.5
TC	3.6	7.1	6.5	0.0	4.5
ST	0.0	7.1	0.0	0.0	1.8
CP	0.0	7.1	0.0	0.0	1.8
CTX	0.0	10.7	0.0	0.0	2.7
CAZ	0.0	7.1	0.0	0.0	1.8
CFX	0.0	7.1	0.0	0.0	1.8
FOM	0.0	0.0	0.0	0.0	0.0
NA	0.0	0.0	0.0	4.2	0.9
CPFX	0.0	7.1	0.0	0.0	1.8
NFLX	0.0	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0

Table 29. Resistance rates among *S.* Infantis, *S.* Schwarzengrund, and *S.* Manhattan detected in humans and food (2015-2018) (%)

	Infantis		**Schwarzengrund**		**Manhattan**	
	Human (n=165)	Food (n=144)	Human (n=71)	Food (n=178)	Human (n=42)	Food (n=42)
ABPC	1.8	11.1	4.2	7.9	2.4	11.9
GM	0.0	0.7	0.0	0.0	0.0	0.0
KM	15.2	38.9	60.6	82.0	0.0	0.0
SM	30.3	78.5	70.4	82.6	90.5	97.6
TC	35.8	84.0	69.0	86.5	88.1	81.0
ST	11.5	23.6	29.6	34.3	2.4	2.4
CP	1.2	2.1	1.4	11.2	0.0	0.0
CTX	1.2	6.3	2.8	0.6	0.0	11.9
CAZ	0.6	6.3	2.8	0.6	0.0	11.9
CFX	0.6	7.6	0.0	0.6	0.0	0.0
FOM	0.0	0.0	0.0	0.6	0.0	0.0
NA	5.5	4.2	16.9	18.5	9.5	14.3
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, 982, and 1,167 *Neisseria gonorrhoeae* strains that were respectively isolated in 2015, 2016, 2017, and 2018 were tested for antimicrobial susceptibility (based on EUCAST breakpoints; Table 30). Ceftriaxone (CTRX)resistant strains respectively accounted for 6.2%, 4.3%, 4.3%, and 3.5%. Strains assessed as resistant based on the CLSI Criteria (MIC ≥ 0.5 μg/mL) accounted for 0.6%, 0.4%, 0.5%, and 0.3%. 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, 42.6% in 2017 and 43.9% in 2018.

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%, 4.0%, and 6.3% of strains respectively between 2015 and 2018. 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%, 11.2%, and 15.9% of strains respectively between 2015 and 2018. 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 70-80%. Penicillins (PCG) would not have a therapeutic effect on more than 80% of strains.

Table 30. The proportion (%) of antimicrobial-resistant *Neisseria gonorrhoeae*

	2015 (618 strains)	2016 (675 strains)	2017 (982 strains)	2018 (1,167 strains)
CTRX	6.2	4.3	4.3	3.5
SPCM	0.0	0.0	0.0	0.0
AZM	13.0	33.5	42.6	43.9
PCG*	38.4 (96.6)	36.3 (96.9)	37.8 (99.0)	31.7 (82.5)
CFIX	36.2	43.2	31.0	28.4
CPFX	79.5	78.0	75.8	66.9

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 31-46 *Salmonella* Typhi strains that were isolated between 2015 and 2018 were tested for antimicrobial susceptibility (Table 24). Ciprofloxacin (CPFX)-non-susceptible strains accounted for 61.7-83.9%, while strains with advanced resistance (MIC ≥ 4) to ciprofloxacin accounted for 5.9-23.9%. During this period, eight strains of multidrug-resistant *Salmonella* Typhi that indicated resistance to ampicillin (ABPC), chloramphenicol (CP) and ST were isolated, along with one strain of cefotaxime (CTX)-resistant *Salmonella* Typhi.

The 13-30 *Salmonella* Paratyphi A strains that were isolated between 2015 and 2018 were tested for antimicrobial susceptibility. Ciprofloxacin (CPFX)-non-susceptible strains accounted for 76.9-100%. No cefotaxime-resistant strains were isolated among the *Salmonella* Paratyphi A.

The 91-156 *Shigella* spp. strains that were isolated between 2015 and 2018 were tested for antimicrobial susceptibility. ST-resistant strains accounted for 73.6-81.0%; ciprofloxacin-non-susceptible strains for 21.2-45.7%; and cefotaxime-resistant strains for 5.1-16.4%.

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

	2015 (32 strains)	2016 (46 strains)	2017 (31 strains)	2018 (34 strains)
ABPC	5.7	2.2	12.9	2.9
CP	5.7	2.2	12.9	5.9
ST	5.7	2.2	12.9	5.9
NA	68.8	63.0	83.9	61.7
CPFX	68.8 (12.5*)	63.0 (23.9*)	83.9 (16.1*)	61.7 (5.9*)
CTX	0.0	0.0	0.0	2.9

* Advanced resistance to fluoroquinolone

Table 32. The proportion (%) of antimicrobial-resistant *Salmonella* Paratyphi A

	2015 (30 strains)	2016 (20 strains)	2017 (13 strains)	2018 (21 strains)
ABPC	0.0	0.0	0.0	0.0
CP	0.0	0.0	0.0	0.0
ST	0.0	0.0	0.0	0.0
NA	80.0	80.0	76.9	100
CPFX	83.3	83.3	76.9	100
CTX	0.0	0.0	0.0	0.0

Table 33. The proportion (%) of antimicrobial-resistant *Shigella* spp.

	2015 (105 strains)	2016 (73 strains)	2017 (91 strains)	2018 (156 strains)
ABPC	21.9	42.5	31.9	19.2
CP	11.4	24.7	26.4	9.0
ST	81.0	80.8	73.6	76.9
NA	63.8	52.1	52.8	45.5
CPFX	45.7	35.6	35.2	21.2
CTX	5.7	16.4	13.2	5.1

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 2018, 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 approximately 50 to 60 (0.4-0.7%) per year.

Table 34. Newly Notified Patients with Culture-positive Pulmonary Tuberculosis: Trends in Drug Susceptibility at the Time of Notification

	2011	2012	2013	2014	2015	2016	2017	2018
Culture-positive patients, N	10,915	11,261	10,523	10,259	10,035	9878	9,580	9,016
INH-resistant, n	386	380	369	349	372	369	383	377
(%)*	(4.8)	(4.6)	(4.8)	(4.6)	(4.9)	(4.8)	(4.9)	(5.0)
RFP-resistant, n	86	73	64	76	77	74	80	87
(%)*	(1.1)	(0.9)	(0.8)	(1.0)	(1.0)	(1.0)	(1.0)	(1.1)
INH & RFP-resistant†, n	60	60	47	56	48	49	52	55
(%)*	(0.7)	(0.7)	(0.4)	(0.5)	(0.5)	(0.6)	(0.7)	(0.6)
SM-resistant, n	-	509	475	469	476	461	557	471
(%)§		(6.1)	(6.2)	(6.2)	(6.3)	(6.0)	(7.1)	(6.3)
EB-resistant, n	-	151	106	130	129	100	106	130
(%)¶		(1.8)	(1.4)	(1.7)	(1.7)	(1.3)	(1.3)	(1.7)

* The denominator was defined as the number of patients with recorded INH- and RFP-susceptibility testing results among all culture-positive patients: 8,046 (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, 7,891 (82.4%) patients in 2017 and 7,570 (84.0%) patients in 2018.

-: 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, 51 patients in 2017 and 47 patients in 2018.

¶ 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, 14 in 2017 and 13 in 2018).

6) *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.[3] *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.[4]

Observational studies in Japan indicate that 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.[5] In a multi-institutional prospective study (20 wards at 12 institutions) using toxigenic cultures and nucleic acid amplification tests (NAAT), the CDI incidence rate was 7.4 cases per 10,000 patient days, rising to 22.2 in ICU wards, suggesting that the incidence rate is higher than indicated by existing reports, with a high risk in ICU wards.[6] Consideration must be given to the impact of such factors as definitions of specimen collection, testing methods, and recurrence, and differences in the average length of admission compared with other countries. CDI surveillance was launched in 2019 via Japan Surveillance for Infection Prevention and Health-care Epidemiology (J-SIPHE). Testing methods and the definition of specimen collection are being selected and clarified, and information gathered.

7) 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 has more than doubled over the past seven years. In 2018, among 305,960 surgical operations undertaken at 802 institutions, SSI were reported in 15,566 cases (5.1%). 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 has been 1.3-1.7 per 1,000 days of ICU stay over the past seven years, with a figure of 1.3 per 1,000 days of ICU stay recorded in 2018. While the incidence of urinary tract infection is around 0.5-0.8 per 1,000 days of ICU stay, the figure has shown a slight rise since 2016. Meanwhile, the incidence of catheter related bloodstream infection is around 0.6-0.8 per 1,000 days of ICU stay, but the figure has declined somewhat since 2017. JANIS monitors cases of infections that occurred between 48 hours after admission to ICU and discharge from ICU.

i. Surgical site infection

Table 35. The trend of reported SSI cases

	2011	2012	2013	2014	2015	2016	2017	2018
Total SSI cases per total surgical operations (%)*	**6.0**	**6.8**	**6.5**	**6.0**	**5.8**	**5.7**	**5.4**	**5.1**
Participated medical institutions	333	363	442	552	671	730	772	802
Total surgical operations	127,731	129,825	161,077	207,244	251,832	274,132	292,031	305,960
Total SSI cases	7,719	8,771	10,445	12,508	14,701	15,674	15,889	15,566

* 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.[7]

ii. Infections at Intensive Care Unit (ICU)

Table 36. Incidence rates of infection at ICU

		2011	2012	2013	2014	2015	2016	2017	2018
Ventilator-associated pneumonia	**Total infection incidence rate***	**1.7**	**1.4**	**1.3**	**1.4**	**1.5**	**1.5**	**1.3**	**1.3**
	Total infections at monitored medical institutions	382	327	324	395	522	499	405	409
Urinary tract infection	**Total infection incidence rate***	**0.5**	**0.5**	**0.6**	**0.5**	**0.5**	**0.6**	**0.7**	**0.8**
	Total infections at monitored medical institutions	111	124	143	148	190	219	213	244
Catheter-related bloodstream infection	**Total infection incidence rate***	**0.7**	**0.7**	**0.8**	**0.7**	**0.7**	**0.8**	**0.7**	**0.6**
	Total infections at monitored medical institutions	168	162	204	205	240	263	213	190

* 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 division, JANIS.[8]

8) Survey of infections and antimicrobial use at long-term care facilities for the elderly

Source: AMR Clinical Reference Center (AMRCRC)

In February and March 2019, funded by a Health and Labor Sciences Research Grant, the AMR Clinical Reference Center (AMRCRC) conducted a survey of healthcare-associated infections and antimicrobial use at long-term care facilities for the elderly.[9] The center randomly selected 1,500 facilities from among the members of the Japan Association of Geriatric Health Services Facilities and conducted a point prevalence survey (PPS). Responses were received from 134 facilities (a response rate of 8.9%). Geriatric health services facilities are classified into five type according to their performance based on their function related to home return. In addition, if previous hospital beds are converted to geriatric health services facility, it is called nursing convalescence type.The majority of responses came from Higher Return-to-home facilities (32.5%) and **Conventional** facilities (60.3%).

The median number of oral antimicrobials deployed in the facilities was four, while the median number of parenteral antimicrobials was two. The main oral antimicrobials used were quinolones and third-generation cephalosporins, while the main parenteral antimicrobials were third-generation cephalosporins and penicillins.

A total of 10,148 patients were admitted to the facilities on the day the survey was carried out. Of these, 172 (1.7%) were using antimicrobials. The median age of the patients was 86.0 years (IQR: 81-91), while the median age of male patients was 84.0 years (IQR: 75-89) and that of female patients was 87.0 years (IQR: 83-92). The top three medical devices being used by patients were peripheral routes and self-inserted or indwelling bladder catheters, which were both used by 33 people (19.4%), and gastrostomy tubes, which were used by 23 people (13.5%). A total of 86 people (50.6%) were not using any medical devices. The top focus of infection were urinary tract infections, affecting 73 people (47.7%); pneumonia, affecting 31 people (20.3%); and upper respiratory tract infections, affecting 15 people (9.8%). The main antimicrobials used to treat urinary tract infections and pneumonia were fluoroquinolones and third-generation cephalosporins. It is necessary to continue to ascertain the status of infections and antimicrobial use at long-term care facilities for the elderly and to promote antimicrobial stewardship.

Table 37. Facility Types

Higher Return-to-home			**Conventional**	**Minimum function**	**Nursing Convalescent**
Super return to home Addition of return-to-home care / home care support functions II		**Return-to-home** Addition of return-to-home care / home care support functions I			
33 (26.2%)	8 (6.3%)	40 (31.7%)	36 (28.6%)	5 (4.0%)	4 (3.2%)

Table 38. Number of antimicrobial agents deployed at facilities: 4 ATC categories

Number of antimicrobial agents based on the 4 ATC categories	Oral Antimicrobials Number of Institutions	Parenteral Antimicrobials Number of Institutions
None	4	25
1 agent	4	29
2 agents	21	27
3 agents	27	13
4 agents	31	13
5 agents	23	6
6 agents	13	2
7 agents or more	3	11
Total	126	126

Table 39. Usage of medical devices by patients using antimicrobials [Multiple answers] n=170 *Missing values: 2

Type of medical device	Number of people (%)
Peripheral route	33 (19.4%)

Self-inserted/indwelling bladder catheter	33 (19.4%)
Gastrostomy tube	23 (13.5%)
Nasogastric tube	12 (7.1%)
Dialysis catheter	3 (1.8%)
Tracheostomy tube	2 (1.2%)
Colostomy equipment	2 (1.2%)
Nephrostomy/cystostomy tube	1 (0.6%)
Other (sputum suction tube, ureteral stent/enterostomy tube)	3 (1.8%)
Not using a medical device	86 (50.6%)
Total	170

Table 40. Focus of infection undergoing treatment [Multiple answers] n=153 *Missing values: 1

Focus of infection or diagnosis	Number of people (%)
Urinary tract infection	78 (51.0%)
Pneumonia	37 (24.2%)
Upper respiratory tract infection	15 (9.8%)
Bronchitis	9 (5.9%)
Cellulitis	7 (4.6%)
Gastroenteritis	2 (1.3%)
Unknown	7 (4.6%)
Other	12 (7.8%)

Breakdown of the 12 cases listed as "Other": 2 pharyngitis, 2 epidermal cyst, 2 toe inflammation, 1 pressure ulcers on the right second and third toe joints, 1 vaginitis, 1 inflammation of the remaining dental root, 1 suspected bile duct calculus, 1 suspected palmoplantar pustulosis, 1 details unclear

(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

Surveys of bacteria derived from diseased animals were carried out using bacteria isolated from food-producing animals which were subjected to pathological appraisal by prefectural livestock hygiene service centers.

i. *Salmonella* spp.

Monitoring of antimicrobial resistance on 11 agents was carried out between 2011 and 2017. Ampicillin (ABPC) resistance in strains isolated from pigs and tetracycline (TC) resistance in strains isolated from pigs and chickens were observed to exceed 50% in 2017, as were kanamycin (KM) and sulfamethoxazole-trimethoprim (ST) resistance in chickens. On the other hand, no strains that indicated resistance to cefotaxime (CTX), which is a critically important antimicrobial for human medicine, were isolated from any livestock. Resistance to ciprofloxacin (CPFX) was less than 5% in strains derived from all livestock, as was resistance to colistin (CL) in cattle-derived strains. It must be noted that the BPs of cefazolin (CEZ) and CPFX were lowered between 2015 and 2016 to bring them into line with the values established by CLSI, and the BP of CL was lowered during this period in light of the EUCAST BP. 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.

Looking at trends in resistance rates between 2011 and 2017, ongoing upward trends were observed in ampicillin (ABPC) resistance among pigs and kanamycin (KM) resistance among chickens. In all other cases, while fluctuations in resistance rates could be seen, no definite trends were observed. It will remain necessary to make judgments based on the results of future surveys.

Table 41. The proportion (%) of antimicrobial-resistant *Salmonella* spp. isolated from diseased animals

Agent	BP	Animal	2011	2012	2013	2014	2015	2016	2017
ABPC	32*	Cattle	28.0	32.9	60.7	61.9	56.6	50.0	36.8
		Pigs	25.4	25.3	45.0	41.4	46.9	41.1	50.0
		Chickens	12.0	9.4	4.0	3.9	14.3	-	4.5
CEZ	32 (8* from 2016)	Cattle	10.0	1.2	8.9	7.9	7.9	22.9	3.5
		Pigs	0.0	0.0	0.0	0.0	6.1	23.2	9.4
		Chickens	0.0	3.1	4.0	0.0	0.0	-	0.0
CTX	4*	Cattle	10.0	1.2	8.9	7.9	7.9	4.3	0.0
		Pigs	0.0	0.0	0.0	0.0	4.1	0.0	0.0
		Chickens	0.0	0.0	4.0	0.0	0.0	-	0.0
GM	16*	Cattle	0.0	0.0	0.0	3.2	7.9	4.3	1.8
		Pigs	6.3	3.6	15.0	15.5	8.2	17.9	4.7
		Chickens	0.0	0.0	2.0	0.0	0.0	-	0.0
KM	64*	Cattle	12.0	3.7	25.0	14.3	21.1	25.7	0.0
		Pigs	9.5	12.0	6.7	8.6	6.1	10.7	4.7
		Chickens	24.0	15.6	22.0	29.4	42.9	-	63.6
TC	16*	Cattle	30.0	32.9	66.1	50.8	55.3	42.9	33.3
		Pigs	61.9	53.0	66.7	60.3	61.2	58.9	50.0
		Chickens	36.0	34.4	30.0	39.2	42.9	-	77.3
NA	32*	Cattle	2.0	7.3	1.8	3.2	11.8	5.7	1.8
		Pigs	15.9	21.7	5.0	15.5	6.1	7.1	20.3
		Chickens	8.0	6.3	8.0	3.9	28.6	-	0.0
CPFX	4 (1* from 2016)	Cattle	0.0	0.0	0.0	0.0	0.0	0.0	1.8
		Pigs	0.0	0.0	0.0	0.0	0.0	3.6	4.7
		Chickens	0.0	0.0	0.0	0.0	0.0	-	0.0
CL	16 (4 from 2016)	Cattle	0.0	0.0	0.0	0.0	0.0	1.4	0.0
		Pigs	0.0	0.0	1.7	0.0	0.0	3.6	6.3
		Chickens	0.0	3.1	2.0	0.0	0.0	-	18.2
CP	32*	Cattle	14.0	12.2	10.7	17.5	22.4	12.9	3.5
		Pigs	12.7	13.3	11.7	25.9	12.2	8.9	21.9
		Chickens	0.0	6.3	6.0	3.9	14.3	-	0.0
TMP (SMX/TMP in 2011)	16* (SMX/TMP 76/4*)	Cattle	2.0	1.2	1.8	6.3	13.2	4.3	1.8
		Pigs	25.4	21.7	36.7	32.8	22.4	21.4	12.5
		Chickens	20.0	15.6	14.0	29.4	42.9	-	59.1
Strains tested (n)		Cattle	50	82	56	63	76	70	57
		Pigs	63	83	60	58	49	56	64
		Chickens	25	32	50	51	7	-	22

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

Table 42. Number of strains of *Salmonella enterica* isolated from diseased food-producing animals by serotype (FY2014-17)

Serotypes	Cattle	Pigs	Chickens	Total	(%)
Typhimurium	74	89	1	164	30.5
4:i:-	87	42	0	129	24.0
Choleraesuis	0	28	0	28	5.2
Schwarzengrund	2	1	14	17	3.2
Derby	2	12	0	14	2.6
Infantis	16	4	8	28	5.2
Braenderup	4	0	5	9	1.7
Newport	7	3	1	11	2.0
Mbandaka	5	1	5	11	2.0
Thompson	10	1	2	13	2.4
Enteritidis	1	0	6	7	1.3
Dublin	7	0	0	7	1.3
Rissen	2	4	0	6	1.1
Stanley	13	0	0	13	2.4

Tennessee	0	0	2	2	0.4
Others	41	24	14	79	14.7
Total	271	209	58	538	100.0

ii. *Staphylococcus aureus*

Monitoring of antimicrobial resistance on 8 agents was carried out between 2011 and 2017. Resistance rates of Ampicillin (ABPC) and tetracycline (TC) in pig-derived strains were observed to exceed 50% in 2017. Resistance rates to all antimicrobials 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 8.2% in pig-derived strains, but less than 4% in strains isolated from cattle and chickens.

