Nippon AMR One Health Report (NAOR) 2024

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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 amount used (or sold) in the areas of human health, animals, food and the environment, with the objective of assessing measures to combat antimicrobial-resistant bacteria and clarify challenges in this area.

Due to the impact of the COVID-19 pandemic, the implementation period of the "National Action Plan on Antimicrobial Resistance (AMR) (2016-2020)" was extended until the end of the fiscal year 2022. In 2023, an updated National Action Plan on Antimicrobial Resistance (AMR) (2023-2027) was developed based on the achievements and experiences of the previous Action Plan. The new plan proposes updated goals and strategies to strengthen and promote AMR control further, reemphasizing the importance of the One Health approach to the AMR challenge and promoting measures that take into account the close relation of human, animal, food and environmental health. Additionally, the data collection and analytical methods regarding trends in antimicrobial resistance (AMR) and antimicrobial drug usage, both domestically and internationally, have been revised. The introduction of genome-based surveillance has enabled a more detailed understanding of the emergence and transmission pathways of drug-resistant bacteria. Furthermore, the importance of deepening international cooperation and collaboration in AMR countermeasures has also been emphasized.

This report has demonstrated Japan's efforts in the One Health approach to AMR both domestically and internationally, and through the results of this survey, the evaluation of AMR countermeasures is conducted, and the challenges are identified, which have been utilized by relevant government ministries, agencies, organisations, and academic societies to promote countermeasures and research on AMR. The content includes more refined analyses that incorporate new insights and data resulting from the introduction of genome analysis.

Future efforts under the new Action Plan are expected to contribute to the further development of Japan's AMR control measures and support effective responses to the AMR challenge in Japan and abroad. We hope that the data and analyses provided by this report will serve as a basis for strengthening AMR measures, promoting new research, and formulating policies by domestic and international stakeholders. Ultimately, we hope that these efforts will result in a more comprehensive and effective approach to the challenge of AMR and contribute to improving people's health and public health of the nation.

This report contains data for up to 10 years. For data from other years, please refer to the Antimicrobial Resistance (AMR) One Health Platform (https://amr-onehealth-platform.ncgm.go.jp/home).

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	Breakpoint
CDI	*Clostridioides* (*Clostridium*) *difficile* Infection
CLSI	Clinical and Laboratory Standards Institute
CRE	Carbapenem-resistant *Enterobacterales*
DID	Defined Daily Dose per 1,000 Inhabitants per Day
DDD(s)	Defined Daily Dose(s)
DOT	Days of Therapy
DOTID	Days of therapy per 1,000 Inhabitants per Day
ESBL	Extended-spectrum β-lactamase
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 and Use Surveillance System
HAI	Healthcare-associated Infection
ICU	Intensive Care Unit
JANIS	Japan Nosocomial Infections Surveillance
JSAC	Japan Surveillance of Antimicrobial Consumption
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 of Health Insurance Claims and Specific Health Checkups of. Japan
PID	Number of patients per 1,000 Inhabitants per Day
PPCPs	Pharmaceuticals and Personal Products
PRSP	Penicillin-resistant *Streptococcus pneumoniae*
SSI	Surgical Site Infection
WHO	World Health Organization
VRE	Vancomycin-resistant *Enterococci*
WOAH	World Organization for Animal Health
VRSA	Vancomycin-resistant *Staphylococcus aureus*
DALY(s)	Disability-adjusted life year(s)
PPS	Point Prevalence Survey

3. Classes and Abbreviations of Antimicrobials

Class			Nonproprietary name	Abbreviation*
Beta-lactam antibiotics	Penicillins		benzylpenicillin (penicillin G)	PCG
			ampicillin	ABPC
			sulbactam/ampicillin	SBT/ABPC
			piperacillin	PIPC
			oxacillin	MPIPC
			tazobactam/piperacillin	TAZ/PIPC
			amoxicillin	AMPC
			clavulanic acid/amoxicillin	CVA/AMPC
	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
			sulbactam/cefoperazone	SBT/CPZ
			cefdinir	CFDN
			cefcapene pivoxil	CFPN-PI
			cefditoren pivoxil	CDTR-PI
			cefixime	CFIX
		4th generation	cefepime	CFPM
			cefpirome	CPR
			cefozopran	CZOP
		Cephalosporins combined with beta-lactamase inhibitor	tazobactam/ceftolozane	TAZ/CTLZ
		Siderophore cephalosporins	cefiderocol	CFDC
	Cephamycins		cefmetazole	CMZ
			cefoxitin	CFX
	Oxacephems		flomoxef	FMOX
			latamoxef	LMOX
	Monobactams		aztreonam	AZT
	Carbapenems		meropenem	MEPM
			doripenem	DRPM
			biapenem	BIPM
			imipenem/cilastatin	IPM/CS
			imipenem/cilastatin/relebactam	REL/IPM/CS
			panipenem/betamipron	PAPM/BP
			tebipenem pivoxil	TBPM-PI
	Penems		faropenem	FRPM
ST			sulfamethoxazole-trimethoprim	ST
			sulfamonomethoxine	SMMX

Class	Nonproprietary name	Abbreviation*
Macrolides	erythromycin	EM
	clarithromycin	CAM
	azithromycin	AZM
	tylosin	TS
	spiramycin	SPM
Macrolides for the treatment of CDI	fidaxomicin	FDX
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
	◎lascufloxacin	LSFX
	◎pazufloxacin	PZFX
	◎norfloxacin	NFLX
	◎prulifloxacin	PUFX
	◎moxifloxacin	MFLX
	◎garenoxacin mesylate hydrate	GRNX
	◎sitafloxacin	STFX
	◎ofloxacin	OFLX
	◎enrofloxacin	ERFX
	oxolinic acid	OA
	nalidixic acid	NA
Glycopeptides	vancomycin	VCM
	teicoplanin	TEIC
Oxazolidinones	linezolid	LZD
	tedizolid	TZD
Polypeptides	polymyxin B	PL-B
	colistin	CL
	bacitracin	BC
Lipopeptides	daptomycin	DAP
Chloramphenicols	chloramphenicol	CP
	florfenicol	FF

Class	Nonproprietary name	Abbreviation*
Other antibacterial agents	fosfomycin	FOM
	salinomycin	SNM
	bicozamycin	BCM
	trimethoprim	TMP
Antitubercular antibiotics	isoniazid	INH
	ethambutol	EB
	rifampicin (rifampin)	RFP
	pyrazinamide	PZA
	rifabutin	RBT
	bedaquiline	BDQ

* 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 agents that act against bacteria: "antimicrobial agents," "antibiotics," "antibiotic agents," and "antibacterial agents." In the areas of agriculture and livestock, 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 agents 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: Chemical substances that inhibit or control the cell activities of microorganisms and other cells (referred to as antimicrobial activity) and are, strictly speaking, produced by microorganisms.

Antibiotic agents: Used as a generic term for anti-microbial agents that act against bacteria.

Reference: The Manual of Antimicrobial Stewardship, 1st edition

In terms of active ingredients (veterinary agents), in terms of effective value (antibiotic feed additives), in terms of active ingredients (agrochemicals), antimicrobial consumption in terms of potency by weight (humans): All these terms refer to active ingredient weight. Quantities in terms of the weight of active ingredients in veterinary agents are calculated from sales data collected from marketing authorization holders for the volume of each agent 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 agents, 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.

Indicators of antimicrobial use:

- **AUD:** Mainly used to ascertain usage in medical institutions, AUD is calculated by dividing the total titer of antimicrobials in a specified period by defined daily dose (DDD) as defined by the World Health Organization (WHO), and correcting the result with the total patient-days. The units used for AUD include DDDs per 100 bed-days and DDDs per 1,000 patient-days. In some countries, AUD is also expressed as DDD.
- **DOT :** DOT is a unit mainly used to grasp the usage in medical institutions. It is calculated by correcting the total days of therapy (DOTs) using antimicrobials in a specified period with the total patient-days. The units used for DOT include DOTs per 100 bed-days and DOTs per 1,000 patient-days.
- **DID (DDDs/1,000 inhabitants/day)**: DID is a unit of measurement of use, mainly in a region or country; DID is expressed per 1,000 inhabitants as the total titer over a period of time divided by DDD, with the denominator corrected for the number of inhabitants per day in the region ('inhabitants'). The DID is expressed as a value per 1,000 inhabitants, corrected for the number of inhabitants per day.
- **DOTID (DOTs/1,000 inhabitants/day)**: DOTID is a unit that uses claims information to determine usage in a region or country. It is expressed per 1,000 inhabitants as the total number of days of antimicrobial treatment (DOTs) over a period of time in the numerator, with the denominator corrected for the number of inhabitants per day in the region.
- **PID (number of patients/1,000 inhabitants/day)**: PID is a unit that uses insurance claims information to determine usage in a region or country. It is expressed as a value per 1,000 inhabitants with the total number of people using antimicrobials over a period of time as the numerator and the denominator corrected for the number of inhabitants per day in the region.

4. Executive Summary

Background:

Japan's "National Action Plan on AMR (2016-2020)" positioned 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.