Table 43. The proportion (%) of antimicrobial-resistant *Staphylococcus aureus* isolated from diseased animal

Agent*	BP	Animal	2011	2012	2013	2014	2015	2016	2017
ABPC	0.5	Cattle	5.5	13.6	11.0	11.1	21.3	7.8	7.4
		Pigs	-	-	-	-	-	75.6	71.4
		Chickens	0.0	25.0	0.0	15.4	50.0	3.7	22.6
SM	64	Cattle	6.4	2.3	2.8	1.1	2.7	1.4	3.4
		Pigs	-	-	-	-	-	33.3	20.4
		Chickens	0.0	10.0	0.0	7.7	16.7	3.7	0.0
GM	16†	Cattle	0.9	2.3	1.8	0.0	1.3	0.0	0.6
		Pigs	-	-	-	-	-	2.2	14.3
		Chickens	0.0	15.0	0.0	0.0	0.0	3.7	9.7
EM	8†	Cattle	1.8	3.4	5.5	0.0	6.7	2.8	1.7
		Pigs	-	-	-	-	-	37.8	38.8
		Chickens	50.0	55.0	0.0	15.4	16.7	22.2	6.5
TC	16†	Cattle	0.0	2.3	8.3	5.5	6.7	0.0	0.0
		Pigs	-	-	-	-	-	57.8	53.1
		Chickens	37.5	5.0	0.0	16.7	16.7	33.3	19.4
CP	32†	Cattle	0.0	0.0	0.9	0.0	1.3	0.0	0.6
		Pigs	-	-	-	-	-	22.2	30.6
		Chickens	0.0	0.0	0.0	15.4	33.3	3.7	3.2
CPFX	4†	Cattle	0.0	0.0	0.9	0.0	1.3	0.7	0.6
		Pigs	-	-	-	-	-	11.1	8.2
		Chickens	25.0	0.0	4.2	15.4	33.3	3.7	3.2
Strains tested (n)		Cattle	109	88	109	91	75	141	175
		Pigs	-	-	-	-	-	45	49
		Chickens	8	20	24	12	6	27	31

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 2017. In 2017, antimicrobial resistance in excess of 50% was observed among strains isolated from food-producing animals as follows: ampicillin (ABPC) and streptomycin (SM) resistance among cattle and chickens; tetracycline (TC) resistance among cattle, pigs, and chickens; nalidixic acid (NA) resistance among pigs and chickens; and colistin (CL), chloramphenicol (CP), and trimethoprim (TMP) resistance among pigs. Resistance rates to all antimicrobials other than cefotaxime (CTX) 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 3.3-8.9%, 11.1-28.5%, and 0.0-52.0, respectively. It must be noted that the BP of cefazolin (CEZ) began to be lowered in 2016 to bring it into line with the value established by CLSI, and the BP of CL was lowered during this period in light of the EUCAST BP. As the BP of CL has changed, resistance rates in strains isolated from pigs have been above 50% since 2016, but no upward trend has been observed in resistance rates using the pre-revision BP. As CL was positioned as a second-line veterinary drug

in 2018, its designation as a feed additive was revoked and its use prohibited. Accordingly, it will be necessary to check trends in resistance rates resulting from these risk management measures going forward.

Looking at trends in resistance rates between 2012 and 2017, an ongoing downward trend was observed in ampicillin (ABPC) resistance among chickens. In the other cases, while fluctuations in resistance rates could be seen, no definite trends were observed. It will remain necessary to make judgments based on the results of future surveys.

Table 44. The proportion (%) of antimicrobial-resistant *Escherichia coli* isolated from diseased animals

Agent	BP	Animal	2012†	2013†	2014†	2015	2016	2017
ABPC	32*	Cattle	-	61.4	57.8	63.8	37.7	50.0
		Pigs	-	65.2	50.4	57.4	74.5	70.7
		Chickens	75.6	54.2	-	60.4	43.5	33.3
CEZ	32 (8* from 2016)	Cattle	-	21.1	6.7	14.9	15.6	15.6
		Pigs	-	10.1	6.1	9.3	34.3	35.0
		Chickens	40.2	16.7	-	14.6	15.2	11.1
CTX	4*	Cattle	-	10.5	6.7	8.5	7.8	8.9
		Pigs	-	2.5	0.0	3.7	2.9	3.3
		Chickens	37.8	14.6	-	10.4	6.5	5.6
SM	32	Cattle	-	-	68.9	78.7	49.4	61.1
		Pigs	-	-	64.3	66.7	74.5	72.4
		Chickens	-	-	-	60.4	56.5	38.9
GM	16*	Cattle	-	17.5	6.7	12.8	10.4	8.9
		Pigs	-	24.1	8.7	19.4	21.6	22.8
		Chickens	6.1	3.1	-	2.1	10.9	5.6
KM	64*	Cattle	-	38.6	26.7	29.8	16.9	26.7
		Pigs	-	34.2	33.9	31.5	46.1	39.0
		Chickens	51.2	35.4	-	39.6	50.0	36.1
TC	16*	Cattle	-	50.9	66.7	66.0	54.5	62.2
		Pigs	-	79.1	75.7	75.9	87.3	78.9
		Chickens	74.4	61.5	-	70.8	78.3	55.6
NA	32*	Cattle	-	29.8	33.3	36.2	18.2	33.3
		Pigs	-	60.1	52.2	50.0	48.0	50.4
		Chickens	73.2	59.4	-	52.1	56.5	55.6
CPFX	4*	Cattle	-	19.3	24.4	34.0	11.7	17.8
		Pigs	-	36.1	23.5	32.4	24.5	28.5
		Chickens	22.0	25.0	-	8.3	8.7	11.1
CL	16 (4* from 2016)	Cattle	-	5.3	6.7	0.0	10.4	20.0
		Pigs	-	3.2	0.0	2.8	56.9§1	52.0§2
		Chickens	2.4	1.0	-	0.0	8.7	0.0
CP	32*	Cattle	-	21.1	28.9	46.8	19.5	28.9
		Pigs	-	64.6	64.3	61.1	69.6	59.3
		Chickens	22	25	-	16.7	21.7	11.1
TMP	16	Cattle	-	22.8	33.3	44.7	23.4	35.6
		Pigs	-	49.4	59.1	64.8	62.7	56.9
		Chickens	31.7	33.3	-	33.3	23.9	13.9
Strains tested (n)		Cattle	-	57	45	47	77	90
		Pigs	-	158	115	108	102	123
		Chickens	82	96	-	48	46	36

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

†-: Not under surveillance.

§1 If the microbiological BP of 16 used by JVARM is applied, CL resistance in pig-derived strains was 2.9% in 2016.

§2 If the microbiological BP of 16 used by JVARM is applied, CL resistance in pig-derived strains was 1.6% in 2017.

Bacteria derived from healthy food-producing animals

Until 2015, surveillance of food-borne pathogenic bacteria and indicator bacteria from healthy animals was carried out using samples of feces collected at farms by livestock hygiene service centers. On the other hand, sampling of feces from healthy food-producing animals began at animal and poultry slaughterhouses in FY2012, as Western countries had positioned such slaughterhouses as places for the collection of samples for antimicrobial resistance monitoring, due to their being closer to the final food product and the fact that they facilitate intensive collection of feces. No major differences were found when the FY2012 and FY2013 results for *Escherichia coli* and *Campylobacter* at animal and poultry slaughterhouses were compared with those from farms, so Japan switched from sampling feces at farms to sampling them at animal and poultry slaughterhouses in FY2016.

Bacteria derived from food-producing animals in farms (until 2015)

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 45. 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 46. 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%.

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 *E. 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 *E. 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 *E. faecalis* ranged between 0.0% and 6.3%, those for *E. faecium* varied from 28.0% to as high as 92.3%.

Table 47. 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 48. 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 49. 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. 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.

Table 50. 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 (from 2012)

i. *Escherichia coli*

Monitoring of antimicrobial resistance on 12 agents was carried out between 2012 and 2017. Streptomycin (SM) resistance in strains isolated from chickens was observed to exceed 40% in 2017, as was tetracycline (TC) resistance in pig- and chicken-derived strains. On the other hand, cefazolin (CEZ) and gentamicin (GM) resistance was less than 10%. In the realm of critically important antimicrobials for human medicine, resistance rates to cefotaxime (CTX), ciprofloxacin (CPFX), and colistin (CL) were respectively less than 5%, less than 13%, and less than 1%. Looking at trends in resistance rates to each agent between 2012 and 2017, an upward trend was observed in kanamycin (KM) resistance among chickens since 2012.

Table 51. The proportion (%) of antimicrobial-resistant *Escherichia coli* derived from animal and poultry slaughterhouses

Agent	BP	Animal	2012	2013	2014	2015	2016	2017
ABPC	32*	Cattle	2.4	6.5	3.0	5.5	7.4	4.8
		Pigs	32.3	26.0	43.0	34.4	36.7	33.7
		Chickens	30.8	35.5	40.1	43.5	36.1	39.3
CEZ	32	Cattle	0.4	0.3	0.0	0.0	1.2	0.8
		Pigs	1.0	0.8	1.1	1.0	1.1	1.2
		Chickens	3.0	7.8	5.8	3.8	7.0	4.7
CTX	4*	Cattle	0.0	0.0	0.4	0.0	0.4	0.4
		Pigs	0.0	0.0	1.1	0.0	1.1	1.2
		Chickens	1.5	4.8	4.1	2.2	5.7	4.7
SM	32	Cattle	14.9	12.3	17.1	12.4	22.1	19.0
		Pigs	44.1	44.9	52.7	39.6	50.0	41.0
		Chickens	39.1	38.6	44.8	41.8	51.3	41.3
GM	16*	Cattle	0.0	0.3	0.0	0.0	0.8	0.0
		Pigs	0.5	2.4	6.5	2.1	3.3	3.6
		Chickens	1.5	1.8	2.9	2.2	5.1	6.0
KM	64*	Cattle	1.2	1.5	0.4	0.7	4.3	1.2
		Pigs	9.7	7.9	9.7	8.3	10.0	10.8
		Chickens	24.1	24.1	33.1	37.5	43.7	36.7
TC	16*	Cattle	19.0	16.4	19.8	18.6	29.8	21.0
		Pigs	58.5	62.2	59.1	45.8	56.7	55.4
		Chickens	49.6	44.0	43.6	54.9	56.3	46.0
NA	32*	Cattle	2.4	1.8	2.3	2.6	2.3	2.0
		Pigs	4.1	11.0	9.7	5.2	15.6	12.0
		Chickens	39.8	36.1	45.3	35.9	35.4	39.3
CPFX	4*	Cattle	0.0	0.6	0.8	0.0	0.4	0.0
		Pigs	1.5	0.8	2.2	3.1	4.4	0.0
		Chickens	6.0	5.4	9.9	4.9	10.1	12.0
CL	16	Cattle	0.0	0.0	0.8	0.0	0.4	0.8
		Pigs	0.0	0.0	0.0	0.0	1.1	0.0
		Chickens	0.8	0.6	0.0	0.5	1.9	0.0
CP	32*	Cattle	5.2	2.3	3.8	2.9	2.3	2.8
		Pigs	23.6	23.6	34.4	25.0	25.6	21.7
		Chickens	11.3	11.4	15.1	9.8	19.6	11.3
SMX/TMP	76/4*	Cattle	2.0	2.9	5.3	2.9	0.4	2.0
		Pigs	23.6	26.8	34.4	30.2	4.4	26.5
		Chickens	24.8	31.9	30.2	28.3	10.1	34.7
Strains tested (n)		Cattle	248	341	263	274	258	252
		Pigs	195	127	93	96	90	83
		Chickens	133	166	172	184	158	150

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

ii. *Campylobacter jejuni*

Monitoring of antimicrobial resistance on 8 agents between 2012 and 2016, and 9 agents adding AZM in 2017 was carried out. Resistance to tetracycline (TC), nalidixic acid (NA), and ciprofloxacin (CPFX) exceeding 40% was observed in cattle- and chicken-derived strains in 2017. On the other hand, rates of resistance to streptomycin (SM), erythromycin (EM), and chloramphenicol (CP) were less than 5%, less than 2%, and less than 7%, respectively. Resistance to CPFX, which is a critically important antimicrobial for human medicine, was 50.5% in cattle-derived strains and 44.8% in chicken-derived strains. Looking at trends in resistance rates to each agent between 2012 and 2017, an upward trend was observed in TC resistance among cattle since 2012.

Table 52. The proportion (%) of antimicrobial-resistant *Campylobacter jejuni* derived from animal and poultry slaughterhouses

Agent*	BP	Animal	2012	2013	2014	2015	2016	2017
ABPC	32	Cattle	0.0	9.1	12.9	8.9	7.4	8.2
		Chickens	19.7	19.8	17.5	19.1	16.2	28.4
SM	32	Cattle	2.4	3.5	3.8	3.2	6.2	4.1
		Chickens	1.4	0.0	3.5	2.1	8.8	1.5
EM	32†	Cattle	0.0	0.7	0.0	1.3	0.0	0.0
		Chickens	0.0	0.0	0.0	0.0	0.0	1.5
AZM	4	Cattle	–	–	–	–	–	0.0
		Chickens	–	–	–	–	–	1.5
TC	16†	Cattle	45.1	52.4	49.2	52.2	63.0	72.2
		Chickens	38.0	44.4	38.6	28.7	33.8	46.3

CP	16	Cattle	0.0	6.3	0.0	1.3	1.2	6.2
		Chickens	0.0	0.0	1.8	0.0	2.9	0.0
NA	32	Cattle	34.1	33.6	50.8	42.7	44.4	48.5
		Chickens	39.4	48.1	29.8	27.7	57.4	46.3
CPFX	4†	Cattle	34.1	29.4	49.2	40.8	44.4	50.5
		Chickens	39.4	39.5	29.8	26.6	51.5	44.8
Strains tested (n)		Cattle	82	143	132	157	81	97
		Chickens	71	81	57	94	68	67

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 between 2012 and 2017 and 9 agents adding AZM in 2017 was carried out. In pig-derived strains in 2017, resistance to streptomycin (SM) exceeding 60%, resistance to tetracycline (TC) exceeding 80%, and resistance to nalidixic acid (NA) and ciprofloxacin (CPFX) exceeding 40% was observed. On the other hand, chloramphenicol (CP) resistance was less than 2%. Resistance to CPFX, which is a critically important antimicrobial for human medicine, was 54.1%.

Table 53. The proportion (%) of antimicrobial-resistant *Campylobacter coli* derived from animal slaughterhouses

Agent*	BP	Animal	2012	2013	2014	2015	2016	2017
ABPC	32	Pigs	23.3	25.5	36.6	24.6	15.4	29.5
SM	32	Pigs	67.4	78.3	69.9	72.3	64.1	68.9
EM	32†	Pigs	32.6	44.3	43.0	26.2	38.5	31.1
AZM	4	Pigs	–	–	–	–	–	31.1
TC	16†	Pigs	84.5	93.4	80.6	87.7	89.7	83.6
CP	16	Pigs	10.9	3.8	7.5	9.2	15.4	1.6
NA	32	Pigs	46.5	53.8	52.7	47.7	61.5	50.8
CPFX	4†	Pigs	46.5	46.2	50.5	47.7	59.0	54.1
Strains tested (n)		Pigs	129	106	93	65	39	61

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 between 2012 and 2014, and 14 agents adding VCM since 2015 was carried out. Resistance to kanamycin (KM), erythromycin (EM), lincomycin (LCM), and tylosin (TS) in strains isolated from chickens was observed to exceed 40% in 2017, 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 0.0% and 3.7%, and no resistance to vancomycin (VCM) was observed.

Among *Enterococcus* spp. in 2017, 4.1% (10 out of 242) 0f cattle-derived strains and 57.4% (85 out of 148) 0f chicken-derived strains were *E. faecalis*, and 1.7% (4 out of 242) of cattle-derived strains and 14.9% (22 out of 148) chicken-derived strains were *E. faecium*,that was generally same trend as before. Resistance to enrofloxacin (ERFX), which is a critically important antimicrobial for human medicine, was 3.7% in pig-derived and 2.7% in chicken-derived strains of *Enterococcus* spp., but whereas the figure for *E. faecalis* was 0.0%, the figures for *E. faecium* were as high as 27.3% and 18.2%, respectively.

Table 54. The proportion (%) of antimicrobial-resistant *Enterococcus* spp. derived from animal slaughterhouses

Agent*	BP	Animal	2012	2014†	2015	2016	2017
ABPC	16§	Cattle	0.0	0.0	0.0	0.0	0.0

		Pigs	0.0	0.0	0.0	0.0	0.0
		Chickens	0.0	0.6	0.0	0.0	0.0
		Cattle	85.6	31.2	14.9	2.9	0.8
DSM	128	Pigs	82.0	55.7	34.4	29.7	28.0
		Chickens	69.2	30.9	49.2	30.6	27.0
		Cattle	61.2	4.2	2.2	0.8	0.0
GM	32	Pigs	43.3	3.4	3.1	4.4	1.2
		Chickens	29.3	5.5	9.4	4.5	3.4
		Cattle	55.2	5.0	4.1	1.3	0.8
KM	128	Pigs	56.2	20.5	31.3	17.6	22.0
		Chickens	68.4	37.0	47.0	41.4	41.9
		Cattle	24.4	21.2	27.1	27.6	26.4
OTC	16	Pigs	61.9	54.5	59.4	64.8	58.5
		Chickens	72.2	58.0	63.0	66.2	52.0
		Cattle	1.5	0.0	0.0	0.4	0.4
CP	32[§]	Pigs	17.5	17.0	10.4	15.4	14.6
		Chickens	13.5	8.8	7.2	10.2	8.8
		Cattle	5.0	3.8	1.5	2.5	2.1
EM	8[§]	Pigs	41.8	28.4	30.2	34.1	26.8
		Chickens	50.4	43.1	42.5	45.2	41.2
		Cattle	27.9	3.1	0.7	2.5	2.1
LCM	128	Pigs	59.8	50.0	34.4	37.4	35.4
		Chickens	52.6	34.3	43.1	47.1	40.5
		Cattle	6.0	1.2	0.4	0.8	0.0
ERFX	4	Pigs	22.7	9.1	2.1	1.1	3.7
		Chickens	9.8	3.9	13.3	3.8	2.7
		Cattle	2.0	2.3	0.7	2.1	2.5
TS	64	Pigs	33.0	21.6	19.8	28.6	24.4
		Chickens	49.6	42.0	35.9	42.7	41.2
		Cattle	-	-	0.0	0.0	0.0
VCM	32	Pigs	-	-	0.0	0.0	0.0
		Chickens	-	-	0.0	0.0	0.0
		Cattle	201	260	269	289	242
Strains tested (n)		Pigs	194	88	96	91	82
		Chickens	133	181	181	157	148

The unit of BP is μg/mL.
* While BC, SNM and VGM were also included in the scope of the survey, as was AZM in 2017, the proportions of BC-, SNM-, VGM- and AZM- resistant strains were not listed because BP could not be established.
† The monitoring was not conducted on *Enterococcus* spp. derived from animal slaughterhouses in FY2013.
§ BP follows CLSI Criteria.
-: Not under surveillance.

Table 55. The proportion (%) of antimicrobial-resistant *Enterococcus faecalis* derived from animal slaughterhouses

Agent*	BP	Animal	2012	2014†	2015	2016	2017
		Cattle	0.0	0.0	0.0	0.0	0.0
ABPC	16[§]	Pigs	0.0	0.0	0.0	0.0	0.0
		Chickens	0.0	0.6	0.0	0.0	0.0
		Cattle	90.6	36.4	35.7	12.5	0.0
DSM	128	Pigs	88.2	62.5	100.0	43.5	38.5
		Chickens	76.9	53.8	72.4	40.6	38.8
		Cattle	68.8	27.3	0.0	0.0	0.0
GM	32	Pigs	76.5	12.5	15.4	8.7	7.7
		Chickens	35.6	9.9	14.3	6.3	3.5
		Cattle	71.9	9.1	14.3	0.0	0.0
KM	128	Pigs	72.9	12.5	69.2	30.4	30.8
		Chickens	71.2	57.1	66.3	55.2	58.8
		Cattle	31.3	27.3	28.6	37.5	10.0
OTC	16	Pigs	64.7	87.5	92.3	73.9	84.6
		Chickens	75.0	67.0	70.4	83.3	65.9
		Cattle	9.4	0.0	0.0	12.5	10.0
CP	32[§]	Pigs	30.6	62.5	53.8	39.1	38.5
		Chickens	17.3	13.2	9.2	15.6	12.9
		Cattle	21.9	9.1	0.0	0.0	10.0
EM	8[§]	Pigs	51.8	62.5	69.2	52.2	61.5
		Chickens	58.7	64.8	60.2	59.4	58.8
		Cattle	34.4	9.1	0.0	0.0	10.0
LCM	128	Pigs	76.5	75.0	92.3	56.5	61.5
		Chickens	57.7	45.1	54.1	59.4	55.3
ERFX	4	Cattle	3.1	0.0	0.0	0.0	0.0

		Pigs	5.9	0.0	7.7	0.0	0.0
		Chickens	2.9	1.1	0.0	2.1	0.0
TS	64	Cattle	6.3	0.0	0.0	0.0	10.0
		Pigs	50.6	62.4	69.2	52.2	61.5
		Chickens	57.7	65.9	53.1	59.4	60.0
VCM	32	Cattle	-	-	0.0	0.0	0.0
		Pigs	-	-	0.0	0.0	0.0
		Chickens	-	-	0.0	0.0	0.0
Strains tested (n)		Cattle	32	11	14	8	10
		Pigs	85	8	13	23	13
		Chickens	104	91	98	96	85

The unit of BP is μg/mL.
* While BC, SNM and VGM were also included in the scope of the survey, as was AZM in 2017, the proportions of BC-, SNM-, VGM-and AZM- resistant strains were not listed because BP could not be established.
† The monitoring was not conducted on *Enterococcus* spp. derived from animal slaughterhouses in FY2013.
§ BP follows CLSI Criteria.
-: Not under surveillance.