Due to the impact of the COVID-19 pandemic, the implementation period of the "National Action Plan on Antimicrobial Resistance (AMR) (2016-2020)" was extended until the end of the fiscal year 2022. In 2023, the Action Plan for AMR Control (2023-2027) was developed, setting updated goals and strategies. The plan reemphasizes the importance of the One Health approach to the AMR challenge, expands the genomic database, and calls for the promotion of measures that take into account the interconnectedness of human, animal, and environmental health. It also emphasizes the importance of international cooperation and joint efforts to combat AMR.

Internationally, Japan submits data to the Global Antimicrobial Resistance and Use Surveillance System (GLASS) established by the World Health Organization (WHO) and to the monitoring of Animal Antimicrobial Use (ANIMUSE) conducted by the World Organization for Animal Health (WOAH), both of which use standardized methodologies.

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 internationally. The data and analyses provided by this report are intended to serve as a basis for strengthening AMR control, promoting new research, and formulating policy by national and international stakeholders.

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). We obtained data on sales and consumption of antimicrobials for human use from IQVIA Solutions Japan K.K., the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), and Japan Surveillance for Infection Prevention and Health-care Epidemiology (J-SIPHE). Data on sales of antimicrobials in animals were obtained from the National Veterinary Assay Laboratory, Ministry of Agriculture, Forestry and Fisheries. 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 volume of domestic shipments of antimicrobials used as agricultural chemicals was obtained from MAFF, while information on outbreaks of infectious diseases and the implementation of infection control measures was obtained from the National Epidemiological Surveillance of Infectious Diseases, JANIS and J-SIPHE.

The research utilized findings from the Ministry of Health and Labour Sciences Research Groups, among others, regarding factors not addressed in current surveillance nor monitoring systems, but considered pertinent from a public health perspective, which include antimicrobial resistance, antimicrobial resistance and residual antimicrobial agents in the environmental, and public awareness of antimicrobial resistance. In the animal field the results of a survey conducted by the Ministry of Agriculture, Forestry and Fisheries on the awareness levels of producers, clinical veterinarians, and pet owners and a survey of attitudes of veterinary students at 14 universities towards antimicrobial resistance were used.

Results:

In Japan, the carbapenem resistance rate in *Enterobacterales*, particularly *Escherichia coli* and *Klebsiella pneumoniae* has remained below 1% during the observed period, despite its global increase in human isolates. While the resistance rates of *E. coli* to third-generation cephalosporins and fluoroquinolones had shown an increasing trend in Japan, in 2021, a slight decrease was observed for the first time, followed by stable or reduced levels in 2022. In 2023, there was a slight increase in the resistance rates. On the other hand, the resistance rates of third generation cephalosporins in *Klebsiella pneumoniae* remained on the rise. The resistance rates of carbapenem in *Pseudomonas aeruginosa* are on a decreasing trend. Internationally, the increase in vancomycin resistance among *enterococci* is a problem. In Japan, although vancomycin (VCM) resistance in *Enterococcus faecium* was 2.6% in 2022, a relatively low level compared to other countries, it has been increasing in recent years, and widespread, multi-center associated hospital outbreaks due to VCM-resistant *E. faecium* were observed in some regions.

Although the percentage of methicillin-resistant *Staphylococcus aureus* (MRSA) had been in an increasing trend again since 2019, started to decrease in 2021. The trend remained the same in 2022 and 2023, but it is still

high compared to other countries. 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.

In research based on genomic analysis, human-derived strains of non-typhoidal *Salmonella* spp. isolated from patients with infectious enteritis or food poisoning are generally considered to have likely been transmitted to humans through animals or food. Occasionally, strains harboring resistance genes that suggest transmission from food to humans have been detected. In *Enterococcus* spp., it was found that human-derived VRE strains and food-derived strains were phylogenetically distinct. The Tricycle Project revealed that food-derived (poultry) strains shared fewer sequence types (STs) with human-derived and environmental strains, whereas human-derived and environmental strains shared a higher number of common STs, accounting for 28.2% of the total (27 strains).

Antimicrobial use based on human antimicrobial sales in Japan was 11.96 DID in 2023, a 17.4% increase compared to 2020 and a 6.2% decrease compared to 2019 before the COVID-19 pandemic. Oral antimicrobial agents accounted for 91.6% of all antimicrobial agents, with a total of 68.1% of oral antimicrobials being comprised of third generation cephalosporins, fluoroquinolones, and macrolides. The three most frequently used antimicrobial classes in 2023 have increased in use by 4.7%, 25.0%, and 17.7%, respectively, compared to 2020 and decreased by 26.2%, 8.1%, and 10.87%, respectively, compared to 2019. Injectable carbapenems have decreased by 6.7% compared to 2020. The proportion of "Access" in the AwaRe classification, a guidance for appropriate antimicrobial use recommended by WHO has gradually increased since 2013, from 11.2% to 22.94% in 2023, while the proportion of "Watch" has been decreasing from 87.41% to 75.98%.

Surveillance of antimicrobial resistance in animals focuses on food-producing animals (cattle, swine, and chickens), aquatic animals (all farmed fish species), and companion animals (dogs and cats). The resistance rate of *Enterobacterales* to carbapenems, an important antimicrobial class in human medicine, were 0.0% for all animal species and bacterial strains, except for *Klebsiella* spp. derived from dogs, where the resistance rate was 1.2% (with one resistant strain). The resistance rates of *Enterococcus* spp. to vancomycin, a major problem in human nosocomial infections, were 0.0% for all.

Among food-producing animals, the resistance rates to tetracyclines in *E. coli* derived from healthy livestock, as an outcome indicator of the Action Plan (2023-2027), were 23.4% in cattle, 55.1% in swine, and 43.0% in chickens. The resistance rates to third-generation cephalosporins were 0% in cattle, 0.7% in swine, and 0.7% in chickens, while the resistance rates to fluoroquinolones were 1.0% in cattle, 3.7% in swine, and 14.8% in chickens. No significant increases or decreases in resistance rates were observed for any of the livestock species or antimicrobial agents.

Among aquatic animals, resistance rates to lincosamides were 58.1% in 2017, 31.5% in 2018, 54.6% in 2019, 53.8% in 2020, 66.2% in 2021, and 82.3% in 2022 in the causative agent of α-hemolytic *streptococci* from diseased fish, showing an increasing trend. Resistance rates to erythromycin (EM) and oxytetracycline (OTC) remained low, at 5.2% and 1.0%, respectively, in 2022. A pilot study of *Vibrio* spp. and pathogenic strains of α-hemolytic *streptococci* from healthy fish (yellowtail) were initiated in 2021. Sampling was conducted from 10 locations across 5 prefectures in 2021 and 2022. In 2021, α-hemolytic *streptococci* were detected at 4 locations in 4 prefectures, while *Vibrio* spp. were found at 10 locations in 5 prefectures. In 2022, α-hemolytic *streptococci* were detected at 2 locations in 2 prefectures, while *Vibrio* spp. were identified at 8 locations in 4 prefectures.

Among companion animals, while *E. coli* isolated from diseased dogs and cats demonstrated lower resistance rate to tetracyclines and aminoglycosides than among food-producing animals, resistance rates to the fluoroquinolones and third generation cephalosporins that are critically important antimicrobials for human medicine tended to be higher. *E. coli* isolated from healthy companion animals (dogs and cats) indicated that they generally remained susceptible to all drugs.

The volume of sales of antimicrobials used for animals (food-producing animals, aquatic animals, and companion animals) was calculated in metric tons (t) of the active ingredients, based on sales reports for antibiotics and synthetic antimicrobials mandated by Article 71-2 of the Regulations for Veterinary Agents (Ordinance of the Ministry of Agriculture, Forestry and Fisheries No. 107 of 2004). In 2022, as in before, tetracyclines represented the largest share of antimicrobial sales, but their sales volume has been declining in recent years, falling below 40% of the total. Third generation cephalosporins and fluoroquinolones accounted for 0.2% and around 1% of the total, respectively. The total volume of veterinary antimicrobial sales remained around 800 t, with 776.9 t in 2022, down 24 t from 800.9 t in 2021. Looking at the figures by class, macrolides decreased by about 23 t, largely due to the decline in the use for aquatic animals (erythromycin). The total sales volume of antimicrobial agents in the livestock sector, newly added as a performance indicator, was 568.0 t, representing a 9.4% decrease compared to 2020. The sales volume of second-line drugs remained approximately the same as in 2020, at 27 t.

The estimated use (or sales) of antimicrobials in 2022, based on sales volumes and other data for each sector, were 527.8 t for humans, 568.0 t for livestock, 201.5 t for aquatic animals, 7.4 t for companion animals, 203.3 t for antimicrobial feed additives, and 134.9 t for agrochemicals, totaling 1,642.9 t.

Observations:

In the human sector, antimicrobial use based on sales of oral antimicrobials, including oral third generation cephalosporins, oral macrolides, and oral fluoroquinolones in 2022 has been on a downward trend since 2020. The resistance rates in methicillin-resistant *Staphylococcus aureus* (MRSA) and *E. coli* to third generation cephalosporins and fluoroquinolones have decreased slightly, while the resistance rate to third generation cephalosporins in *K. pneumoniae* has been increasing and should continue to be monitored closely. On the other hand, VCM-resistant *E faecium* has been observed in widespread hospital outbreaks involving multiple facilities, with the number of cases reported in the Infectious Disease Surveillance consistently exceeding the performance indicator since 2020. Continued comprehensive outbreak response in the region is required.