Table 56. The proportion (%) of antimicrobial-resistant *Enterococcus faecium* derived from animal slaughterhouses

Agent*	BP	Animal	2012	2014†	2015	2016	2017
ABPC	16§	Cattle	0.0	0.0	0.0	0.0	0.0
		Pigs	0.0	0.0	0.0	0.0	0.0
		Chickens	2.4	0.0	0.0	0.0	0.0
DSM	128	Cattle	22.7	33.3	0.0	25.0	0.0
		Pigs	30.3	58.3	0.0	28.6	27.3
		Chickens	28.6	13.9	16.1	30.0	18.2
GM	32	Cattle	2.3	0.0	0.0	0.0	0.0
		Pigs	0.0	0.0	0.0	0.0	0.0
		Chickens	3.6	2.8	3.2	10.0	9.1
KM	128	Cattle	34.1	33.3	16.7	0.0	50.0
		Pigs	30.3	25.0	72.7	28.6	72.7
		Chickens	34.5	33.3	35.5	40.0	45.5
OTC	16	Cattle	9.1	0.0	16.7	0.0	0.0
		Pigs	42.4	41.7	9.1	42.9	54.5
		Chickens	63.1	58.3	64.5	60.0	31.8
CP	32§	Cattle	0.0	0.0	0.0	0.0	0.0
		Pigs	0.0	25.0	0.0	0.0	9.1
		Chickens	4.8	8.3	6.5	0.0	9.1
EM	8§	Cattle	11.4	0.0	33.3	25.0	0.0
		Pigs	15.2	58.3	54.5	57.1	45.5
		Chickens	32.1	30.6	35.5	20.0	27.3
LCM	128	Cattle	9.1	0.0	0.0	0.0	0.0
		Pigs	39.4	50.0	9.1	28.6	27.3
		Chickens	31.0	19.4	29.0	20.0	27.3
ERFX	4	Cattle	36.4	0.0	16.7	25.0	0.0
		Pigs	45.5	25.0	0.0	0.0	27.3
		Chickens	65.5	13.9	71.0	30.0	18.2
TS	64	Cattle	9.1	0.0	0.0	0.0	0.0
		Pigs	12.1	16.7	0.0	28.6	18.2
		Chickens	26.2	19.4	22.6	20.0	27.3
VCM	32	Cattle	-	-	0.0	0.0	0.0
		Pigs	-	-	0.0	0.0	0.0
		Chickens	-	-	0.0	0.0	0.0
Strains tested (n)		Cattle	44	6	6	4	4
		Pigs	84	12	11	7	11
		Chickens	64	36	31	10	22

The unit of BP is μg/mL.
* While BC, SNM and VGM were also included in the scope of the survey, as was AZM in 2017, the proportions of BC-, SNM-, VGM-and AZM resistant strains were not listed because BP could not be established.
† The monitoring was not conducted on *Enterococcus* spp. derived from animal slaughterhouses in FY2013.
§ BP follows CLSI Criteria.
-: Not under surveillance.

v. *Salmonella* spp.

Monitoring of antimicrobial resistance on 12 agents was carried out between 2012 and 2017 in chicken-derived strains. Among chicken-derived strains in 2017, resistance to streptomycin (SM) exceeding 60%, resistance to tetracycline (TC) exceeding 70%, and resistance to kanamycin (KM) and sulfamethoxazole-trimethoprim

(SMX/TMP) exceeding 40% was observed. 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 1.3%, and no resistance to colistin (CL) or ciprofloxacin (CPFX) was observed. Looking at trends in resistance rates to each agent between 2012 and 2017, while a decline was observed in ampicillin (ABPC) resistance since 2012, a rise in kanamycin (KM) resistance has been observed over the same period.

The *Salmonella* serotypes most commonly isolated from poultry slaughterhouses in FY2015-17 were Schwarzengrund, Infantis, Typhimurium, and Manhattan. In a comparison of *Salmonella* serotypes isolated from poultry slaughterhouses with those isolated from food (about 90% from domestic chicken meat) and from humans (source: Nippon AMR One Health Report 2018: Table 18) (Table 59, Figure 1), the same trends were observed in *Salmonella* serotypes isolated from poultry slaughterhouses as in those isolated from food. The top five serotypes isolated from poultry slaughterhouses were the same as those isolated from food, respectively accounting for 98% and 84% of all serotypes from those sources, which suggested a relationship between them. On the other hand, the serotypes isolated from humans were more diverse than those isolated from poultry slaughterhouses and food, with the top five serotypes isolated from poultry slaughterhouses accounting for 24% of human-derived strains, which suggested the possibility that there are variety of origin other than poultry or their food products. In a comparison of resistance rates of Schwarzengrund and Infantis, which are the top two serotypes accounting for the majority of strains isolated from poultry slaughterhouses (Table 60, Figure 2) (source: Nippon AMR One Health Report 2018: Table 28), although similarities between food-derived and poultry slaughterhouse-derived strains were found among both serotypes, there are some differences between human-derived strains and food-derived strains and poultry-derived strains. This fact suggested the possibility that there are also other causes than poultry and their food products.

Table 57. The proportion (%) of antimicrobial-resistant *Salmonella* spp. derived from poultry slaughterhouses

Agent	BP	Animal	2012	2013	2014	2015	2016	2017
ABPC	32*	Chickens	31.9	22.9	17.2	13.0	13.5	6.3
CEZ	32	Chickens	7.4	5.9	3.1	1.6	1.9	1.3
CTX	4*	Chickens	7.4	5.1	2.3	1.6	1.9	1.3
SM	32	Chickens	77.7	84.7	85.9	76.4	77.9	61.4
GM	16*	Chickens	0.0	0.0	0.0	0.0	0.0	0.0
KM	64*	Chickens	31.9	42.4	57.8	69.1	72.1	78.5
TC	16*	Chickens	74.5	82.2	85.2	83.7	82.7	79.8
CP	32*	Chickens	0.0	0.8	1.6	1.6	0.0	0.6
CL	16	Chickens	0.0	0.0	0.0	0.0	0.0	0.0
NA	32*	Chickens	29.8	19.5	17.2	15.4	12.5	15.2
CPFX	4*	Chickens	0.0	0.0	0.0	0.0	0.0	0.0
SMX/TMP	76/4*	Chickens	31.9	48.3	51.6	57.7	56.7	61.4
Strains tested (n)		Chickens	94	118	128	123	104	158

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

Table 58. Serotypes of *Salmonella enterica* derived from poultry slaughterhouses (FY2015-17)

Serotypes	Number of strains isolated	(%)
Schwarzengrund	252	65.5
Infantis	75	19.5
Typhimurium	28	7.3
Manhattan	11	2.9
Agona	8	2.1
Others	19	4.9
Total	385	100.0

Table 59. Serotypes of *Salmonella enterica* derived from poultry slaughterhouses, food, and humans (FY2015-17)

From poultry slaughterhouses (n=385)	%
Schwarzengrund	65.5
Infantis	19.7
Typhimurium	7.8
Manhattan	2.9
Agona	2.1
Others	2.1
Total	100

From food (n=351)*	%
Schwarzengrund	33.3
Infantis	36.5
Typhimurium	2.8
Manhattan	8.3
Agona	3.7
Others	15.4
Total	100

From humans (n=1185)*	%
Schwarzengrund	4.4
Infantis	12.2
Typhimurium	4.7
Manhattan	3.1
Enteritidis	10.6
Saintpaul	8.0
04:i:-	7.6
Thompson	7.3
Chester	2.6
Stanley	2.5
Others	36.9
Total	100

*Source: Nippon AMR One Health Report 2018: Table 18

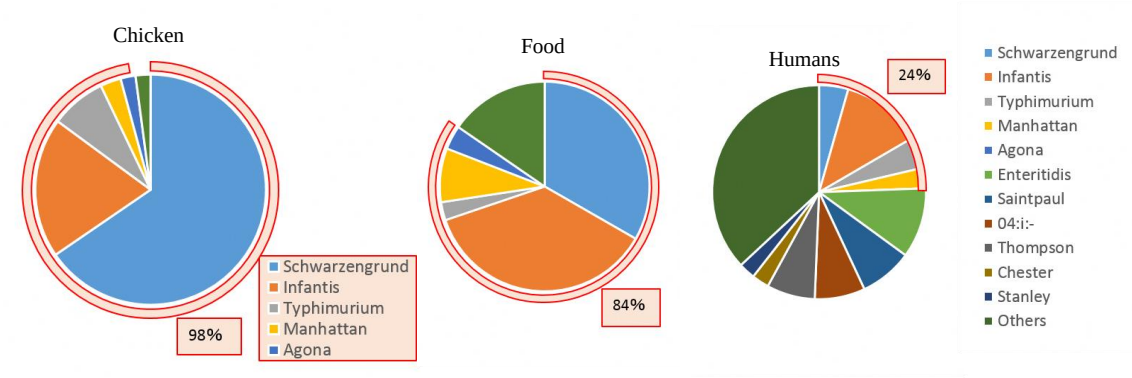

Figure 1. Proportions of the top 5 serotypes of *Salmonella enterica* derived from poultry slaughterhouses isolated in food and humans (2015-17) (figures for proportions in human-derived and food-derived strains are quoted from Nippon AMR One Health Report 2018: Table 18)

Table 60. Resistance rates among *S.* Infantis and *S.* Schwarzengrund strains isolated from poultry slaughterhouses (chicken), food, and humans (2015-17)

	Infantis			Schwarzengrund		
	Chicken (n=75)	Food (n=117)*	Humans (n=144)*	Chicken (n=252)	Food (n=128)*	Humans (n=52)*
ABPC	5.3	10.3	0.7	1.2	7.8	3.8
GM	0.0	0.9	0	0.0	0	0
KM	44.7	40.2	13.9	91.7	82.8	61.5
SM	73.7	76.9	27.8	74.2	85.2	75
TC	84.2	83.8	33.3	88.1	86.7	73.1
CP	0.0	2.6	0	1.2	11.7	0
CTX	5.3	5.1	0.7	0.4	0.8	3.8
NA	5.3	4.3	6.3	11.1	17.2	21.2
CPFX	0.0	0.9	0	0.0	0	0

*Source: Nippon AMR One Health Report 2018: Table 28

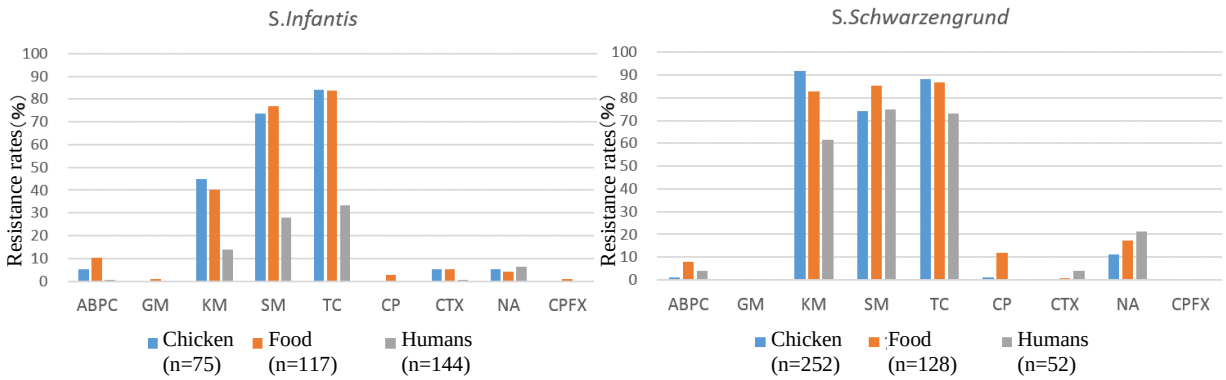

Figure 2. Resistance rates among *S*. Infantis and *S*. Schwarzengrund strains derived from humans, food, and poultry slaughterhouses (2015-17) (figures for resistance rates in human-derived and food-derived strains are quoted from Nippon AMR One Health Report 2018: Table 28)

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. *piscicida* 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. Between 2011 and 2016, strains were provided by four to six prefectures, increasing to nine in 2017. 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 and antimicrobial susceptibility monitoring of *Lactococcus garvieae* and *Vibrio* spp. is now being carried out.

i. *Lactococcus garvieae* derived from diseased fish

The monitoring of antimicrobial resistance was conducted on 4 agents that had efficacy on the streptococcal diseases from 2011 to 2017. 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 (≤ 4μg/ml) in all strains, suggesting that the susceptibility was maintained.

Table 61. The proportion (%) of antimicrobial-resistant *Lactococcus garvieae*

Agent[*1]	BP	2011	2012	2013	2014	2015	2016	2017[*2]
EM	8	0.0	10.3	0.0	0.0	3.7	8.0	1.9
LCM	4	92.6	76.9	71.4	62.5	59.3	76.0	61.0
OTC	8	0.0	12.8	0.0	0.0	3.7	8.0	0.0
Strains tested (n)		27	39	21	16	27	25	105

The unit of BP is μg/mL.
*[1]: 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.
*[2]: Monitoring focused only on *Seriola* until 2016, but was expanded in 2017 to include strains derived from all farmed fish species .

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

The monitoring of antimicrobial resistance was conducted on 5 agents that had efficacy against pseudotuberculosis from 2011 to 2014. The number of tested strains was small, with just 3 being tested in 2015, while no strains were isolated at all in 2016. In strains tested between 2011 and 2014, the resistance rate varied particularly for ampicillin (ABPC) and for oxolinic acid (OA). However, the resistance rate remained at 7.1% or lower both for bicozamycin (BCM) and for fosfomycin (FOM). Although the proportion of florfenicol (FF) resistant strains was not calculated given that no bimodal MIC distribution was observed, MIC values were low (≤ 1 μg/ml) in all strains, suggesting that the susceptibility was maintained. The strains tested in 2015 showed a low MIC value to all the tested agents.

Table 62. 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.
No data for 2015 are shown, because only three strains were tested.

iii. *Vibrio* spp. derived from diseased fish

Monitoring of agents effective against vibriosis began to be carried out in 2017 in respect of strains derived from diseased fish. Oxytetracycline (OTC) showed bimodal MIC distribution, with a resistance rate of 12.8%. Although the MIC distribution of florfenicol (FF) and oxolinic acid (OA) was not bimodal, all strains showed low MIC values (FF: MIC ≦2 μg/ml; OA: MIC ≦1 μg/ml), which suggested that susceptibility to these agents was maintained. Sulfamonomethoxine (SMMX), however, did not show bimodal MIC distribution, so the resistance rate could not be calculated.

Table 63. Trends in resistance rates among *Vibrio* spp. (%)

Agent*	BP	2017
OTC	4	12.8
Strains tested (n)		39

The unit of BP is μg/mL.
* While FF, OA and SMMX were also included in the scope of survey, thier resistance proportion were not listed because BP cannot be established.

iv. *Vibrio parahaemolyticus* derived from aquaculture environment

Monitoring of five agents approved as aquatic drugs (EM, LCM, OTC, OA and FF) was carried out using the 53 and 50 strains derived from aquaculture environments in 2011 and 2012.

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

3) Companion animals

Source: Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

Routine monitoring of antimicrobial-resistant bacteria derived from diseased dogs and cats was launched in FY2017, as part of efforts to strengthen monitoring under the AMR Action Plan. Bacterial strains from diseased

dogs and cats were collected from small animal clinical laboratories. The country was divided into six regional blocks—Hokkaido and Tohoku, Kanto, Chubu, Kinki, Chugoku and Shikoku, and Kyushu and Okinawa—and the number of strains allocated on the basis of the number of notifications of veterinary clinic (small animal and other animals) establishment received. 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, surveillance of healthy dogs and cats was launched in 2018. As monitoring of healthy dogs and cats is currently being carried out, details are not provided in this report.

i. *Escherichia coli*

Monitoring of 15 agents was carried out. Ampicillin (ABPC) and nalidixic acid (NA) resistance in dog- and cat-derived strains was high at around 60% in 2017 and 2018. On the other hand, the rate of resistance to gentamicin (GM), kanamycin (KM), chloramphenicol (CP), colistin (CL), and fosfomycin (FOM) in strains isolated from dogs and cats was less than 20%. The rates of resistance to critically important antimicrobials for human medicine in dog- and cat-derived strains respectively were as follows: around 40% to cefotaxime (CTX); less than 1.0% to CL; and around 50% to ciprofloxacin (CPFX). No resistance to meropenem (MEPM) was observed.

Table 64. Resistance rates of *Escherichia coli* derived from diseased dogs and cats (%)

Agent	BP	Animal	2017	2018
ABPC	32*	Dogs	55.3	63.0
		Cats	64.0	65.6
CEZ	32*	Dogs	31.2	47.4
		Cats	37.5	49.5
CEX	32†	Dogs	31.7	42.9
		Cats	41.9	47.3
CTX	4*	Dogs	26.1	41.6
		Cats	33.8	40.9
MEPM	4*	Dogs	0.0	0.0
		Cats	0.0	0.0
SM	32†	Dogs	29.6	29.9
		Cats	32.4	34.4
GM	16*	Dogs	14.1	18.8
		Cats	12.5	15.1
KM	64*	Dogs	6.5	7.8
		Cats	8.1	12.9
TC	16*	Dogs	28.1	27.3
		Cats	24.3	28.0
CP	32*	Dogs	12.6	16.9
		Cats	13.2	15.1
CL	4†	Dogs	1.0	0.6
		Cats	0.0	0.0
NA	32*	Dogs	61.8	72.7
		Cats	58.8	68.8
CPFX	4*	Dogs	43.2	51.9
		Cats	39.0	48.4
FOM	256*	Dogs	0.5	3.9
		Cats	1.5	1.1
ST	76/4*	Dogs	24.6	27.9
		Cats	22.1	34.4
Strains tested (n)		Dogs	199	154
		Cats	136	93

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

† BP follows EUCAST Criteria.

ii. *Klebsiella* spp.

Monitoring of 15 agents was carried out. Among the collected *Klebsiella* spp., *K. pneumoniae* was the most common, followed by *K. oxytoca*. No other species were collected. Resistance to cefazolin (CEZ) and nalidixic acid (NA) was observed to exceed 50% in dog-derived strains, as was resistance to CEZ, cephalexin (CEX), cefotaxime (CTX), streptomycin (SM), gentamicin (GM), tetracycline (TC), NA, ciprofloxacin (CPFX), and sulfamethoxazole-trimethoprim (SMX/TMP) in cat-derived strains. On the other hand, resistance to colistin (CL) and fosfomycin (FOM) was below 20% in strains derived from both dogs and cats, as was resistance to kanamycin (KM) in dog-derived strains. Looking at rates of resistance to critically important antimicrobials for human medicine, resistance to CTX and CPFX in dog-derived strains was below 50%, whereas the figures were above 80% in cat-derived strains. The CL resistance rate in both dog- and cat-derived strains was below 5%, while no resistance to meropenem (MEPM) was observed in strains derived from either type of animal.

Table 65. Resistance rates of *Klebsiella* spp. derived from diseased dogs and cats (%)

Agent	BP	Animal	2017	2018
ABPC§	32*	Dogs	90.3	93.9
		Cats	96.2	100.0
CEZ	32*	Dogs	47.2	51.0
		Cats	84.6	90.0
CEX	32†	Dogs	44.4	46.9
		Cats	84.6	80.0
CTX	4*	Dogs	41.7	38.8
		Cats	80.8	80.0
MEPM	4*	Dogs	0.0	0.0
		Cats	0.0	0.0
SM	32†	Dogs	26.4	34.7
		Cats	57.7	55.0
GM	16*	Dogs	26.4	28.6
		Cats	61.5	55.0
KM	64*	Dogs	8.3	12.2
		Cats	23.1	20.0
TC	16*	Dogs	33.3	42.9
		Cats	57.7	65.0
CP	32*	Dogs	25.0	32.7
		Cats	26.9	45.0
CL	4†	Dogs	1.4	0.0
		Cats	3.8	0.0
NA	32*	Dogs	51.4	61.2
		Cats	84.6	95.0
CPFX	4*	Dogs	44.4	49.0
		Cats	84.6	90.0
FOM	256†	Dogs	15.3	16.3
		Cats	7.7	15.0
ST	76/4*	Dogs	41.7	46.9
		Cats	76.9	70.0
Strains tested (n)		Dogs	72	49
		Cats	26	20

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.
§ Resistance rates for ABPC are just for reference purpose due to intrinsic resistance

iii. Coagulase-positive *Staphylococcus* spp.

The most common coagulase-positive *Staphylococcus* spp. in both dogs and cats was *S. pseudintermedius*. *S. aureus*, *S. schleiferi* subsp. *Coagulans*,, and *S. intermedius* were also collected.

In the case of *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% in both 2017 and 2018, as was oxacillin (MPIPC) resistance in strains isolated from cats. More than 50% of strains

isolated from dogs and more than 60% of those isolated from cats were observed to be resistant to AZM and CPFX, which are critically important antimicrobials for human medicine.

In *S. aureus* isolated from cats resistance to MPIPC, cefazolin (CEZ), cephalexin (CEX), cefoxitin (CFX), cefotaxime (CTX), EM, AZM, and CPFX was observed to exceed 50%. On the other hand, the SM resistance rate was less than 10% and no CP resistance was observed. Rates of resistance to CTX, AZM, and CPFX, which are critically important antimicrobials for human medicine, were observed to be more than 60%.