The proportion of antimicrobial-resistant bacteria and the volume of antimicrobial use have increased in many countries in the post-COVID-19 era, with a rise in antimicrobial use observed in 2023 in Japan as well. Given that the impact of the COVID-19 pandemic is also to be considered, it is essential to closely monitor future trends. The data in this report demonstrates that further promotion of measures against AMR will be required.

Unnecessary use of third generation cephalosporins, fluoroquinolones, and macrolides must be continuously reduced, and the Manual of Antimicrobial Stewardship employed to promote the proper use of antimicrobials, primarily in respect of acute respiratory tract infections. In November 2023, the Manual of Antimicrobial Stewardship was updated to include a section on the appropriate use of antimicrobial agents in hospitalized patients. This edition is expected to improve patient outcomes and promote the proper use of antimicrobial agents in hospitals. In promoting the appropriate use of antimicrobials, it is essential that appropriate antimicrobials are available when needed, and it is important to ensure a stable supply of basic antimicrobials.

Strengthening educational and awareness-raising activities and the use of monitoring systems are also important in AMR control. The new Action Plan calls for the formulation of effective countermeasures through detailed analysis of information on antimicrobial resistance and antimicrobial use in each region. Systems such as JANIS, National Epidemiological Surveillance of Infectious Disease, J-SIPHE, J-SIPHE for clinics or OASCIS (Online monitoring system for antimicrobial stewardship at clinics) and the AMR One Health Platform should be used to promote antimicrobial selection and infection control measures according to local conditions. Furthermore, in promoting the appropriate use of antimicrobials, it is necessary to continue education and awareness-raising activities using various methods for the public and healthcare professionals.

Among animals, the resistance rates of *Enterobacterales* to carbapenems, an important antimicrobial class for human medicine, were 0.0 % for all animal species and bacterial strains, except for one strain of *Klebsiella* spp. derived from companion animals. The resistance rates of *enterococci* to vancomycin, a major problem in nosocomial infections in humans, were 0.0% for all animal species and bacterial strains. However, in bacteria isolated from diseased companion animals, some strains showed high rates of resistance to third generation cephalosporins and fluoroquinolones. Therefore, in addition to the dissemination of the "Guide for Antimicrobial Use in Companion Animals", it is necessary to continue and strengthen measures against antimicrobial resistance in the companion animal sector.

It was considered that the resistance rates of *E. coli* from healthy food-producing animals to third generation cephalosporins and fluoroquinolones, an outcome indicator of the National Action Plan on AMR (2023-2027), have remained at a low level, which have shown little fluctuation. Regarding tetracycline, which is also used as a performance indicator, although the sales volume in swine decreased by approximately 10%, no significant increase or decrease in resistance rates was observed in any livestock species. The usage of veterinary antimicrobial agents in the livestock sector and the usage of second-line drugs have been newly established as performance indicators. Moving forward, it is essential to reduce the overall opportunity for antimicrobial use by promoting the development, practical application, and use of vaccines, improving management standards for animal husbandry hygiene, and other measures. Furthermore, efforts must be made to ensure the appropriate and prudent use of antimicrobial agents, while analyzing and evaluating the factors that maintain resistance rates and the trends in resistance rates to various antimicrobial agents in order to address the issue effectively.

Japan's AMR response has been conducted in coordination with international movements. Stronger international collaboration and a stronger approach from a One Health perspective will be key to the success of AMR control measures. In addition, it is important to strengthen educational and awareness-raising activities to raise awareness and encourage behavior change among the public, which has not been sufficiently effective; disseminate guidelines to support the appropriate use of antimicrobial agents; and strengthen surveillance systems to measure and evaluate the effectiveness of AMR control measures.

In response to these challenges, the new Action Plan emphasizes collaboration with various stakeholders and cooperation within the international community. It is essential to build and strengthen these cooperative frameworks to achieve Japan's AMR control goals. The effective response to the AMR challenge by sharing knowledge and experience domestically and internationally, and by promoting research that can assess risks in humans, animals, and the environment in a cross-sectional manner, is critical to the future success of AMR control. These efforts will

support effective responses to the AMR challenge both in Japan and overseas and could contribute to strengthening Japan's role in the international community. Efforts should be directed toward achieving a more comprehensive and effective approach to the AMR challenge, with the goal of improving the health and public health of the people. The new Action Plan continues to call for government-wide education and awareness-raising activities, but it is important to further explore effective methods are needed.