Table 66. Resistance rates of *Staphylococcus pseudintermedius* derived from diseased dogs and cats (%)

Agent*	BP	Animal	2017	2018
MPIPC	0.5†	Dogs	38.5	56.6
		Cats	68.6	81.8
GM	16†	Dogs	6.6	54.2
		Cats	13.7	63.6
TC	16†	Dogs	44.3	67.5
		Cats	52.9	81.8
CP	32†	Dogs	41.8	49.4
		Cats	64.7	72.7
EM	8†	Dogs	54.9	74.7
		Cats	70.6	86.4
AZM	8†	Dogs	53.3	74.7
		Cats	66.7	86.4
CPFX	4†	Dogs	58.2	75.9
		Cats	88.2	100.0
Strains tested (n)		Dogs	122	83
		Cats	51	22

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

Agent	BP	Animal	2017	2018
MPIPC	4†	Cats	61.9	70.6
CEZ	4$	Cats	61.9	64.7
CEX	16$	Cats	61.9	70.6
CFX	8$	Cats	61.9	64.7
CTX	8$	Cats	61.9	64.7
SM	32$	Cats	4.8	5.9
GM	16†	Cats	47.6	58.8
TC	16†	Cats	14.3	41.2
CP	32†	Cats	0.0	0.0
EM	8†	Cats	66.7	76.5
AZM	8†	Cats	66.7	76.5
CPFX	4†	Cats	61.9	76.5
Strains tested (n)		Cats	21	17

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.

The most common *Enterococcus* spp. in both dogs and cats was *E. faecalis*, followed by *E. faecium*. In addition, several strains of E. casseliflavus/gallinarum, E. avium, and E. durans were also collected. In 2017 and 2018, rates of resistance to tetracycline (TC) were in excess of 60% in both dog- and cat-derived strains, while gentamicin (GM) and chloramphenicol (CP) resistance rates were below 25%. Between 28.2% and 49.1% of dog- and cat-derived strains were observed to be resistant to CPFX, a critically important antimicrobial for human medicine.

Table 68. Resistance rates of Enterococcus spp. derived from diseased dogs and cats (%)

Agent *	BP	Animal	2017	2018
ABPC	16†	Dogs	26.7	20.5
		Cats	17.3	31.6
GM	32§	Dogs	22.9	15.4
		Cats	19.4	24.6
TC	16†	Dogs	65.6	67.9
		Cats	70.4	73.7
CP	32†	Dogs	20.6	14.1
		Cats	20.4	15.8
EM	8†	Dogs	61.8	39.7
		Cats	41.8	54.4
CPFX	4†	Dogs	42.7	28.2
		Cats	34.7	49.1
Strains tested (n)		Dogs	131	78
		Cats	98	57

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

A 2018 research project to promote food safety, which was funded by a Ministry of Health, Labour and Welfare research grant, found that the status of resistance among microbes isolated from food was as follows (FY2018 Health and Labor Sciences Research Grant General Report on the Research Project to Promote Food Safety: Principal Investigator Haruo Watanabe). With the cooperation of 23 local public health institutes across Japan, the research team used standardized methods to isolate strains of *Salmonella*, *Escherichia coli*, and *Campylobacter* contaminating food (mainly chicken) and to measure their antimicrobial resistance. In the case of *Salmonella* strains isolated between 2015 and 2018, 40.3% of patient-derived strains and 89.6% of food-derived strains demonstrated resistance to at least one of the 18 antimicrobial agents. Looking at the serotypes of strains derived from human patients that were also isolated from food, there were strong similarities in terms of resistance trends between *S.* Infantis, *S.* Schwarzengrund, and *S.* Manhattan strains derived from human patients and those derived from food, strongly suggesting a relationship between resistant bacteria derived from food and those derived from human patients. On the other hand, 36.3% of human patient-derived strains of *Salmonella* isolated between 2015 and 2018 and 56.3% of food-derived strains demonstrated resistance to at least one agent. A new common protocol and decision table were drawn up for *Campylobacter* and the standardized method was used for susceptibility tests and decisions. In the case of *C. jejuni*, there were strong similarities in terms of resistance trends between strains derived from human patients and those derived from food, strongly suggesting a relationship between resistant bacteria derived from food and those derived from human patients. In addition, 360 strains of *E. coli* derived from healthy individuals were tested for susceptibility to 17 antimicrobial agents. Of these, 37.5% were resistant to one or more agents. Resistance to CTX was found in 5.3% of these strains, while 9.4% were found to be fluoroquinolone-resistant. *E. coli* derived from healthy individuals also demonstrated quite a high resistance rate. (Detailed data concerning resistance in Salmonella isolated from food is provided in (1) 4) ii. Non-typhoidal *Salmonella* spp.)

Tests conducted by Tokyo Metropolitan Institute of Public Health on *E. coli* strains isolated from commercially available chicken meat (241 strains isolated from domestic chicken meat and 36 strains isolated from imported chicken meat) found resistance to the antimicrobial agents KM (domestic 35.7%, imported 8.3%), TC (domestic 46.9%, imported 19.4%), ABPC (domestic 42.3%, imported 27.8%), CP (domestic 22.8%, imported 5.6%), ST (domestic 29%, imported 19.4%), SM (domestic 37.3%, imported 30.1%), NA (domestic 19.9%, imported 36.1%), and GM (domestic 5%, imported 19.4%). The rate of CTX resistance in strains derived from domestic chicken meat fell from 10.1% in 2012 to 3.6% in 2015, reaching 5.8% in 2018. *E. coli* with a plasmid-mediated colistin resistance gene was detected in 4 samples of domestic chicken meat (2.5%), but not in any imported chicken meat.

In all cases, the resistance gene was *mcr-1*. The *mcr-1* gene was detected in 3 samples of chicken liver and 1 of chicken tenderloin.

(Veterinary field) Surveillance of the ESBL/AmpC beta-lactamase-producing *E. coli* carrier status of layers

Surveillance of the ESBL/AmpC beta-lactamase-producing *E. coli* carrier status of egg-laying chickens has been carried out (National Institute of Health Sciences and others). Of the layers, 42.9% (35/82) tested positive for ESBL/AmpC *E. coli*, with younger birds (56.1%, 23/41) having a higher tendency to carry the microbe than older birds (29.3%, 12/41). When the genotypes of all 68 ESBL/AmpC strains isolated were determined, the most common was found to be CTX-M-1 (39.7%, 27/68), followed by CMY-2 (30.9%, 21/68).

(4) Environment

Waste resulting from human activities is discharged into the environment (rivers or the sea) after being treated at sewage treatment plants (water reclamation centers) until it meets effluent standards. Attention to environmental AMR based on the One Health approach focuses on evaluating the risks posed by antimicrobial-resistant bacteria (genes) by determining which antimicrobial-resistant bacteria (genes) exist in environmental water discharged without adequate treatment and how they could circulate into our daily lives. With few quantitative reports available at present concerning the extent to which antimicrobial-resistant bacteria (AMR bacteria: ARB) and the antimicrobial-resistance genes (AMR genes: ARGs) that stem from them are continuing to impose a burden after being excreted into the environment, a systematic nationwide survey is regarded as essential. Accordingly, a research group funded by a Ministry of Health, Labour and Welfare research grant has been formed for the purpose of conducting ongoing environmental AMR surveillance for the Japanese government. Led by Hajime Kanamori, the research group is conducting a study entitled “Research to Establish Methods of Surveying Antimicrobial-resistant Bacteria and Antimicrobials in the Environment” from 2018 to 2020.

In the first year of the study (FY2018), next-generation sequencers were used to establish a comprehensive technique for sequencing ARGs (metagenomic analysis) in environmental water (Pathogen Genomics Center, National Institute of Infectious Diseases). Metagenomic analysis was then carried out on samples of wastewater from sewage treatment plants provided by 27 local governments (108 samples in total, collected in summer (August) and winter (February)). The number of decoded reads of the ARGs in question was detected based on a database of ARG sequences associated with antimicrobials used in clinical settings and food-producing animals. In addition, the fragments per kilobase of exon per million mapped fragments (FPKM) method, which normalizes based on ARG base length and total decoded reads in the metagenome, was used to calculate the relative concentration of ARGs and conduct a comparative analysis between samples. The ARG levels detected in summer and winter samples were about the same, with a tendency to be slightly higher in winter. Sulfonamide-resistant genes were detected at significantly higher levels in winter (p=0.03166). The Class 1 integron sulfonamide resistance gene (*sul1*) known to have been widely acquired and propagated among *Enterobacteriaceae* is thought to be a contributory factor. As the research group’s metagenomic analysis technique conforms to metagenomic analysis techniques used globally, the study is believed to have provided information that will be important when comparing reports from different countries. The group plans to continue conducting nationwide surveillance twice a year (in summer and winter) with the assistance of local governments and put in place Japanese environmental AMR (resistome) infrastructure.

In terms of global surveillance, Denmark (The National Food Institute, DTU (WHO Collaborating Centre and European Union Reference Laboratory for Antimicrobial Resistance in Foodborne Pathogens)) is leading a WHO-supported environmental surveillance initiative called the Global Sewage Surveillance Project (GSSP).[9] As the surveillance targets not only environmental AMR, but also contamination with viruses such as the poliovirus, it is focusing primarily on inlet water from sewage treatment plants. The first output from the project provided the

results of metagenomic analysis of 79 samples of inlet water from sewage treatment plants (in 60 countries) collected in January and February 2016. The highest level of ARG contamination among these 60 countries was 4616.9 FPKM in Brazil and African countries also recorded a high level of ARG contamination, with an average of 2034.3 FPKM. Oceania (New Zealand and Australia) had the lowest level, with an average of 529.5 FPKM. While Asia (excluding Japan) did not have as high a level of ARG contamination as Africa, the ARG composition (resistome) was very similar (27% dissimilarity). ARG FPKM and resistome analysis brought to light results demonstrating a strong correlation between a country's population and economic activity on the one hand and its public health measures on the other. Japan has been involved in this project since 2017, providing pre-treatment inlet water, and a follow-up GSSP report that includes the evaluation of the Japanese samples is awaited. As the GSSP focuses on (untreated) inlet water samples from sewage treatment plants, it is difficult to carry out a comparative analysis based on the same standards as the aforementioned Japanese environmental AMR study, but it does at least provide important quantitative values for determining whether or not the wastewater from Japanese sewage treatment plants, which records levels of up to 100 FPKM, necessitates further environmental purification.

In addition to ARG in wastewater, it is vital to identify the presence of ARB that could potentially exist and proliferate in the environment. Information on the situation within Japan is starting to emerge from the findings of the aforementioned MHLW research group, including reports that, at a water reclamation center in Tokyo Bay, a KPC-2-producing *Klebsiella pneumoniae* strain rarely found in Japan, even in clinical isolates, has been isolated,[11] that KPC-2 was found in *Aeromonas* rarely isolated in wound infections,[12] and that *E. coli* with NDM-5 carbapenemase, which has acquired broader-spectrum activity than NDM-1, has been isolated.[13] A report has also been published on a comprehensive AMR study carried out on hospital wastewater, inlet and outlet water from sewage treatment plants, and river water in the Yodo River basin in Osaka. Its estimates suggest that a diverse array of ARB will be isolated from outlet water from sewage treatment plants and that hospital wastewater will impose an environmental AMR burden unless ozone treatment is carried out.[14] 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 ARB in environmental water, and it will be crucial to develop techniques for intensively eliminating or reducing ARB alone.

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. As the contamination of vegetables believed to result from the use of river water for irrigation[15] and assessments of the risk of exposure through water-based recreation[16] are starting to be reported, albeit only little by little, the risk environment is being envisaged to a certain degree. At this point, it is difficult to set definite standards for discussing environmental risk. However, it is vital to quantitatively monitor and evaluate environmental AMR, conduct research that could assist in appraising health risks, and undertake risk assessments and reviews of major literature from both within Japan and overseas, as shedding light on the major factors contributing to the environmental AMR load and investigating whether it is developing into a risk to human and animal health are matters of urgency.

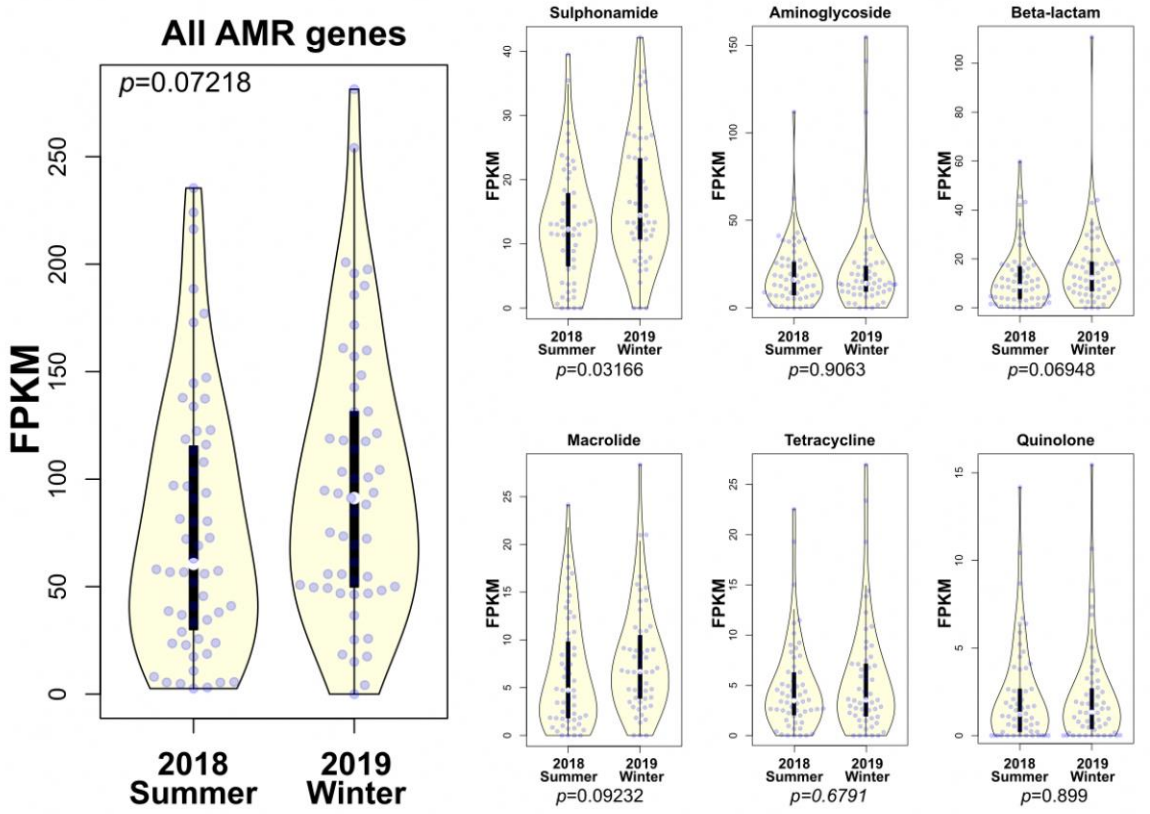

Figure 3. Metagenomic analysis (Metagenomic DNA-Seq) of wastewater discharged from Japanese sewage treatment plants (water reclamation centers)

The quantity of antimicrobial resistant genes in each category detected was standardized using fragments per kilobase of exon per million mapped fragments (FPKM).

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7. Current Volume of Use of Antimicrobials in Japan

(1) Antimicrobials for humans (based on volume of sales)

Source: IQVIA Solutions Japan K.K.

Tables 69 and 70 show the usage of antimicrobials in Japan between 2013 and 2018, based on the amount of sales. Overall use of antimicrobials in Japan in 2018 amounted to 13.3 DID (DDDs/1,000 inhabitants/day). A comparison with DID in major countries in 2017 shows that this was lower than France (29.2 DID), Italy (23.4 DID), and the UK (19.1 DID), but higher than Sweden (11.6 DID) and the Netherlands (10.1 DID), and about the same as Germany (13.7 DID). No major changes in the use of antimicrobials were observed between 2013 and 2016, but usage has been declining since 2017, falling by 10.6% from the 2013 level by 2018.

Oral antimicrobial use in 2018 (Table 69) was 12.3 DID, accounting for 92.0% of all antimicrobials. Antimicrobials subject to a reduction target of 50% under Japan's National Action Plan on AMR, namely oral cephalosporins (3.2 DID), oral fluoroquinolones (2.3 DID), and oral macrolides (4.0 DID) together accounted for 77.5% of all oral antimicrobials (the figure for oral cephalosporins is the total for first- (0.1 DID), second- (0.3 DID), and third-generation (2.8 DID) oral cephalosporins). While this trend has not changed since 2013, use of oral cephalosporins, oral fluoroquinolones, and oral macrolides fell by 18.4%, 17.0%, and 18.0% respectively over that period. On the other hand, use of parenteral antimicrobials increased by 10.0% between 2013 and 2018 (Table 70).

Table 71 shows antimicrobial use based on the AWaRe classification recommended by the WHO as an indicator of antimicrobial stewardship. Carried in the 20th edition of the WHO Model Lists of Essential Medicines, the AWaRe classification is an antimicrobial classification system that is applied as an indicator of antimicrobial stewardship. It classifies antimicrobials into four categories: Access (first- or second-choice antimicrobials used for treating common infections, regarding whose resistance potential there is little concern, and which should be made widely available by all countries in high-quality formulations at a reasonable cost. Examples include ampicillin and cephalexin), Watch (antimicrobials that should be used only for a limited number of conditions or applications, as their resistance potential is a source of concern. Examples include vancomycin, meropenem, levofloxacin, and ceftriaxone), Reserve (antimicrobials that should be used as the last resort when no other alternatives can be used. Examples include tigecycline, colistin, and daptomycin), and Unclassified. The WHO has set a target of at least 60% of antimicrobial consumption being from medicines in the Access Group. While consumption of antimicrobials in the Access Group as a proportion of total use is lower in Japan than other countries, at around 15%,[6] the figure has risen gradually over the years from 11.9% to 17.1%, with the percentage of antimicrobials in the Watch Group falling from 79.0% to 73.3%.

A survey of oral and parenteral antimicrobial use in terms of potency by weight from a One Health perspective (Table 72) 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 69. Trends in oral antimicrobial use in Japan based on the volume of sales

	2013	2014	2015	2016	2017	2018
Tetracyclines	0.76	0.75	0.77	0.80	0.81	0.88
Amphenicols	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Penicillins with extended spectrum	0.88	0.89	0.99	0.97	0.95	1.01
Beta Lactamase-sensitive penicillins	<0.01	<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	0.29
1st generation cephalosporins	0.07	0.07	0.07	0.07	0.07	0.08

2nd generation cephalosporins	0.30	0.29	0.29	0.29	0.28	0.28
3rd generation cephalosporins	3.53	3.41	3.46	3.32	3.08	2.83
Carbapenems	0.01	0.02	0.02	0.02	0.01	0.01
Other cephalosporins and penems	0.14	0.14	0.13	0.12	0.12	0.11
Combinations of sulfonamides and trimethoprim, including derivatives	0.25	0.27	0.29	0.31	0.33	0.36
Macrolides	4.83	4.50	4.59	4.56	4.18	3.96
Lincosamides	0.01	0.01	0.02	0.01	0.02	0.02
Fluoroquinolones	2.82	2.83	2.71	2.75	2.57	2.34
Other quinolones	0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Other antibacterials	0.10	0.10	0.10	0.10	0.09	0.08
Total	13.93	13.50	13.67	13.57	12.76	12.25

* As a unit, defined daily doses (DDDs) per 1,000 inhabitants per day (DID) is used.
* Figures for DDD are those for January 1, 2018.
* Figures shown here for antimicrobial use in 2013 differ from those shown in the FY2017 report, because of differences in the DDD values defined by the World Health Organization at the time of calculation.

Table 70. Trends in parenteral antimicrobial use in Japan based on the volume of sales

	2013	2014	2015	2016	2017	2018
Tetracyclines	0.02	0.02	0.02	0.02	0.02	0.02
Amphenicols	<0.01	<0.01	<0.01	<0.01	<0.01	< 0.01
Penicillins with extended spectrum	0.04	0.04	0.04	0.04	0.04	0.05
Beta Lactamase-sensitive penicillins	<0.01	<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	0.21
1st generation cephalosporins	0.13	0.13	0.14	0.14	0.15	0.15
2nd generation cephalosporins	0.11	0.11	0.10	0.10	0.10	0.09
3rd generation cephalosporins	0.18	0.19	0.21	0.22	0.23	0.24
4th generation cephalosporins	0.06	0.05	0.05	0.05	0.05	0.04
Monobactams	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Carbapenems	0.11	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	<0.01
Macrolides	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Lincosamides	0.02	0.02	0.02	0.02	0.02	0.02
Streptogramins	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Streptomycin	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Other aminoglycosides	0.05	0.05	0.05	0.04	0.04	0.04
Fluoroquinolones	0.04	0.04	0.04	0.04	0.04	0.04
Glycopeptides	0.03	0.03	0.03	0.03	0.03	0.03
Polymyxins	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Metronidazole	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Other antibacterials	0.02	0.02	0.02	0.02	0.02	0.02
Total	0.96	0.96	1.00	1.03	1.05	1.06

* As a unit, defined daily doses (DDDs) per 1,000 inhabitants per day (DID) is used.
* Figures for DDD are those for January 1, 2018.
* Figures shown here for antimicrobial use in 2013 differ from those shown in the FY2017 report, because of differences in the DDD values defined by the World Health Organization at the time of calculation.

Table 71. Trends in antimicrobial use in Japan based on the AWaRe classification

AWaRe classification	2013	2014	2015	2016	2017	2018
Access (%)	1.77 (11.9)	1.82 (12.6)	1.97 (13.4)	2.02 (13.8)	2.08 (15.1)	2.27 (17.1)
Watch (%)	11.77 (79.0)	11.32 (78.3)	11.37 (77.5)	11.25 (77.1)	10.45 (75.7)	9.76 (73.3)
Reserve (%)	0.08 (0.5)	0.07 (0.5)	0.07 (0.5)	0.07 (0.5)	0.07 (0.5)	0.06 (0.5)
Unclassified (%)	1.28 (8.6)	1.25 (8.6)	1.27 (8.7)	1.26 (8.6)	1.21 (8.8)	1.22 (9.2)
Total	14.90	14.46	14.68	14.60	13.81	13.31

* As a unit, defined daily doses (DDDs) per 1,000 inhabitants per day (DID) is used.
* Figures for DDD are those for January 1, 2018.
* This data used AWaRe classification as of October 2019.