5. Outcome Indices for the Action Plan

Human-related indices for the Action Plan (2016-2020): proportion (%)[*] of specified antimicrobial-resistant bacteria

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2020 (target value[†])
Proportion of penicillin-non-susceptible *Streptococcus pneumoniae*, CSF specimens[§]	47.0	40.5	36.4	29.1	38.3	32.0	33.3	59.5	50.9	50.8	15% or lower
Proportion of penicillin-non-susceptible *Streptococcus pneumoniae*, non-CSF specimens[§]	2.5	2.7	2.1	2.1	2.2	2.2	3.5	3.4	3.8	3.7	
Proportion of fluoroquinolone-resistant *Escherichia coli*	36.1	38.0	39.3	40.1	40.9	41.4	41.5	40.4	39.6	38.7	25% or lower
Proportion of methicillin-resistant *Staphylococcus aureus*	49.1	48.5	47.7	47.7	47.5	47.7	47.5	46.0	45.5	45.2	20% or lower
Proportion of carbapenem-resistant *Pseudomonas aeruginosa* (Imipenem)	19.9	18.8	17.9	16.9	16.2	16.2	15.9	15.8	14.8	13.9	10% or lower
Proportion of carbapenem-resistant *Pseudomonas aeruginosa* (Meropenem)	14.4	13.1	12.3	11.4	10.9	10.6	10.5	10.3	9.5	8.8	10% or lower
Proportion of carbapenem-resistant *Escherichia coli* (Imipenem)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.04	0.1	0.2% or lower (maintain at the same level) [¶]
Proportion of carbapenem-resistant *Escherichia coli* (Meropenem)	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.1	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	0.2	0.3	0.2	0.2	0.2	0.1	0.2	0.2% or lower (maintain at [¶]
Proportion of carbapenem-resistant *Klebsiella pneumoniae* (Meropenem)	0.6	0.6	0.5	0.4	0.5	0.4	0.4	0.4	0.4	0.3	0.2% or lower (maintain at the same level) [¶]

CSF, cerebrospinal fluid

[*] Prepared based on JANIS data. Data were provided every two years from 2013, but annual data have been provided since 2017.

[†] Target values were quoted from the National Action Plan on AMR.[1] Comparison to 2013

[§] 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 number of specimens is around 100 (59 in 2023), therefore assessment of the resistance rate should be done with caution.

[¶] The National Action Plan on 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 (2023-2027): proportion (%) of specified antimicrobial-resistant bacteria[*1]

	2020	2021	2022	2023	2027 (target value[†])
Number of vancomycin-resistant *enterococci* infections	136	124	133	-	80 or less (maintained 2019 level)
Proportion of methicillin resistant *Staphylococcus aureus* (blood)[*2]	35.9	35.1	33.9	32.5	20% or less
Proportion of fluoroquinolone resistant in *Escherichia. coli* (urine)[*3]	35.4	34.6	34.0	32.8	30% or less (maintained)
Proportion of carbapenem (meropenem) resistant *Pseudomonas aeruginosa* (blood)[*2]	7.1	7.0	6.3	5.0	3% or less
Proportion of carbapenem (meropenem) resistant *Escherichia coli*	0.1	0.1	0.1	0.1	0.2 or less [§]
Proportion of carbapenem (meropenem) resistant *Klebsiella pneumoniae*	0.4	0.4	0.4	0.3	0.2% or less [§]

[*]1Compiled from JANIS data (partly cited from AMED Research on Enhancing Surveillance of Antimicrobial Resistance and Promotion of Comprehensive Countermeasures against Antimicrobial Resistance) and from National Epidemiological Surveillance of Infectious Diseases.

[†]Target values are taken from AMR Action Plan Reference 7. Comparison to 2020.

[*]2Bloodstream infections contribute significantly to the disease burden, and with the intent of excluding the effects of bacterial carriage, blood samples are taken.

[*]3Urine specimens are used to target urinary tract infections in outpatient settings where drug-resistant bacteria are directly related to treatment.

[§] The AMR Action Plan (Ref. 1) states that the carbapenem resistance rates for *E. coli* and *Klebsiella pneumoniae* in 2014 were 0.1% and 0.2%, and that the resistance rates in 2020 will be maintained at the same level.

Human-related indices for the Action Plan (2016-2020): use of antimicrobials (DID) [†] (based on volume of sales)

	2013	2014	2015	2016	2017	2018	2019	2020	Change form 2013	2020 (Target[*])
All antimicrobials	14.52	14.08	14.23	14.15	13.36	12.91	12.75	10.18	29.9%↓	33%↓
Oral cephalosporins	3.91	3.78	3.82	3.68	3.43	3.19	3.02	2.24	42.7%↓	50%↓
Oral fluoroquinolones	2.83	2.83	2.71	2.75	2.57	2.42	2.32	1.66	41.4%↓	50%↓
Oral macrolides	4.83	4.5	4.59	4.56	4.18	3.96	3.84	2.93	39.4%↓	50%↓
Intravenous antimicrobials	0.9	0.9	0.94	0.96	0.98	0.99	1.01	0.87	3.3%↓	20%↓

DID: Defined daily dose per 1,000 inhabitants per day

[*]Target values were quoted from [1].

[†] Prepared from [2] and [3].

Human-related indices for the Action Plan (2023-2027): use of antimicrobials (DID) [†] (based on volume of sales)

	2020	2021	2022	2023	Change from 2020	2027 (Target*)
All antimicrobials	10.18	9.77	9.78	11.96	17.4% ↑	15%↓
Oral third generation cephalosporins	1.85	1.70	1.63	1.94	4.7% ↑	40%↓
Oral fluoroquinolones	1.66	1.48	1.52	2.07	25.0% ↑	30%↓
Oral macrolides	2.93	2.72	2.66	3.45	17.7% ↑	25%↓
Intravenous antimicrobials	0.07	0.07	0.07	0.06	6.7% ↓	20%↓

DID: Defined daily dose per 1,000 inhabitants per day

[*]Target values were quoted from [7].

[†] Prepared from [2] and [3].

Animal-related indices for the Action Plan (2016-2020): proportion (%) of specified antimicrobial-resistant bacteria

		2014*	2015*	2016	2017	2018	2019	2020	2021	2020 (target value**)
Proportion of tetracycline-resistant *Escherichia coli*[****]	(farms)	45.2	39.9							33% or lower
	(Animal slaughterhouses)		39.8	47.6	40.8	43.6	44.3	45.0	40.7	
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	2.4	2.1	1.1	2.1	1.4	1.4	
Proportion of fluoroquinolone-resistant *Escherichia coli*[****]	(farms)	4.7	3.8							The same level as in other G7 nations
	(Animal slaughterhouses)		2.7	5.0	4.0	4.7	5.1	5.2	4.2	

* Prepared from [4] with partial modification. JVARM "Results of Monitoring of Antimicrobial Resistant Bacteria Isolated from Food-producing Animals on Farms"

** Target values for 2020 were quoted from [1].

*** See [5] and [6].

**** MICs greater than 16 μg/mL for tetracyclines, 4 μg/mL for third generation cephalosporins, and 4 μg/mL for fluoroquinolones are considered resistant.

Animal-related indices for the Action Plan (2023-2027): proportion (%) of specified antimicrobial-resistant bacteria

		2020	2021	2022	2027 (Target[§])
Proportion of tetracycline-resistant *Escherichia coli*[*]	Cattle	19.8	23.8	23.4	Cattle 20% or less Swine 50% or less Chicken 45% or less
	Swine	62.4	52.0	55.1	
	Chicken	52.9	46.2	43.0	
Proportion of third generation cephalosporin-resistant *Escherichia coli*[*]	Cattle	0.0	0.0	0.0	Cattle 1% or less Swine 1% or less Chicken 5% or less
	Swine	0.0	2.0	0.7	
	Chicken	4.1	2.1	0.7	
Proportion of fluoroquinolone-resistant *Escherichia coli*[*]	Cattle	0.4	0.0	1.0	Cattle 1% or less Swine 2% or less Chicken 15% or less
	Swine	1.1	2.0	3.7	
	Chicken	18.2	14.5	14.8	

[§]Target values for 2027 were quoted from [7].

*MICs greater than 16 μg/mL for tetracyclines, 4 μg/mL for third generation cephalosporins, and 1 μg/mL for fluoroquinolones are considered resistant.

Animal-related indices for the Action Plan (2023-2027): use of antimicrobials (t) (based on volume of sales)

	2020	2021	2022	2027 (Target[†]) (Change from 2020)
Total use of veterinary antimicrobials in the livestock sector	626.8	598.1	568.0	15%↓
Total use of second-line[※] veterinary antimicrobials in the livestock sector	26.7 t	27.6	27.0	Maintain below 27 t

† Target values for 2027 were quoted from [7].

※Third generation cephalosporins, 15-membered ring macrolides (tulathromycin, gamithromycin), fluoroquinolones, colistin

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6. Current Status of Antimicrobial-resistant Bacteria in Japan

(1) Humans

1) Gram-negative bacteria

Source: JANIS

As for the recent status of gram-negative bacteria, despite recent global increase of carbapenem (imipenem (IPM) and meropenem (MEPM))-resistant *Enterobacteriales* 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. Resistance rates to third generation cephalosporins such as cefotaxime (CTX) and fluoroquinolones such as levofloxacin (LVFX) in *E. coli*, which had been increasing up until 2020, showed a slight decrease for the first time in 2021 and remained flat and decreased in 2022, but in 2023, they slightly increased. The rise in the rate of resistance to third generation cephalosporins would appear to reflect the increase in bacteria with ESBL genes. As such, there appears to be a particular need for measures targeted at the rise of these resistant bacteria. On the other hand, third generation cephalosporin-resistant *K. pneumoniae* continues to increase and behaves differently from third generation cephalosporin-resistant *E.coli*. Both species should continue to be monitored closely for future trend.