Table 72. 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	2018
Tetracyclines	7.1	6.9	7.1	7.2	7.0	7.3
Amphenicols	0.2	0.1	0.1	0.1	0.1	0.1

Penicillins with extended spectrum	53.7	53.6	57.6	56.3	54.5	57.3
Beta Lactamase-sensitive penicillins	1.7	1.8	1.7	1.5	1.4	1.3
Combinations of penicillins, including beta lactamase inhibitors	88.1	95.4	105.8	114.6	124.1	131.9
1st generation cephalosporins	25.0	24.9	25.2	26.3	27.2	28.4
2nd generation cephalosporins	28.5	27.4	27.0	26.7	25.9	26.0
3rd generation cephalosporins	97.7	95.1	97.8	95.9	91.2	86.6
4th generation cephalosporins	6.6	6.1	6.0	5.7	5.5	4.8
Monobactams	0.1	0.1	0.1	0.1	0.1	0.1
Carbapenems	9.9	9.9	10.1	10.2	10.1	9.8
Other cephalosporins and penems	4.8	4.7	4.6	4.3	4.0	3.8
Combinations of sulfonamides and trimethoprim including derivatives	45.8	49.9	53.7	58.6	62.1	65.7
Macrolides	108.0	101.4	103.4	102.9	94.5	89.7
Lincosamides	2.8	2.7	2.6	2.5	2.4	2.4
Streptogramins	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Streptomycin	0.1	0.1	0.1	0.1	0.1	0.1
Other aminoglycosides	1.0	0.9	0.9	0.8	0.8	0.7
Fluoroquinolones	61.3	60.2	56.6	57.4	53.2	49.7
Other quinolones	0.5	0.4	0.3	0.3	0.2	0.1
Glycopeptides	2.2	2.1	2.3	2.4	2.5	2.4
Polymyxins	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Metronidazole (parenteral)	<0.1	<0.1	0.2	0.2	0.2	0.2
Other antibacterials	17.5	16.5	16.6	16.7	14.3	13.8
TOTAL	562.6	560.2	579.7	591.0	581.4	582.2

* Unit: tons (t).

(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 2017, the volume of sales of veterinary antimicrobials ranged between 749.47 t and 872.09 t. The approximately 91 t increase in sales over this period was mainly accounted for by increases in macrolides (approximately 63 t), primarily 16-membered macrolides used in pigs and erythromycin used in aquatic animals (seawater fish). Tetracyclines represented the largest share of antimicrobial sales over the period monitored, accounting for between 39.8% and 43.6%.

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

Table 73. Amounts of veterinary antimicrobials in terms of active ingredients by type (t)

	2013	2014	2015	2016	2017
Penicillins	78.17	77.96	83.73	99.75	101.02
Cephalosporins (total)	5.58	5.50	5.89	6.45	6.65
1st generation cephalosporins	(4.71)	(4.58)	(4.98)	(5.41)	(5.50)
2nd generation cephalosporins	(0.19)	(0.20)	(0.12)	(0.16)	(0.18)
3rd generation cephalosporins	(0.68)	(0.71)	(0.79)	(0.88)	(0.96)
Aminoglycosides	39.52	40.64	35.47	47.86	44.76
Macrolides	77.70	70.43	98.41	134.12	140.83
Lincosamides	38.99	43.26	28.66	21.87	25.26
Tetracyclines	340.52	324.85	333.86	331.55	347.05
Peptides	11.78	9.98	14.54	14.02	19.99
Other antibiotics	25.98	28.85	32.39	31.96	36.19
Sulfonamides	103.90	97.57	96.67	95.85	99.06
Quinolones	1.01	1.91	1.71	1.74	1.84
Fluoroquinolones	5.53	5.63	7.35	6.08	6.83
Amphenicols	21.53	26.15	29.73	26.49	27.11
Furan and derivatives	14.46	1.76	1.24	1.57	1.36
Other synthetic antibacterials	15.02	13.97	13.35	12.12	13.09
Antifungal antibiotics	1.18	1.03	1.08	1.12	1.07
Total	780.88	749.47	784.06	832.56	872.09

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

The marketing authorization holders also submit the percentage of sales for each species of domestic animal estimated from information on the distributors, so the estimated volumes for each species sold are calculated based on those estimated percentages. In terms of active ingredients, pigs accounted for the largest amount, followed by seawater fish. As described above, the increase in sales for these animal spiecies is the primary factor behind the rise in sales volumes.

Animals vary widely in weight, ranging from chicks that weigh just a few dozen grams to dairy cows that weigh more than 600 kg, and the number of animals kept also differs according to the species, so the number of animals and the weight per animal must be taken into account in comparisons by animal species. Accordingly, there is a comparison method which involves using animal weights and numbers to calculate biomass weight (total weight of animals) and expressing figures for antimicrobial use as usage per unit of biomass weight. While there was hitherto no internationally standardized method for calculating biomass weight, the OIE has recently set out a method for calculating biomass weight as part of its collection of veterinary antimicrobial usage data,[14] so consideration is being given to using this evaluation method in Japan.

Table 74. Estimated amounts of veterinary antimicrobials in terms of active ingredients by type of animal (t)

	2013	2014	2015	2016	2017
Beef cattle	23.02	20.35	23.77	25.00	25.92
Dairy cow	31.73	30.45	32.48	35.10	34.55
Horse	2.18	2.01	2.10	2.31	2.17
Pig	502.64	490.42	503.13	521.64	551.96
Broiler	65.90	70.14	62.36	64.79	63.03
Layer	23.29	23.67	19.36	20.75	16.61
Fish (Seawater)	112.36	93.41	123.02	143.03	159.07
Fish (Freshwater)	6.84	5.61	7.28	10.10	9.07
Ornamental fish	0.72	1.07	1.60	1.95	1.74
Dog/Cat	9.67	9.13	8.86	7.79	7.97
Others	2.54	3.22	0.09	0.10	0.00
Total	780.88	749.47	784.05	832.56	872.09

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 75. During the period 2013 to 2017, the estimated volume of sales ranged between 640.25 t and 694.24 t. The approximately 44 t increase in sales over this period was mainly accounted for by increases in penicillins (approximately 24 t) and 16-membered macrolides such as tylosin (approximately 22 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 41.2 to 44.0%. In contrast, third-generation cephalosporins and fluoroquinolones, which are critically important antimicrobials for human medicine, each accounted for less than 1% of veterinary antimicrobials used for food-producing animals, at less than 1 t and around 5 t, respectively.

Table 75. 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	2017
Penicillins	59.50	61.96	67.25	83.56	84.68
Cephalosporins (total)	3.12	3.06	3.22	3.34	3.44
1st generation cephalosporins	(2.45)	(2.34)	(2.52)	(2.52)	(2.51)

2nd generation cephalosporins	(0.19)	(0.20)	(0.12)	(0.16)	(0.18)
3rd generation cephalosporins	(0.49)	(0.51)	(0.58)	(0.65)	(0.74)
Aminoglycosides	37.40	38.66	34.07	47.46	44.37
Macrolides	56.00	53.30	60.36	72.68	71.96
Lincosamides	35.88	36.61	23.65	15.62	19.39
Tetracyclines	286.74	275.83	276.24	280.66	286.01
Peptides	11.77	9.97	14.54	14.01	19.98
Other antibiotics	25.71	28.43	32.23	31.55	35.72
Sulfonamides	95.62	88.43	84.40	78.57	84.10
Quinolones	0.22	0.20	0.20	0.16	0.31
Fluoroquinolones	4.64	4.73	6.41	5.19	5.93
Amphenicols	19.66	25.14	27.39	24.82	25.34
Furan and derivatives	0.00	0.00	0.00	0.00	0.00
Other synthetic antibacterials	14.98	13.92	13.32	12.07	13.02
Antifungal antibiotics	0.00	0.00	0.00	0.00	0.00
Titak	651.24	640.25	643.28	669.68	694.24

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

2) Aquatic animals

The estimated volumes of veterinary antimicrobials sold for aquatic animals (seawater fish, freshwater fish, and ornamental fish) in terms of active ingredients are summarized in Table 76. In the period from 2013 to 2017, the estimated volume of sales ranged between 100.09 t and 169.88 t, accounting for between 13.4% and 19.5% of the total volume of veterinary antimicrobial sales. Tetracyclines (ranging between 49.01 t and 61.05 t) took up the largest share in the overall volume of sales until 2015, but the top spot has been taken by a macrolide (erythromycin) since 2016, with sales totaling between 61.44 t and 68.87 t. The approximately 50 t increase in the volume of sales between 2013 and 2017 was due to a rise in sales of a macrolide (erythromycin), which was attributed to an outbreak of streptococcosis (*Lactococcus garvieae*), for which the agent is indicated.

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

Table 76. The estimated volumes of sales of veterinary antimicrobials used for aquatic animals (seawater fish, freshwater fish, and ornamental fish) in terms of active ingredients (unit: tons)

	2013	2014	2015	2016	2017
Penicillins	16.31	13.87	14.38	14.62	14.66
Cephalosporins (total)	0.00	0.00	0.00	0.00	0.00
1st generation cephalosporins	0.00	0.00	0.00	0.00	0.00
2nd generation cephalosporins	0.00	0.00	0.00	0.00	0.00
3rd generation cephalosporins	0.00	0.00	0.00	0.00	0.00
Aminoglycosides	0.00	0.00	0.00	0.00	0.00
Macrolides	21.70	17.13	38.05	61.44	68.87
Lincosamides	3.02	6.56	4.90	6.12	5.73
Tetracyclines	53.78	49.01	57.62	50.89	61.05
Peptides	0.00	0.00	0.00	0.00	0.00
Other antibiotics	0.27	0.42	0.16	0.42	0.47
Sulfonamides	7.68	8.59	11.71	16.74	14.39
Quinolones	0.79	1.71	1.51	1.58	1.53
Fluoroquinolones	0.00	0.00	0.00	0.00	0.00
Amphenicols	1.87	1.01	2.33	1.67	1.77
Furan and derivatives	14.46	1.76	1.24	1.57	1.36
Other synthetic antibacterials	0.02	0.04	0.02	0.04	0.06

Antifungal antibiotics	0.00	0.00	0.00	0.00	0.00
Total	119.91	100.09	131.91	155.08	169.88

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 77. In the period from 2013 to 2017, 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 was not originally monitored under JVARM and is therefore excluded from the values in the table for 2015 and earlier. Accordingly, with the full cooperation of the Japan Animal Drugs & Instruments Dealers Association and Federation of Japan Pharmaceutical Wholesalers Association, the Ministry of Agriculture, Forestry and Fisheries began monitoring the actual usage of human antimicrobials in 2016 based on the amount sold. The results of its surveillance revealed that the volume of human antimicrobials sold for use in companion animals is about the same as the volume of veterinary antimicrobials sold for that purpose.

Table 77. The estimated volumes of sales of veterinary and human antimicrobials used for companion animals (cats and dogs) in terms of active ingredients (unit: tons)

	2013	2014	2015	2016		2017
	Veterinary antimicrobials	Veterinary antimicrobials	Veterinary antimicrobials	Veterinary antimicrobials	Human antimicrobials	Veterinary antimicrobials
Penicillins	2.36	2.13	2.08	1.57	1.93	1.68
Cephalosporins (total)	2.45	2.44	2.67	3.12	3.23	3.21
1st generation cephalosporins	(2.26)	(2.23)	(2.46)	(2.89)	(3.12)	(2.99)
2nd generation cephalosporins	(0.00)	(0.00)	(0.00)	(0.00)		(0.00)
3rd generation cephalosporins	(0.20)	(0.20)	(0.21)	(0.23)	(0.11)	(0.22)
Aminoglycosides	2.07	1.97	1.40	0.41	0.02	0.39
Macrolides	0.00	0.00	0.00	0.00	0.17	0.00
Lincosamides	0.09	0.09	0.11	0.13	0.10	0.13
Tetracyclines	0.00	0.00	0.00	0.00	0.28	0.00
Peptides	0.01	0.01	0.01	0.01	0.00	0.01
Other antibiotics**	0.00	0.00	0.00	0.00	0.22	0.00
Sulfonamides	0.60	0.55	0.56	0.53	0.19	0.57
Quinolones	0.00	0.00	0.00	0.00	0.00	0.00
Fluoroquinolones	0.90	0.90	0.94	0.89	0.11	0.90
Amphenicols	0.00	0.00	0.00	0.00	0.12	0.01
Furan and derivatives	0.00	0.00	0.00	0.00	0.00	0.00
Other synthetic antibacterials***	0.02	0.01	0.01	0.01	0.08	0.01
Antifungal antibiotics	1.18	1.03	1.08	1.12	0.00	1.07
Total	9.67	9.13	8.86	7.79	6.48	7.97

* The figures in parentheses are included in the Cephalosporins (total).
** Includes fosfomycin and rifamycin.
*** Includes trimethoprim, penems, carbapenems, isoniazid, and ethambutol.

(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 78. While the volume of such additives distributed remained at more or less the same level in the period 2013 to 2017, 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 (not used in humans), which account for the majority. The designation of the polypeptide colistin as a feed additive was revoked in July 2018, while that of the macrolide tylosin was revoked

in May 2019. With tetracyclines also due to have their designation revoked in December 2019, distribution of these antimicrobials will cease from the time of their revocation.

Table 78. Volume of distribution of antibiotic feed additives in terms of effective value (unit: tons)

	2013	2014	2015	2016	2017
Aminoglycosides	0.0	0.0	0.0	0.0	0.0
Polypeptides	35.0	28.3	29.6	32.1	15.2
Tetracyclines	1.6	2.2	2.6	2.0	0.0
Macrolides	5.6	5.3	5.5	1.4	3.5
Polysaccharides	0.2	0.0	0.1	0.1	0.1
Polyethers	136.0	142.5	141.7	159.9	165.5
Other antimicrobials	20.8	18.3	12.5	14.6	19.8
Synthetic antimicrobials	35.9	29.3	24.4	18.1	17.1
Total	235.1	225.9	216.4	228.2	221.2

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 79 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 2017, the volume of shipments of antimicrobials used as agrochemicals remained at around the 150 t mark, ranging between 142.72 t and 153.63 t.

Table 79. The volume of shipment in Japan of antimicrobials that are used as agrochemicals, in terms of active ingredients (unit: tons).

	2013	2014	2015	2016	2017
Streptomycin	36.12	36.21	35.49	39.80	45.32
Oxytetracycline	10.52	12.00	12.54	10.50	9.61
Kasugamycin	20.53	20.96	21.24	20.56	13.14
Validamycin	23.11	25.50	24.97	24.80	22.07
Oxolinic acid	40.08	40.79	41.16	42.17	44.00
Polyoxins	16.24	15.49	15.25	15.80	8.57
Total	146.59	150.94	150.66	153.63	142.72

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 80 and 81 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 13-16%, and macrolides at 11-13%. Use of every tetracyclines, 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 80. Current volume of antimicrobial use in Japan (t)

	2013	2014	2015	2016	2017
Penicillins	221.7	228.7	248.7	272.2	281.0
Cephalosporins	168.3	163.7	166.5	165.6	160.5
Monobactams	0.1	0.1	0.1	0.1	0.1
Carbapenems	9.9	9.9	10.1	10.2	10.1
Aminoglycosides	97.1	98.7	93.1	109.1	104.0
Macrolides	191.3	177.2	207.3	238.5	238.9
Lincosamides	41.8	45.9	31.3	24.4	27.7

Tetracyclines	359.7	346.0	356.1	351.2	363.7
Peptides and glycopeptides	49.0	40.4	46.5	48.5	37.7
Sulfonamides*	149.7	147.5	150.4	154.4	161.1
Fluoroquinolones	66.8	65.8	63.9	63.5	60.1
Other quinolones	41.5	43.1	43.2	44.2	46.1
Amphenicols, thiamphenicols and derivatives	21.7	26.3	29.8	26.6	27.2
Furan and derivatives	14.5	1.8	1.2	1.6	1.4
Polysaccharides	0.2	0.0	0.1	0.1	0.1
Polyethers	136.0	142.5	141.7	159.9	165.5
Polyoxins	16.2	15.5	15.3	15.8	8.6
Others*	138.3	132.4	124.4	118.5	122.8
Total	1723.9	1685.5	1729.7	1804.3	1816.2

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

Table 81. 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

	2017					
	Humans	Food-producing animals	Aquatic animals	Companion animals	Antimicrobial feed additives	Agrochemicals
Penicillins	179.9	84.7	14.7	1.7	0.0	0.0
Cephalosporins	153.8	3.4	0.0	3.2	0.0	0.0
Monobactams	0.1	0.0	0.0	0.0	0.0	0.0
Carbapenems	10.1	0.0	0.0	0.0	0.0	0.0
Aminoglycosides	0.8	44.4	0.0	0.4	0.0	58.5
Macrolides	94.5	72.0	68.9	0.0	3.5	0.0
Lincosamides	2.4	19.4	5.7	0.1	0.0	0.0
Tetracyclines	7.0	286.0	61.1	0.0	0.0	9.6
Peptides and glycopeptides	2.5	20.0	0.0	0.0	15.2	0.0
Sulfonamides	62.1	84.1	14.4	0.6	0.0	0.0
Fluoroquinolones	53.2	5.9	0.0	0.9	0.0	0.0
Other quinolones	0.2	0.3	1.5	0.0	0.0	44.0
Amphenicols, thiamphenicols and derivatives	0.1	25.3	1.8	0.0	0.0	0.0
Furan and derivatives	0.0	0.0	1.4	0.0	0.0	0.0
Polysaccharides	0.0	0.0	0.0	0.0	0.1	0.0
Polyethers	0.0	0.0	0.0	0.0	165.5	0.0
Polyoxins	0.0	0.0	0.0	0.0	0.0	8.6
Others*	14.5	48.7	0.5	0.0	36.9	22.1
Total	581.3	694.3	169.9	6.9	221.2	142.7
Total for year						1,816.2

*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) Research into antimicrobial stewardship

The following study of antimicrobial stewardship in Japan has been carried out using medical insurance claims data.

Research into antimicrobial stewardship in Japan using medical insurance claims data.

Disease	Patients	Medical Insurance Claims Data	Survey Period	Year Reported
General outpatient consultations	Adults and children	National Health Insurance	2012-2013	2019 (paper)[1]
Acute respiratory tract infections	Adults and children	Social insurance	2005	2009 (paper)[2]
	Children	Social insurance	2005-2014	2018 (paper)[3]
	Adults and children	Social insurance	2013-2015	2019 (paper)[4]
	Adults and children	Social insurance	2012-2017	2019 (paper)[5]
Hemolytic streptococcal infections	Children	Social insurance	2012-2015	2018 (paper)[7]
Acute diarrhea	Children	Social insurance	2012-2015	2019 (paper)[8]
Acute cystitis	Adults	Social insurance	2013-2016	2019 (Report)
Acute pyelonephritis	Adults and children	Social insurance	2013-2016	2019 (Report)

1) Outpatient prescriptions of antimicrobials for adults and children

i) Survey of antimicrobial use among adults and children seen as outpatients based on National Health Insurance claims data (survey period: April 2012-March 2013)

In a study of outpatient prescriptions of antimicrobials in Japan carried out using National Health Insurance data, 7,770,481 claims for outpatient consultations between April 2012 and March 2013 were analyzed, resulting in the finding that antimicrobials had been prescribed in 682,822 of them (860 per 1,000 population).[1] Third-generation cephalosporins accounted for 35% of all antimicrobials prescribed, followed by macrolides at 32% and fluoroquinolones at 21%. Looking at the purpose of use, 60% of the antimicrobials prescribed were for respiratory tract infections (22% for upper respiratory tract infections, 18% for tonsillitis, 11% for bronchitis, and 10% for sinusitis), followed by gastroenteritis (9%), urinary tract infections (8%), and skin and soft tissue infections (5%). By disease, the rates of prescribing antimicrobials were as follows: 35% for viral upper respiratory tract infections, 54% for tonsillitis, 53% for bronchitis, 57% for sinusitis, and 30% for acute gastroenteritis. In the cases of both acute upper respiratory tract infections and acute gastroenteritis, antimicrobials were prescribed more often for patients aged under 65 than for those aged 65 or above and more often by clinics than by hospitals (Tables 82 and 83).

Table 82. Odds ratios of antimicrobial prescription for acute upper respiratory tract infections

Characteristics	Number of antimicrobial prescriptions (%)	Odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Age			
0–9	44413 (50.4)	1.66 (1.64 - 1.69)	1.48 (1.46 - 1.50)
10–19	20822 (65.1)	3.08 (3.00 - 3.15)	2.75 (2.69 - 2.82)
20–64	85952 (54.6)	1.98 (1.95 - 2.00)	1.92 (1.89 - 1.94)
≥65	121289 (37.9)	1	1
Sex			
Male	112643 (47.4)	1.13 (1.12 - 1.14)	1.10 (1.08 - 1.11)
Female	155038 (44.4)	1	1
Medical institution			
Clinic	233078 (49.8)	4.48 (4.27 - 4.70)	4.24 (4.03 - 4.45)
Hospital with less than 200 beds	23012 (30.8)	2.01 (1.91 - 2.11)	2.07 (1.97 - 2.18)
Hospital with 200-499 beds	9327 (28.2)	1.77 (1.68 - 1.89)	1.71 (1.62 - 1.80)
Hospital with 500 or more beds	2064 (18.2)	1	1

Table 83. Odds ratios of antimicrobial prescription for acute diarrhea

Characteristics	Number of antimicrobial prescriptions (%)	Odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)

Age			
0-9	10809 (37.0)	1.92 (1.86 - 1.98)	1.76 (1.71 - 1.82)
10–19	4395 (38.7)	2.07 (1.98 - 2.16)	1.92 (1.83 - 2.00)
20–64	12310 (32.4)	1.57 (1.53 - 1.61)	1.55 (1.51 - 1.60)
≥65	13795 (23.4)	1	1
Sex			
Male	18547 (30.9)	1.09 (1.06 - 1.12)	1.04 (1.01 - 1.06)
Female	21831 (29.1)	1	1
Medical institution			
Clinic	33712 (32.9)	2.03 (1.82 - 2.27)	1.88 (1.68 - 2.10)
Hospital with less than 200 beds	4056 (21.7)	1.15 (1.02 - 1.29)	1.17 (1.04 - 1.32)
Hospital with 200-499 beds	2214 (18.9)	0.97 (0.86 - 1.09)	0.93 (0.82 - 1.05)
Hospital with 500 or more beds	396 (19.4)	1	1

As a result, it was determined that most antimicrobials are prescribed for upper respiratory tract infections and gastroenteritis, conditions for which antimicrobials are not deemed necessary. These diseases will likely be the main focus of future efforts to promote antimicrobial stewardship. In addition, antimicrobials were prescribed more often for patients aged under 65 than for those aged 65 or above and more often at clinics than at hospitals. The need to put in place testing systems and ensure that rapid tests for microorganisms become prevalent at clinics will be considered going forward.

2) Acute upper respiratory tract infections in adults and children

i) Survey of antimicrobial use to treat nonbacterial upper respiratory tract infections in adults and children based on social insurance claims data (survey period: January-March 2005)

A study of 24,134 medical insurance claims made between January and March 2005 found that 4,325 gave the diagnosis as a nonbacterial upper respiratory tract infection.[2] Antimicrobials were prescribed for 60% of the patients seen for an acute upper respiratory tract infection, with 46% of all antimicrobials being accounted for by third-generation cephalosporins, 27% by macrolides, and 16% by quinolones. In addition, antimicrobials were prescribed more frequently at clinics than at hospitals (Table 84).

Table 84. Antimicrobial prescriptions as a percentage and odds ratio

		As a percentage of all consultations (%)	Odds ratio	Adjusted odds ratio
Patient characteristics	Age			
	>15 years	60.5	1	1
	≤15 years	57.6	0.89	0.82
	Sex			
	Male	60.9	1	1
	Female	59	0.92	0.87
Characteristics of consultation	Time			
	Normal hours	60.9	1	1
	Out of hours	48	0.59	0.86
	Prescription			
	External prescription	65.4	1	1
	Internal prescription	70.2	1.25	1.29
Characteristics of medical institution	Type of medical institution			
	Clinic	64	1	1
	Public educational institution	40	0.37	0.38
	Public non-educational institution	41.9	0.64	0.44
	Private educational institution	53.3	0.4	0.65
	Private non-educational institution	48.3	0.53	0.54
	University hospital	50	0.56	0.63
	Place			
	Prefecture A	61.2	1	1
	Prefecture B	57.9	0.85	0.83
	Prefecture C	49.6	0.6	0.63

Prefecture D	52.9	0.69	0.73
Prefecture E	56.7	0.8	0.77
Prefecture F	65.4	1.16	1.11
Other prefectures	67.2	1.26	1.24

ii) Survey of antimicrobial use to treat acute upper respiratory tract infections in children based on social insurance claims data (survey period: January 2005 - September 2014)

In a study concerning the prescription of antimicrobials for acute upper respiratory tract infections in children, the JMDC database was used to examine antimicrobials prescribed at outpatient consultations between January 2005 and September 2014 to pediatric patients from birth up to the age of 6, but who had not yet started school.[3] Analysis of 1,492,548 medical insurance claims for 155,556 children showed that third-generation cephalosporins were the most frequently prescribed antimicrobials (38.3%), followed by macrolides (25.8%) and penicillins (16.0%). Examining the situation by disease name, acute bronchitis was the most common condition for which antimicrobials were prescribed (11.9%), followed by acute upper respiratory tract infection (10.1%), and asthma (7.5%) (Table 85).

Table 85. Name of diagnosed condition for which antimicrobials were prescribed

ICD10 Code		N	%
A00-B99	Certain infectious and parasitic diseases		
A09	Other gastroenteritis and colitis of infectious and unspecified origin	165,589	5.3
A49	Bacterial infection of unspecified site	36,066	1.2
B34	Viral infection of unspecified site	28,939	0.9
	Other	55,295	1.8
H60-H95	Diseases of the ear and mastoid process		
H60	Otitis externa	57,546	1.8
H61	Other disorders of external ear	85,960	2.7
H65	Nonsuppurative otitis media	65,073	2.1
H66	Suppurative and unspecified otitis media	113,118	3.6
	Other	67,91	0.2
J00-J99	Diseases of the respiratory system		
J00	Acute nasopharyngitis [common cold]	156,581	5
J01	Acute sinusitis	136,536	4.4
J02	Acute pharyngitis	164,851	5.3
J03	Acute tonsillitis	37,591	1.2
J04	Acute laryngitis and tracheitis	24,906	0.8
J06	Acute upper respiratory infections of multiple and unspecified sites	316,157	10.1
J11	Influenza, virus not identified	59,336	1.9
J18	Pneumonia, organism unspecified	24,891	0.8
J20	Acute bronchitis	373,819	11.9
J30	Vasomotor and allergic rhinitis	215,312	6.9
J32	Chronic sinusitis	76,964	2.5
J40	Bronchitis, not specified as acute or chronic	59,974	1.9
J45	Asthma	235,157	7.5
	Other	65,210	2.1
Other		573,903	18.1

Antimicrobials were more often prescribed for nonbacterial upper respiratory tract infections in children who were older and male, at clinics, by physicians in specialties other than pediatrics, and during out of hours consultations (Table 86).

Table 86. Odds ratios of factors related to antimicrobial prescriptions for nonbacterial upper respiratory tract infections

	Number of cases in which antimicrobials were prescribed for upper respiratory tract infection (%)	Odds ratio	95% confidence interval	Adjusted odds ratio	95% confidence interval
Age					

0-1	76,134 (8.7)	1		1	
2-3	47,906 (11.6)	1.37	1.36 1.39	1.3	1.28 1.31
4-5	21,252 (15.5)	1.93	1.90 1.96	1.72	1.69 1.74
Sex					
Female	66,681 (9.9)	1		1	
Male	78,611 (10.4)	1.06	1.05 1.07	1.06	1.04 1.07
Medical institution					
Clinic	133,312 (10.3)	1		1	
Hospital with less than 200 beds	3289 (8.9)	0.85	0.82 0.88	0.69	0.67 0.72
Hospital with 200 or more beds	8691 (9.2)	0.89	0.87 0.91	0.67	0.66 0.69
Clinical department					
Pediatrics	39 176 (6.5)	1		1	
Not pediatrics	106 116 (12.8)	2.11	2.08 2.14	2.13	2.10 2.15
Time of consultation					
Normal hours	133 817 (9.9)	1		1	
Out of hours	11 343 (15.3)	1.64	1.61 1.68	1.53	1.50 1.57

This study showed that prescriptions of antimicrobials for upper respiratory tract infections in preschool children are common in Japan and that third-generation cephalosporins are the most common antimicrobial prescribed for them. It emerged that antimicrobials were more likely to be prescribed by physicians in specialties other than pediatrics and during out of hours consultations, suggesting a need to raise awareness among clinicians of antimicrobial stewardship.

iii) Survey of antimicrobials used to treat acute upper respiratory tract infections in adults and children based on social insurance claims data (survey period: January 2013 - December 2015)

A study using the JMDC database—a database of medical insurance claims for some social insurance programs—analyzed 4.6 million prescriptions issued to patients seen for acute upper respiratory tract infections from among 8.65 million people's medical insurance claims arising between January 2013 and December 2015.[4] The results showed that 40.7% of the antimicrobials prescribed were accounted for by third-generation cephalosporins, 32.8% by macrolides, and 14.7% by quinolones. The proportion of prescriptions varied according to the age of the patient, with the highest proportion of cephalosporin prescriptions being accounted for by patients aged between 0 and five years, and the figures falling steadily up to the age of around 40, after which they level off. The 0-5 age group also accounted for the highest proportion of penicillin prescriptions, falling to 5.9% by the age of 10 and then leveling off. On the other hand, there was a sharp upsurge in the proportion of prescriptions for fluoroquinolones among patients over the age of 20. The proportion of prescriptions for macrolides peaked in the 10-15 age group.

iv) Survey of antimicrobials used to treat acute upper respiratory tract infections in adults and children based on social insurance claims data (survey period: April 2012 - July 2017)

The JMDC database was also used for a study that extracted information about patients, diagnoses, treatment, and medical facilities for the period April 2012 to July 2017 and examined trends in the prescription of antimicrobials and associated factors. Of the Of the 8,983,098 patients, 17,208,787 consultations were identified with nonbacterial upper respiratory tract infections. The average number of prescriptions was 31.65 per 100 consultations for nonbacterial upper respiratory tract infections, and there was a 19.2% decline between the first month and the last month of the survey period (Figure 4).

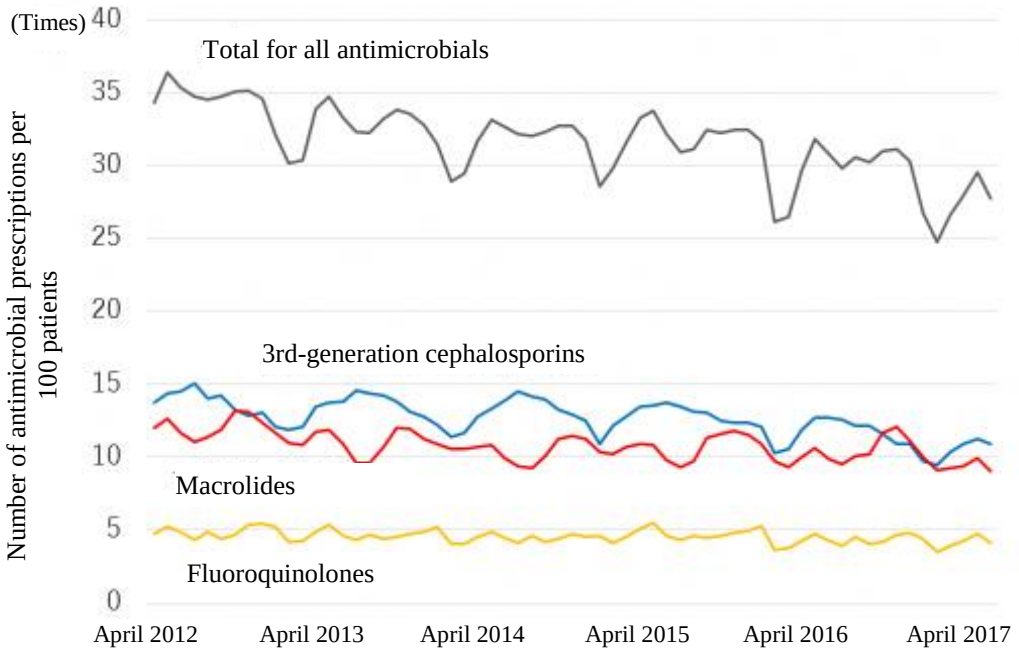

Figure 4. Trends in the number of antimicrobial prescriptions per 100 patients with nonbacterial acute respiratory tract infections

Broad-spectrum antimicrobials (third-generation cephalosporins, macrolides, and fluoroquinolones) accounted for 89% of all antimicrobials prescribed. Examination of the factors in the prescription of antimicrobials revealed that the proportion of antimicrobial prescriptions issued was higher among patients in the 13-18, 19-29, and 30-39 age groups than among those aged 60 and above, while antimicrobial prescription rates were high in the fields of internal medicine and otolaryngology. Clinics and clinics with beds accounted for a higher proportion of antimicrobial prescriptions than other medical institutions (Table 87).

Table 87. Multivariate analysis of factors in the prescription of antimicrobials

	Odds ratio	95% confidence interval	Adjusted odds ratio	95% confidence interval
Sex				
Male	1		1	
Female	0.954	0.952 0.956	0.956	0.954 0.958
Age				
0-3	0.547	0.544 0.550	0.621	0.617 0.625
4-6	0.855	0.850 0.860	0.970	0.964 0.977
7-12	1.079	1.072 1.085	1.193	1.186 1.201
13-18	1.443	1.434 1.453	1.517	1.506 1.527
19-29	1.634	1.624 1.644	1.629	1.619 1.639
30-39	1.596	1.586 1.605	1.554	1.545 1.563
40-49	1.462	1.454 1.471	1.423	1.415 1.432
50-59	1.222	1.215 1.230	1.206	1.198 1.213
60-	1		1	
Insured person				
Insured person	1.715	1.711 1.719	1.105	1.101 1.109
Insured person's family member	1		1	
Clinical department				
Internal medicine	1.313	1.307 1.318	1.218	1.212 1.223
Pediatrics	0.724	0.721 0.728	0.901	0.897 0.906
Otorhinolaryngology	1.275	1.268 1.081	1.245	1.238 1.251
Other	1		1	

Medical institution				
Clinic with no beds	1.870	1.862 1.878	2.217	2.207 2.227
Clinic with beds	1.647	1.633 1.661	1.861	1.845 1.877
University hospital	0.684	0.670 0.698	0.713	0.698 0.728
Public hospital	0.684	0.677 0.692	0.788	0.779 0.797
Other	1		1	
Time of consultation				
Normal hours	1		1	
Out of hours	0.956	0.953 0.959	0.957	0.954 0.960
Fiscal year				
2012	1		1	
2013	0.937	0.934 0.941	0.938	0.934 0.941
2014	0.906	0.903 0.910	0.897	0.897 0.900
2015	0.879	0.876 0.882	0.857	0.854 0.860
2016	0.813	0.810 0.816	0.784	0.781 0.787
2017	0.780	0.776 0.785	0.698	0.693 0.702
Month				
1	1		1	
2	0.902	0.897 0.906	0.926	0.922 0.931
3	0.952	0.947 0.956	1.006	1.001 1.011
4	1.094	1.089 1.099	1.275	1.269 1.282
5	1.165	1.159 1.170	1.360	1.354 1.367
6	1.099	1.094 1.104	1.334	1.328 1.341
7	1.096	1.091 1.102	1.315	1.308 1.322
8	1.104	1.098 1.111	1.300	1.292 1.307
9	1.104	1.123 1.135	1.326	1.319 1.333
10	1.15	1.144 1.155	1.310	1.303 1.316
11	1.153	1.147 1.158	1.281	1.275 1.287
12	1.118	1.113 1.124	1.226	1.220 1.232

This study used medical insurance claims data for the period April 2012 to July 2017, but showed a lower rate of antimicrobial prescription than the aforementioned study using medical insurance claims data from 2005.[2] This is attributed to the fact that the use of antimicrobials to treat nonbacterial upper respiratory tract infections has been moderated, but it could also be affected by the fact that the study rigorously excluded cases that also included the names of bacterial infections as comorbidities. While this study showed that antimicrobials were prescribed on 31.65 occasions for every 100 cases of a nonbacterial upper respiratory tract infection, the use of antimicrobials in accordance with guidelines for non-influenza acute upper respiratory tract infections was reportedly 5-7%,[6] so it was anticipated that nonbacterial upper respiratory tract infections would remain a key focus of efforts to promote antimicrobial stewardship. The prescription of antimicrobials to those in the younger generation of workers (19-29 and 30-39 age brackets) was particularly high. By specialty, physicians in the fields of internal medicine and otolaryngology were more likely to prescribe antimicrobials than pediatricians.

3) Group A Streptococcus infections infections in children

Survey of antimicrobials used to treat Group A Streptococcus infections in children based on social insurance claims data (survey period: April 2012 - December 2015)

A study of the prescription of antimicrobials for Group A Streptococcus infections in children extracted information from the JMDC database about patients under the age of 18 whose diagnosis was given as Group A Streptococcus infections and examined the extent of the prescription of antimicrobials to them.[7] The study investigated medical insurance claims data for 5,030 outpatients suffering from Group A Streptococcus infections and found that the most common type of antimicrobial prescribed was third-generation cephalosporins at 53.3% of all prescriptions, followed by penicillins (40.1%) and macrolides (2.6%) (Table 88).

Table 88. Antimicrobial prescriptions by clinical department

Antimicrobial	Total	Pediatrics	Internal medicine	Other clinical department	*p*-value
Penicillins (%)	2017 (40.1)	1236 (39.5)	714 (43.1)	67 (27.2)	<0.001
Penicillins with beta-lactamase inhibitors (%)	20 (0.4)	9 (0.3)	7 (0.4)	4 (1.6)	0.019
Cephalosporins (%)	2760 (54.9)	1765 (56.4)	837 (50.6)	158 (64.2)	<0.001

3rd-generation cephalosporins (%)	2679 (53.3)	1709 (54.6)	817 (49.4)	153 (62.2)	<0.001
Macrolides (%)	130 (2.6)	66 (2.1)	55 (3.3)	9 (3.7)	0.023
Tetracyclines (%)	5 (0.1)	2 (0.1)	3 (0.2)	0 (0)	0.42
Fluoroquinolones (%)	21 (0.4)	10 (0.3)	11 (0.7)	0 (0)	0.18
Penems (%)	25 (0.5)	19 (0.6)	5 (0.3)	1 (0.4)	0.19
Other (%)	13 (0.3)	9 (0.3)	0 (0)	4 (1.6)	<0.001

Other includes ST, clindamycin, and fosfomycin

An out of hours consultation was an independent factor in the prescription of penicillins, while a consultation by a physician with a specialism other than pediatrics or internal medicine was a factor in penicillins not being prescribed (Table 89).

Table 89. Factors in the prescription of antimicrobials

	N	Number of prescriptions for penicillins (%)	Prevalence ratio (95% confidence interval)	*p*-value
Age				
<3 years	148	59 (39.9)	0.84 (0.69-1.02)	0.075
3-6	2662	1125 (42.3)	Ref.	–
7-12	1962	743 (37.9)	0.90 (0.84-0.97)	0.004
>12	258	90 (34.9)	0.86 (0.72-1.02)	0.08
Sex				
Male	2711	1093 (40.3)	1.01 (0.94-1.08)	0.845
Female	2319	924 (39.8)	Ref.	–
Time of consultation				
Normal hours	3101	1173 (37.8)	Ref.	
Out of hours	1929	844 (43.8)	1.10 (1.03-1.18)	0.007
Facility				
Clinic	4543	1734 (38.2)	Ref.	
Public hospital/university hospital	168	104 (61.9)	1.70 (1.48-1.94)	<0.001
Other	319	179 (56.1)	1.61 (1.44-1.79)	<0.001
Clinical Department				
Pediatrics	3129	1236 (39.5)	Ref.	–
Internal medicine	1655	714 (43.1)	0.96 (0.89-1.04)	0.35
Other	246	67 (27.2)	0.57 (0.46-0.71)	<0.001

Most guidelines recommend that Group A Streptococcus infections be treated with a 10-day course of penicillin. However, in this study, third-generation cephalosporins were the most commonly prescribed antimicrobial. In Japan, there is a tendency to prefer a five-day course of treatment with a cephalosporin.

4) Acute diarrhea in children

Survey of antimicrobials used to treat acute diarrhea in children based on social insurance claims data (survey period: April 2012 - December 2015)

A study of acute diarrhea in children extracted information from the JMDC database about patients under the age of 18 whose diagnosis was given as acute diarrhea and analyzed the extent of the prescription of antimicrobials to them.[8] The study examined medical insurance claims data for 4,493 outpatients suffering from acute diarrhea and found that 29.6% of them had been prescribed antimicrobials. Fosfomycin was the most commonly prescribed antimicrobial (20.3%), followed by cephalosporins (4.5%), and macrolides (3.5%) (Table 90).

Table 90. Background of patients diagnosed with acute diarrhea

	Total	Child	Not pediatrics	*P*
Total number seeking outpatient consultations	4493	1842	2651	
Age, median value (SD)	6.63 (0.07)	5.64 (3.45)	7.45 (5.52)	<0.001
Sex, N (%)				
Male	2651 (59.0)	1049 (56.9)	1561 (58.8)	0.20

Time of consultation, N (%)				
Out of hours	1618 (36.0)	554 (30.1)	1064 (40.1)	<0.001
Medical institution type, N (%)				
Clinic	2881 (64.1)	1789 (97.1)	1092 (41.2)	<0.001
Public hospital	625 (13.9)	30 (1.6)	595 (22.4)	
University hospital	150 (3.4)	0 (0)	150 (5.7)	
Other	837 (18.6)	23 (1.2)	814 (30.7)	
Test, N (%)				
Stool culture	725 (16.1)	293 (15.9)	432 (16.3)	0.73
Rotavirus antigen	824 (18.3)	364 (19.8)	460 (17.4)	0.04
Adenovirus antigen	155 (3.4)	65 (3.5)	90 (3.4)	0.81
Norovirus antigen	313 (7.0)	180 (9.8)	133 (5.0)	<0.001
Diagnosis, N (%)				
Bacterial	1938 (43.1)	792 (43.0)	1146 (43.2)	0.88
Antimicrobial prescribed, N (%)				
Fosfomycin	914 (20.3)	508 (27.6)	406 (15.3)	<0.001
Penicillins	39 (0.9)	10 (0.5)	30 (1.1)	0.001
Penicillins with beta-lactamase inhibitors	9 (0.2)	3 (0.2)	6 (0.2)	0.75
Cephalosporins	204 (4.5)	64 (3.5)	140 (5.3)	<0.001
Macrolides	137 (3.5)	66 (3.6)	71 (2.7)	0.083
Tetracyclines	11 (0.2)	9 (0.5)	2 (0.1)	0.01
Fluoroquinolones	143 (3.2)	18 (1.0)	125 (4.7)	<0.001
Penems	25 (0.6)	5 (0.3)	4 (0.2)	1
Antidiarrheal drugs, N (%)				
Probiotics	2098 (46.7)	897 (48.7)	1201 (45.3)	0.025
Galactosidases	17 (0.4)	10 (0.5)	7 (0.3)	0.145
Loperamide	49 (1.1)	18 (1.0)	31 (1.2)	0.542
Berberine	21 (0.5)	2 (0.1)	19 (0.7)	0.003
Aluminum silicate	84 (1.9)	39 (2.1)	45 (1.7)	0.003
Albumin tannate	128 (2.8)	94 (5.1)	34 (1.3)	<0.001
Goreisan	210 (4.7)	164 (8.9)	46 (1.7)	<0.001

Antimicrobials were prescribed significantly more often in out of hours consultations, for diseases listed as bacterial infections, in consultations at clinics, and in consultations with pediatricians. (Table 91).

Table 91. Factors in the prescription of antimicrobials

	Total	Antimicrobial prescriptions	%	Prevalence	95% confidence interval	*p*-value
Age, years						
<3	1126	158	14	0.81	0.70 0.92	0.002
3-6	1735	562	32.4	Focus		
7-12	1006	351	34.9	0.89	0.82 0.97	0.007
12	626	259	41.4	0.89	0.80 0.99	0.028
Sex						
Male	2610	762	29.2	0.97	0.91 1.03	0.34
Female	1883	568	30.2	Focus		
Timing of consultation						
Normal hours	2875	825	28.7	Focus		
Out of hours	1618	505	31.2	1.18	1.10 1.26	<0.001
Diagnosis						
Nonbacterial	2555	198	7.7	Focus		
Bacterial	1938	1132	58.4	7.03	6.09 8.11	<0.001
Medical institution						
Clinic	2881	1059	36.8			
Public hospital/university hospital	775	113	14.6	0.58	0.49 0.69	<0.001
Other	837	158	18.9	0.82	0.72 0.93	0.003
Clinical department						

Not pediatrics	2651	695	26.2			
Not pediatrics	1842	635	34.5	1.11	1.02 1.20	0.014

This study revealed that fosfomycin is frequently used in Japan as an antimicrobial, but as antimicrobials are not needed to treat acute diarrhea, as a general rule, this suggested that efforts to raise awareness among clinicians are required.

5) Uncomplicated cystitis in adults

Survey of antimicrobials used to treat acute cystitis in adults based on social insurance claims data (survey period: January 2013 - December 2016)

The JMDC database was used to examine the prescription of antimicrobials for uncomplicated cystitis in adults in the project entitled 'Research Concerning the Implementation of the Antimicrobial Resistance (AMR) Action Plan (2017: H29-shinkougyousei-shitei-005),' which was funded under the programs for research projects to promote health and labor administration and research projects to promote administration in the areas of emerging/re-emerging infectious diseases and immunization. The study looked at data from 48,678 medical insurance claims for the period from January 2013 to December 2016, investigating the type of antimicrobial prescribed and the administration period. Cephalosporins and faropenem accounted for 41.5% of all antimicrobials prescribed for uncomplicated cystitis, while fluoroquinolones accounted for a further 53.2%, totaling 94.7% overall. Third-generation cephalosporins accounted for 93.8% of prescriptions for cephalosporins and faropenem (Table 92).

Table 92. Changes in the number of antimicrobial prescriptions

Type of antimicrobial	2013	2014	2015	2016
Tetracyclines (%)	79 (0.7)	97 (0.8)	77 (0.6)	88 (0.7)
Penicillins (%)	139 (1.3)	199 (1.7)	190 (1.5)	202 (1.5)
Cephalosporins and faropenem (%)	4,353 (41.0)	4,872 (40.7)	5,348 (41.8)	5,627 (42.4)
1st-generation cephalosporins (%)	51 (0.5)	69 (0.6)	68 (0.5)	69 (0.5)
2nd-generation cephalosporins (%)	233 (2.2)	250 (2.1)	241 (1.9)	246 (1.9)
3rd-generation cephalosporins (%)	3996 (37.6)	4453 (37.2)	4886 (38.2)	5161 (38.9)
Faropenem (%)	73 (0.7)	100 (0.9)	153 (1.2)	151 (1.1)
ST (%)	69 (0.6)	102 (0.9)	87 (0.7)	90 (0.7)
Macrolides and clindamycin (%)	164 (1.5)	211 (1.8)	197 (1.5)	190 (1.4)
Fluoroquinolones (%)	5,732 (54.0)	6,393 (53.4)	6,799 (53.1)	6,960 (52.4)
Fosfomycin (%)	80 (0.8)	99 (0.8)	107 (0.8)	127 (1.0)
Total	10616	11973	12805	13284

Figures show the number of times each antimicrobial was prescribed as a proportion of the total number of times that antimicrobials were prescribed in each year

The median value for the number of days for which antimicrobials were administered for uncomplicated cystitis between 2013 and 2016 was five days in all cases except ST (four days) (Table 93).

Table 93. Changes in the median value for the number of days of administration of antimicrobials

Type of antimicrobial	2013	2014	2015	2016	Total
Penicillins with beta-lactamase inhibitors	5 [5, 5.75]	5 [5, 7]	5 [5, 7]	5 [5, 7]	5 [5, 7]
1st-generation cephalosporins	5 [5, 7]	5 [3, 7]	5 [3.25, 7]	5 [3, 7]	5 [3, 7]
2nd-generation cephalosporins	5 [3, 5]	5 [3, 7]	5 [3, 7]	5 [4, 7]	5 [3, 7]
3rd-generation cephalosporins	5 [5, 7]	5 [5, 7]	5 [5, 7]	5 [5, 7]	5 [5, 7]
Faropenem	5 [5, 7]	5 [5, 7]	5 [5, 7]	5 [5, 7]	5 [5, 7]
ST	5 [3, 5]	3 [3, 5]	4 [3, 5]	4 [3, 5]	4 [3, 5]
Fluoroquinolones	5 [4, 5]	5 [4, 5]	5 [4, 5]	5 [4, 5]	5 [4, 5]
Fosfomycin	4 [3, 5]	5 [4, 5]	5 [4, 5]	5 [4, 5]	5 [4, 5]

Figures show median values, while figures in brackets show the interquartile range. The total column shows the median value and interquartile range totaled for the period 2013 to 2016.

This study showed that there is a disproportionate tendency to use cephalosporins (particularly third-generation cephalosporins) and fluoroquinolones as antimicrobials in the treatment of uncomplicated cystitis in Japan. This tendency differs substantially from the drugs recommended in Western guidelines. As the antimicrobials recommended in Western countries include antimicrobials that are unable to be used in Japan, this point must also be borne in mind when considering which antimicrobial to choose. In addition, the number of days for which fluoroquinolones were administered was higher than the number of days recommended in Japanese guidelines.

6) Acute pyelonephritis in adults and children

Survey of antimicrobials used to treat acute pyelonephritis in adults and children based on social insurance claims data (survey period: January 2013 - December 2016)

The project entitled 'Research Concerning the Implementation of the Antimicrobial Resistance (AMR) Action Plan (2017: H29-shinkougyousei-shitei-005),' which was funded under the programs for research projects to promote health and labor administration and research projects to promote administration in the areas of emerging/re-emerging infectious diseases and immunization, examined acute pyelonephritis in adults and children. Using the JMDC database, this study focused on data for patients during the period January 2013 to December 2016, where the disease name was given as acute pyelonephritis, antimicrobials were prescribed within three days of diagnosis, and urine tests were carried out. The study examined the incidence rate of acute pyelonephritis and the proportion of cases in which antimicrobials were used. Out of a total of 3,743,174 people and 11,884,471 person-years, 20,067 cases of acute pyelonephritis were observed. Male children were more likely to suffer from it in infancy (incidence rate: under 3 months (F/M): 0.83/3.61; 3-11 months (F/M): 1.58/2.97), but no difference between the genders was seen among young children (aged 1-3) (1-3 years (F/M): 0.53/0.53). Among the 4-14 years age bracket, the incidence was higher among female children and increased with age (4-14 years (F/M): 0.80/0.52; 15-75 years (F/M): 3.06/1,11) (Table 94).

Table 94. Incidence rate of acute pyelonephritis

	<3 months	3-11 months	1-3	4-14	15-75
Male	3.61	2.97	0.53	0.52	1.11
Female	0.83	1.58	0.53	0.80	3.06

Urine culture samples were more likely to be taken from younger patients (under 1 year: 89.8%; 1-3 years: 61.0%; 4-14 years: 27.6%; 15-75 years: 30.3%). The most commonly used antimicrobials were third-generation cephalosporins (20.3% oral/10.5% injection) and fluoroquinolones (28.8%). ST was used in 5.4% of cases (Table 95).

Table 95. Percentage of cases of acute pyelonephritis in which antimicrobials were administered

ATC 4th level	Percentage (%)
Broad-spectrum penicillins	4.1
Penicillins with beta-lactamase inhibitors	2.9
1st- and 2nd-generation cephalosporins	6.6
3rd-generation cephalosporins	33.8
(Oral)	10.4
(Injection)	23.4
Carbapenems	1.9
ST	5.4
Macrolides	6.4
Aminoglycosides	3.1
Fluoroquinolones	28.8
Other	7.0

In Japan, which has good access to medical care, the incidence rate was high among male children through infancy. After the age of one, the incidence rate was higher among females, as is the case in existing reports from Western countries.[9]

The fact that the proportion of cases in which urine culture samples are taken declines with age and that broad-spectrum antimicrobials (third-generation cephalosporins and fluoroquinolones) are prescribed in a high proportion of cases among all age brackets suggest a need to recommend that medical professionals take samples for culture and to consider the selection of antimicrobials with reference to Japan's antibiogram.

(7) 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.[10] 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).[11]

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.[12] 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.[10] 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.[11]

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.[13] 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.

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8. Public Awareness regarding Antimicrobial Resistance in Japan

(1) Survey of the general public

1) Survey of attitudes among the 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.[1, 2] 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 96. 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 97. 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 98. Does each statement below apply to you? (%)

		2017 (n=3,390)	2018 (n=3,192)
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 99. 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 attitudes among patients at medical institutions

Nakahama *et al.* conducted a survey of attitudes in which a questionnaire was distributed to 1,200 patients and their families who were seen at 17 medical institutions (2 hospitals, 15 clinics) in Osaka Prefecture, Okayama Prefecture, and Niigata Prefecture between November and December 2018.[3] Broken down by specialty, the medical institutions consisted of 7 specializing in internal medicine, 5 in pediatrics, 4 in otolaryngology, and 1 in urology. People in their 30s and 40s made up the majority (55.7% in total) of respondents.

Almost all the respondents had been prescribed antimicrobials at some point in the past, with 83.7% of them stating that they had been prescribed antimicrobials for a common cold. As many as 81.8% of respondents stated that antimicrobials are effective against colds, with many stating that they were effective in alleviating cold symptoms and preventing bacterial bronchitis and pneumonia. While people who thought that antimicrobials were effective based on past experience accounted for the largest share (45.6%), as many as 28.4% responded that they had been told of their effectiveness by a physician.

The proportion who had requested a prescription for antimicrobials during a consultation for a cold was 25.9%, 86.1% of whom stated that they would continue to do so. If told by a physician that antimicrobials were not effective against a cold, 72.6% "would be convinced" and 19.3% "would not be convinced, but would give up asking," while just 8.1% stated that they would seek a consultation with another physician. While responses by patients and their family members were divided into responses from those seen in an ordinary clinical department and those seen at one specializing in pediatrics, the responses showed more or less the same tendencies.

The results of this study showed that most patients seen at medical institutions had had previous experience of being prescribed antimicrobials and that most were under the misapprehension that antimicrobials are effective against colds. While most patients who had previously requested that antimicrobials be prescribed stated that they would continue to request them in future, most respondents also stated that they would be convinced by an explanation from their physician, suggesting the importance of doctor-patient communication.

Table 100. Diseases for which patients had been prescribed antimicrobials in the past (multiple responses permitted) (%)

n=1,138	Percentage
Common cold	83.7
Bronchitis	29.1
Otitis media	23.0
Abscess	18.3
Sinusitis	17.6
Pneumonia	12.9
Diarrhea	11.6
Cystitis	10.0
Other	7.6

Table 101. Are antimicrobials effective against colds? (%)

n=1,144	Percentage

Yes	81.8
No	18.2

Table 102. How are antimicrobials effective against colds? (Multiple responses) (%)

N=897 (those who replied that antimicrobials are effective against colds)	Percentage
Alleviate cold symptoms	69.6
Prevent bacterial bronchitis/pneumonia	48.8
Prevent the cold from infecting others	17.3
Highly significant in elderly people and small children	17.1
Other	3.9

Table 103. Who first told you that antimicrobials are effective against colds? (%)

N=908 (those who replied that antimicrobials are effective against colds)	Percentage
They were effective in my experience	45.6
Physician	28.4
Family member	9.7
Friend/acquaintance	4.5
Read it somewhere	4.3
Do not remember	17.4

Table 104. Have you ever asked a physician for a prescription for an antimicrobial to treat a cold? (%)

n=1,170	Percentage
Yes	25.9
No	74.1

Table 105. Will you ask a physician for a prescription for an antimicrobial to treat a cold in future? (%)

N=287 (those who replied that they had asked for an antimicrobial prescription)	Percentage
Yes	86.1
No	13.9

Table 106. What would you do if your physician explained to you that antimicrobials are not effective against colds? (%)

N=270 (those who replied that they had asked for an antimicrobial prescription)	Percentage
Would be convinced	72.6
Would not be convinced, but would give up asking	19.3
Would seek a consultation with another physician	8.1

(2) Survey of healthcare providers

1) Survey of attitudes among clinicians

Nakahama et al. conducted a survey of awareness among clinicians.[4] 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 107. 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 108. 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
New quinolones	7.5	9.0	6.5
Others	8.5	5.3	11.1

Table 109. 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 110. 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.[5] 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 antimicrobialresistant bacteria.

Table 111. 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 112. 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 113. 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 114. 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 115. 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) Survey of attitudes among physicians working at clinics

In February 2018, the Japanese Society of Chemotherapy and Japanese Association for Infectious Diseases Joint Investigative Committee for Outpatient Antimicrobial Stewardship conducted a survey of attitudes among physicians working at clinics.[6] Questionnaires were distributed to a random selection of 1,500 clinics across Japan, with valid responses received from 269 respondents (a response rate of 17.9%). Of the clinics, 50.6% specialized in internal medicine, while 11.2% specialized in pediatrics.

About half (49.8%) replied that "Between 0 and 20%" of patients or family members of patients diagnosed with a cold request a prescription for antimicrobials, with 18.6% stating that they were asked by "21-40%" and 19.0% by "41-60%," while some stated that the figure was even higher than that. Of the respondents, 32.9% stated that when asked for a prescription for antimicrobials, they "explain and do not prescribe," while 12.7% "prescribe as requested" and 50.4% "explain, but prescribe if they are still not convinced." From this, it can be seen that quite a few patients and their family members request antimicrobials and while more than 80% of respondents explain that they are not necessary, those physicians frequently end up prescribing them.

Asked to compare their frequency of prescribing antimicrobials with the situation before, 38.1% stated that the frequency had "decreased," while 61.9% stated that it was "unchanged," with none stating that it had increased. More than half of respondents stated that they would be able to reduce the quantity of oral antimicrobials they used by 2020. This suggests that the policy of reducing the quantity of oral antimicrobials used has been shared with physicians at clinics. The majority of respondents cited information for the public and explanatory materials for patients as being needed to achieve the action plan's objectives.

Table 116. Proportion of patients or family members of patients diagnosed with a cold who request a prescription for antimicrobials (%)

n=253	Percentage
0-20%	49.8
21-40%	18.6
41-60%	19.0
61-80%	9.1
>=81%	3.6

Table 117. FluoroquinolonesResponse to patients or family members of patients who request a prescription for antimicrobials for a cold (%)

n=252	Percentage
Explain, but prescribe if they are still not convinced	50.4
Explain and do not prescribe	32.9
Prescribe as requested	12.7
Other	4.0

Table 118. Frequency of prescribing antimicrobials over the last year compared with the situation before (%)

n=265	Percentage
Increased	0
Decreased	38.1
Unchanged	61.9

Table 119. Amount by which physicians will be able to reduce the amount of oral antimicrobials used at their clinics by 2020 (%)

n=259	Percentage
10% reduction	7.3
20% reduction	12.7
30% reduction	13.1

40% reduction	2.7
50% reduction	11.2
Reduction of 51% or more	6.9
Increase	0
No change	27.4
Don't know	18.5

Table 120. What is needed to reduce the amount of oral antimicrobials prescribed and achieve the action plan's objectives? (%)

N=268 (multiple responses permitted)	Percentage
Information for the public	66.8
Explanatory materials for patients	54.5
Manuals for treating infections in outpatients	32.8
Education at schools	13.4
Incentives linked to treatment provided for by medical insurance	10.8
Monitoring and guidance by the government	8.6
Other	6.7

(3) Surveys of animal producers and clinical veterinarians

Following on from the surveys of antimicrobial resistance awareness among animal producers and livestock veterinarians carried in last year's report (conducted in FY2017), the Japan Livestock Industry Association conducted surveys again in FY2018, funded under the Japan Racing Association's Livestock Industry Promotion Project (Project to Promote Greater Awareness and Application of Measures to Combat Antimicrobial Resistance). In FY2018, the online questionnaires were conducted among animal producers and livestock veterinarians nationwide via prefectures and livestock-focused organizations between November 5 and December 20, 2018.

It must be noted that the results below summarize only the situation among those animal producers who responded to the questionnaire.

1) Survey of animal producers

In FY2018, responses were received from 324 individuals, 163 (50%) of whom were involved in handling cattle, with 79 (24%) handling pigs and 82 (25%) handling chickens. Looking at each topic considered in the questionnaire, approximately 25% 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 70% 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, with around 50% responding that they "Have taken steps to reduce the use of antimicrobials by using feed which does not contain antimicrobial feed additives, wherever possible."

Approximately 85% 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.

About 20% of animal producers who participated in the FY2017 survey also took part in the FY2018 survey. While the figure for awareness of "what kind of antimicrobial feed additives the feed contains" had fallen 6.5% from the 2017 result, no other major fluctuations were observed, with changes in the other figures within the ±5% range. Ongoing efforts to raise awareness using a variety of measures are required in order to change attitudes among animal producers.

Table 121. Awareness of topics among animal producers (%)

	Total		Cattle		Pigs		Chickens	
	2017 (n=320)	2018 (n=324)	2017 (n=141)	2018 (n=163)	2017 (n=94)	2018 (n=79)	2017 (n=85)	2018 (n=82)
Japan's National Action Plan on Antimicrobial Resistance	29.4	24.7	22.7	20.9	44.7	41.8	23.5	15.9
Antimicrobial-resistant bacteria make it harder to treat bacterial infections in both humans and livestock	77.8	80.9	73.8	77.3	89.4	92.4	71.8	76.8
Using antimicrobials causes antimicrobial-resistant bacteria to increase	80.6	84.9	77.3	83.4	88.3	89.9	77.6	82.9
Concerns about the transmission of antimicrobial-resistant bacteria to humans via livestock	68.8	68.8	63.8	60.7	80.9	83.5	63.5	70.7
There is feed which contains antimicrobial feed additives and feed which does not*	80.3	81.5	76.6	76.1	86.2	91.1	80	82.9
(*Of whom) What kind of antimicrobial feed additives the feed contains	75.1	68.6	68.5	58.1	84	84.7	75	70.6
(*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	56.1	57.4	54	45.7	58.3	50	57.4
Preventing outbreaks of disease through improvements in the rearing environment and the use of vaccines reduces the use of antimicrobials	86.3	84.6	80.1	77.3	95.7	93.7	85.9	90.2
(Of whom) Have actually put these measures into practice	79.7	76.6	75.2	69.8	87.8	90.5	76.7	74.3

2) Survey of livestock veterinarians

Responses were received from 385 respondents, 255 (66%) of whom were veterinarians involved in treating and providing hygiene guidance concerning dairy cows, while 259 (67%) dealt with beef cows, 91 (24%) with pigs, 34 (9%) with chickens, and 35 (9%) with other livestock (multiple answers to the question about the type of livestock dealt with were permitted, so there is some overlap).

Approximately 50% 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.

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 75% 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, chickens, and other.

About 30% of clinical veterinarians who participated in the previous year's survey took part again this year. Awareness of Japan's National Action Plan on Antimicrobial Resistance had risen by 7.3% from the previous survey. No other major fluctuations were observed, with changes in the other figures within the ±5% range. To further increase awareness among livestock veterinarians, it will be necessary to undertake more proactive efforts to raise awareness at training sessions and the like, using videos, guidebooks on antimicrobial therapy, and other tools developed to encourage the prudent use of antimicrobials.

Table 122. Awareness of topics among livestock veterinarians (%)

	Total		Dairy cattle		Beef cattle		Pigs		Chickens		Other	
	2017 n=534	2018 n=385	2017 n=362	2018 n=255	2017 n=346	2018 n=259	2017 n=131	2018 n=91	2017 n=57	2018 n=34	2017 n=47	2018 n=35
Japan's National Action Plan on Antimicrobial Resistance	44.4	51.7	34.8	44.7	35.3	45.2	61.1	60.4	64.9	70.6	66	74.3
Basic concept of the prudent use of veterinary antimicrobial products for the production of animal products	77	80.3	73.2	80	76	78.8	87.8	82.4	91.2	85.3	78.7	80
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	91.9	89	90.2	90.5	91.1	95.4	96.7	98.2	100	93.6	94.3
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	88.1	86.5	87.1	87.3	88.8	96.2	95.6	100	94.1	76.6	68.6
Conduct antimicrobial susceptibility tests in routine practice when using antimicrobials	66.3	76.1	69.3	81.5	65.6	71.8	75.6	80.2	61.4	67.6	61.7	74.3
Aware of what kinds of antimicrobial feed additives are found in feed in the context of treatment using antimicrobials	58.4	61	50.3	51	56.1	56.4	74.8	78	84.2	79.4	66	74.3

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9. Way Forward

This document follows on from last year's report in presenting information on the current status of antimicrobial resistance in Japan 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. Following on from 2017, figures for 2018 show that the total usage of all antimicrobials and 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. More specifically, it will be necessary to reduce the unnecessary prescription of antimicrobials, particularly in cases of acute respiratory tract infection, based on the Manual of Antimicrobial Stewardship, among other materials. As regional information about resistant bacteria is being put together, it would be desirable to select the type of antimicrobial to be prescribed with reference to the regional situation. Furthermore, it will be necessary to continue using various techniques for education and awareness activities targeting the public and medical professionals, to achieve further progress in antimicrobial stewardship.

In animals, total usage estimated from the volume of sales showed increases mainly in macrolides (erythromycin used in aquatic animals and 16-membered macrolides used in food-producing animals) and penicillin derivatives for food-producing animals between 2013 and 2017. Accordingly, measures to curb the diseases thought to be the causes of these increases will be required. In terms of antimicrobial resistance rates among *Escherichia coli*, which have been set as 2020 targets, the rates of resistance to third-generation cephalosporins and fluoroquinolones, which are critically important antimicrobials for human medicine, among *Escherichia coli* have been kept at a low level. At the same time, while tetracycline resistance fell in 2015 from the year before, the decline has since halted. Accordingly, further efforts to ensure the prudent use of antimicrobials by encouraging a change in behavior among producers and veterinarians will be required if the 2020 targets are to be met.

Following on from 2018, this report makes comparisons between the volume of antimicrobial use (or sales) in the fields of human medical care, veterinary care, and agriculture. 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 food and the environment. 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.[1] 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.[1] 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 2019, 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	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. A March 2017 notification issued by the Director of the Tuberculosis and Infectious Diseases Control Division, Health Service Bureau, MHLW imposed on local public health institutes and other organizations a requirement to test strains isolated from notified cases of CRE infection. Since then, data concerning the detection of major carbapenemase genes in strains isolated from notified cases of CRE infection have been collected and analyzed within the framework of the monitoring of trends in outbreaks of infection and have been published in the Infectious Agents Surveillance Report (IASR), among others.

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 addition, pathogen surveillance focused primarily on CRE was launched in 2017 and, with data on resistance genes set to be gathered and analyzed for VRE and MDRA in due course, it is anticipated that information that will be valuable in devising measures to combat antimicrobial-resistant bacteria will be collected and utilized.

(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

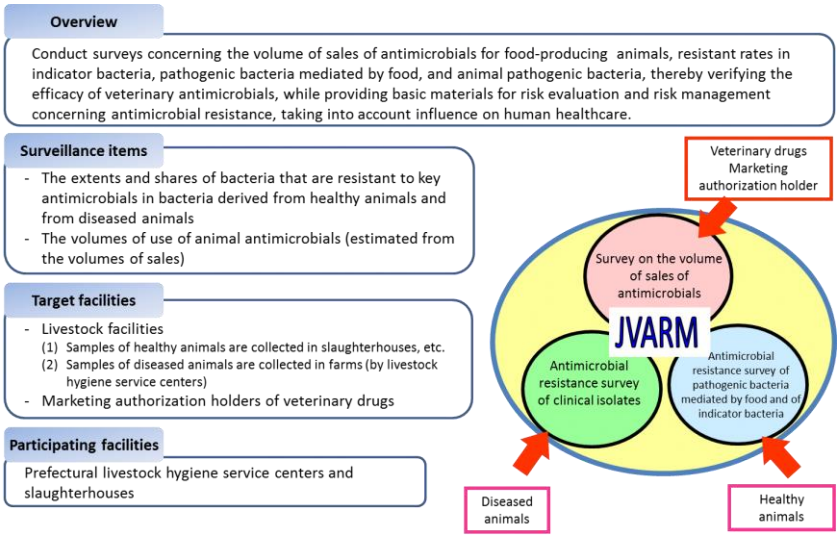


Figure 2. System for antimicrobial resistance monitoring in healthy food-producing animals at animal and poultry slaughterhouses

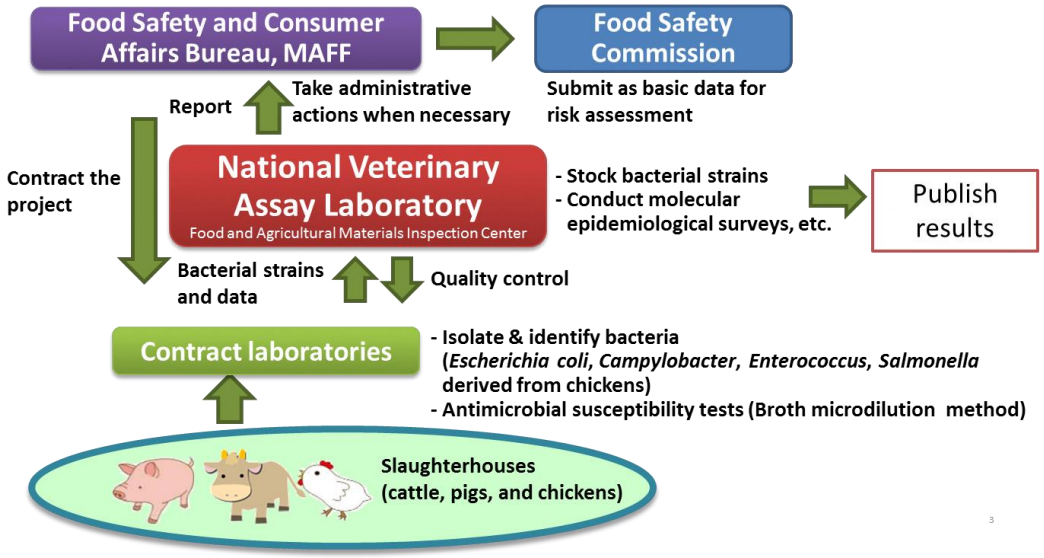
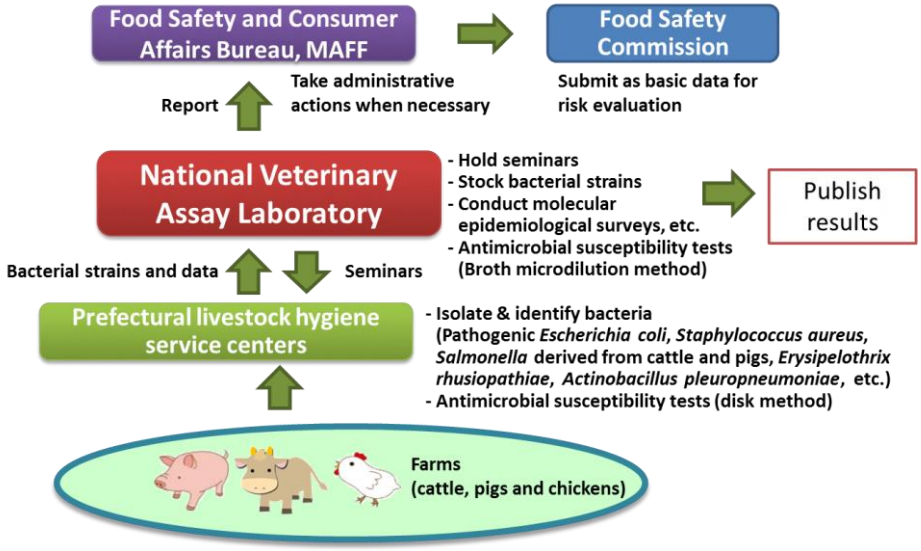
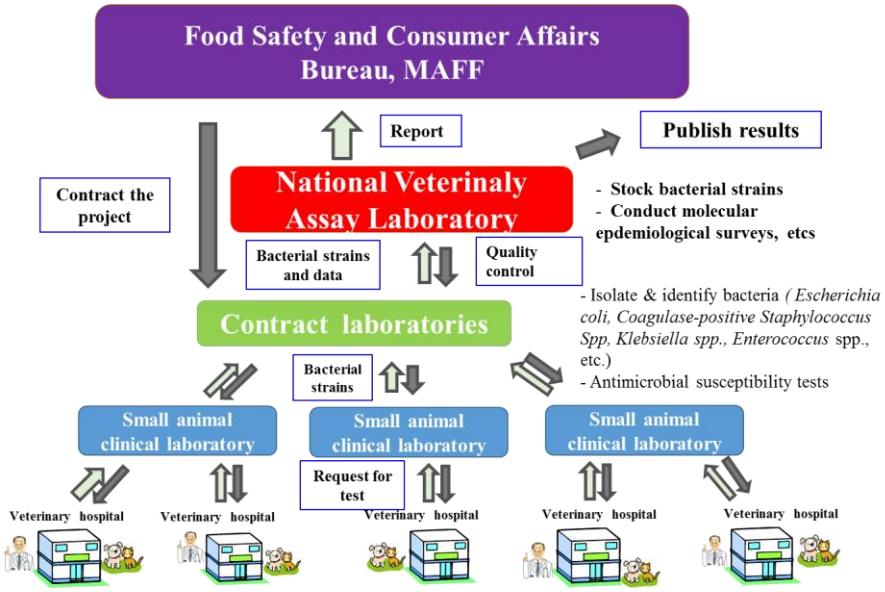


Figure 3. System for antimicrobial resistance monitoring in diseased food-producing animals



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 [2]. 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) and in healthy dogs and cats in FY2018.

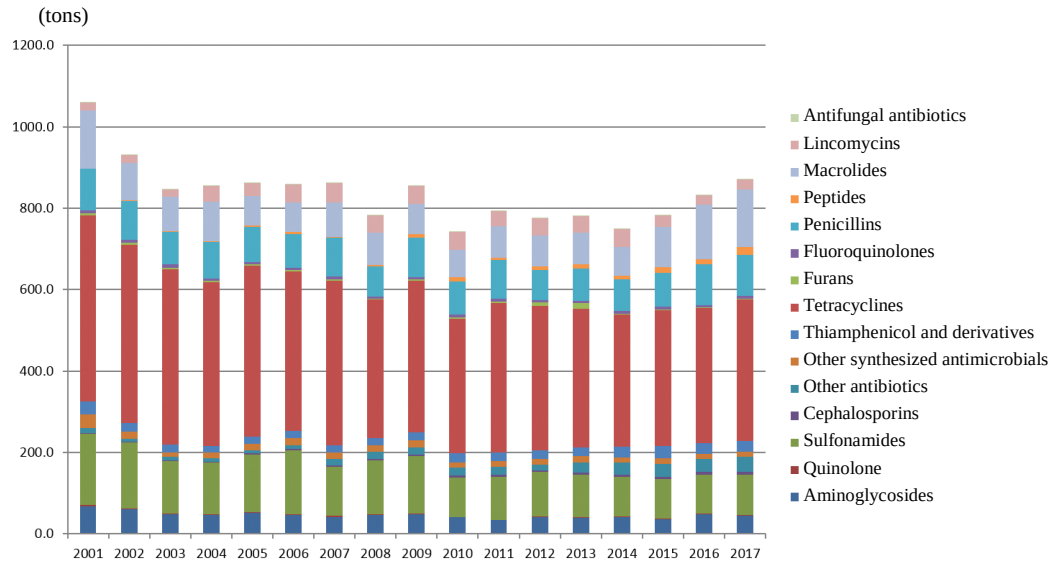
Figure 4. System for antimicrobial resistance monitoring in diseased dogs and cats (from FY2017)



2) Monitoring details on the volumes of sales of antimicrobials

An annual monitoring is conducted on the volumes of sales of veterinary antimicrobials, based on the reported quantities of veterinary drugs handled by marketing authorization holders, pursuant to Article 71-2 of the Veterinary Drug Control Regulations (MAFF Ordinance No. 107 of 2004). Starting 2001, the monitoring has included the volume of sales by active pharmaceutical ingredient, and the estimated persentage of sales by animal species, in addition to the volumes of sales by antimicrobial class and route of administration. When monitoring began, the volume of sales was in excess of 1,000 tons. While the figures declined for a while after that, an upward trend has been seen over the last few years (Figure 5). Since the 2018 report, usage volumes (sales volumes) by weight (tons) are indicated in all fields, enabling figures for total volumes to be compared between fields. Whereas usage of cephalosporins and fluoroquinolones was higher among humans, usage of tetracyclines and aminoglycosides was higher among animals. The total weight of antimicrobial use in agrochemicals was less than in humans or animals, with oxolinic acid and streptomycin accounting for the majority of this.

Figure 5. Changes in veterinary antimicrobial sales by antimicrobial type (2001-2017)



3) Monitoring details on antimicrobial resistance

For the monitoring of clinical isolates, bacterial strains derived from diseased animals 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 training 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.[3]

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).

4) System for the antimicrobial resistance monitoring

A nationwide JVARM network is currently being established with the cooperation of prefectural livestock hygiene service centers. 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

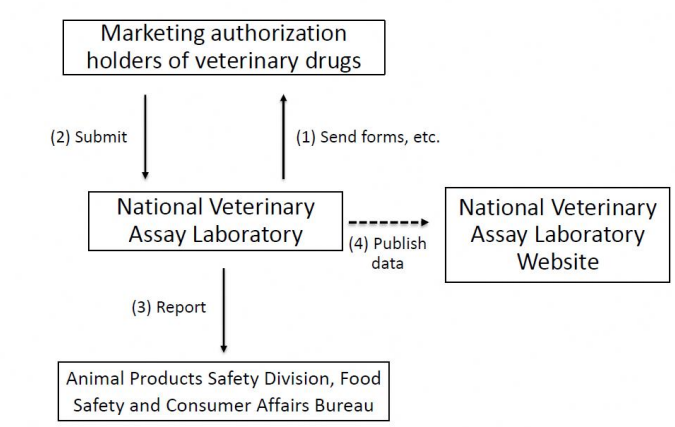
discontinued in FY2016 and efforts to monitor food-borne pathogenic bacteria and indicator bacteria from healthy animals switched to sampling at animal and poultry slaughterhouses.

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.

5) 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)

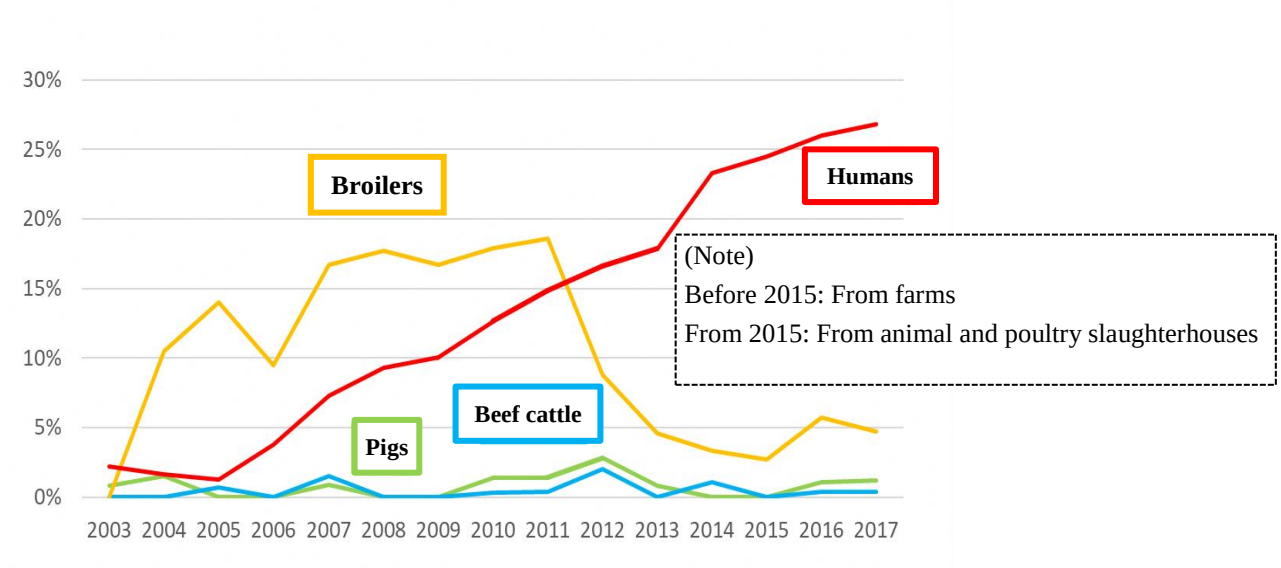
Figure 6. Monitoring on the sales volumes of antimicrobials



6) Collaboration with JANIS

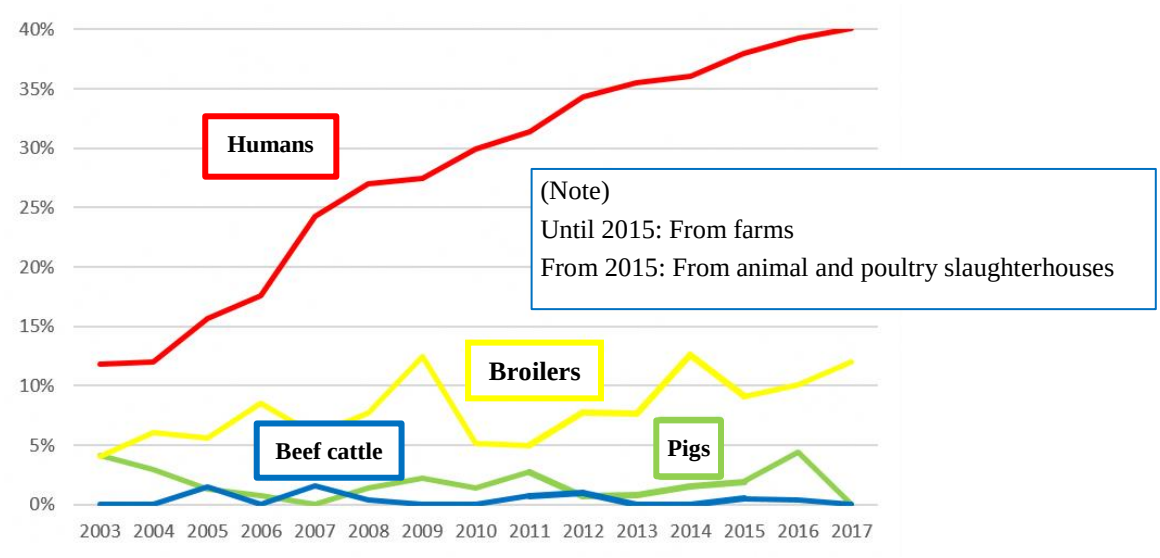
Since FY2012, collaboration has been promoted between JVARM and JANIS (Japan Nosocomial Infections Surveillance). The data of *Escherichia coli* derived from healthy animals collected under JVARM are converted into a format comparable with JANIS data, and the results are published as antibiograms on the website of the National Veterinary Assay Laboratory.[4] 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. [5] 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, the proportion of fluoroquinolone-resistant strains derived from pigs and beef cattle was below 5%, while the figure for broilers was less than 13%, indicating different trends between humans and food-producing animals.

7) Prospects

JVARM still faces three key tasks: 1) monitoring bacteria derived from companion animals to promote the prudent use of antimicrobials in companion animals and analyzing studies of the volume of human antimicrobials used in companion animals; 2) conducting more advanced surveillance and analysis of antimicrobial resistance genes (ARG) through whole genome analysis and comparing the results with figures for humans; and 3) evaluating the volume of use of veterinary antimicrobials based on biomass weights calculated using the standardized technique set out by the OIE. While continuing to carry out monitoring in existing veterinary fields, JVARM will move forward with monitoring focused on these tasks in 2019. 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 patientdays. 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.[9]

2) Survey methods

Antimicrobial susceptibility tests were conducted by the disk method, in accordance with the CLSI standards in US.[9] 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.[10] 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 21 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.[10] The monitoring was targeted at *Salmonella* spp. strains that were isolated from human patients and from food in 2015 and 2018. 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 21 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. As these data are vital to the One Health approach, which covers the environment, animals, food, and humans, a system has been established that uses conversion software to integrate the data with JANIS and JVARM data to facilitate integrated evaluation of all three.

(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 [7] have been received from across the globe since 2017.[8]

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

AMR Clinical Reference Center
http://amrcrc.ncgm.go.jp/

Nippon AMR One Health Report
https://amr-onehealth.ncgm.go.jp/

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 Antituberculosis 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 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, 6th meeting on 10/22/2018, and 7th meeting on 10/17/2019.

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