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. Resistance rates (%) of *Escherichia coli*

	BP (2014-)	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
ABPC	32	49.2 (170,597)	50.5 (257,065)	51.2 (288,052)	51.7 (307,143)	52.2 (325,553)	52.6 (336,351)	51.9 (337,433)	50.4 (340,248)	49.9 (358.902)	50.8 (390,307)
PIPC	128	42.5 (175,763)	44.1 (270,452)	44.9 (305,604)	45.2 (327,773)	46.0 (342,066)	46.4 (343,183)	45.6 (339,444)	44.0 (338,450)	43.5 (352,001)	44.7 (383,984)
TAZ/ PIPC	4/128	1.7 (89,442)	1.7 (179,722)	1.8 (218,008)	1.7 (241,519)	1.7 (263,131)	3.2 (285,685)	2.8 (290,567)	2.6 (303,907)	2.6 (326,287)	3.0 (366,049)
CEZ*	8	33.3 (183,542)	35.8 (268,898)	36.8 (303,608)	37.3 (324,109)	38.7 (347,491)	39.0 (361,167)	38.7 (360,415)	37.4 (363,330)	37.2 (379,774)	37.7 (419,588)
CMZ	64	1.0 (163,342)	0.9 (260,844)	1.0 (300,089)	0.9 (325,296)	0.9 (348,832)	0.9 (365,259)	0.8 (372,259)	0.8 (376,435)	0.7 (398,172)	0.8 (440,165)
CTX*	4	23.3 (140,186)	24.5 (209,404)	26.0 (230,911)	26.8 (241,843)	27.5 (251,068)	28.3 (257,856)	28.3 (257,134)	26.8 (251,869)	26.8 (258,317)	27.0 (266,719)
CTRX	4	-	-	-	-	-	-	-	-	-	30.0 (339,842)
CAZ*	16	9.5 (183,970)	10.8 (275,671)	11.6 (310,281)	12.0 (330,029)	12.4 (352,819)	14.0 (367,538)	13.9 (369,898)	13.0 (372,255)	12.8 (390,324)	13.4 (426,145)
CFPM	32	12.8 (129,606)	15.0 (236,705)	15.8 (273,587)	16.1 (296,143)	16.7 (321,745)	18.1 (337,526)	17.5 (341,664)	16.8 (344,555)	16.2 (362,758)	15.6 (403,673)
AZT*	16	16.1 (143,046)	17.6 (216,494)	18.4 (239,952)	18.7 (258,193)	19.3 (273,064)	21.0 (283,965)	20.4 (284,169)	19.2 (286,755)	19.1 (301,651)	19.3 (322,701)
IPM*	4	0.1 (163,181)	0.1 (251,050)	0.1 (284,316)	0.1 (304,633)	0.1 (321,043)	0.1 (328,665)	0.1 (328,031)	0.1 (330,003)	0.04 (342,379)	0.1 (361,944)
MEPM*	4	0.2 (144,913)	0.2 (269,893)	0.2 (317,987)	0.1 (340,687)	0.1 (365,600)	0.1 (379,637)	0.1 (383,513)	0.1 (387,094)	0.1 (407,162)	0.1 (449,222)
AMK	64	0.2 (184,788)	0.1 (281,641)	0.1 (317,913)	0.1 (339,871)	0.1 (362,591)	0.1 (374,518)	0.1 (378,104)	0.1 (380,774)	0.1 (400,312)	0.1 (438,273)
LVFX	8	36.1 (178,497)	38.0 (274,687)	39.3 (310,705)	40.1 (336,310)	40.9 (360,329)	41.4 (374,719)	41.5 (379,538)	40.4 (381,447)	39.6 (398,196)	38.7 (439,872)

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 (2012) (M100-S22) Criteria was applied to determine BP after 2014.

ii. *Klebsiella pneumoniae*

Table 2. Resistance rates (%) of *Klebsiella pneumoniae*

	BP (2014-)	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
ABPC	32	76.3 (90,220)	76.9 (131,700)	76.3 (147,500)	77.4 (152,477)	79.4 (158,654)	80.1 (159,790)	79.7 (157,459)	77.7 (160,188)	77.5 (174,552)	80.5 (199,842)
PIPC	128	21.9 (91,761)	21.1 (136,347)	21.8 (154,260)	21.8 (161,254)	22.9 (165,430)	24.5 (161,590)	25.1 (156,799)	26.7 (158,472)	27.6 (169,964)	30.2 (195,028)
TAZ/ PIPC	4/128	2.0 (46,941)	2.0 (91,503)	2.2 (110,189)	2.2 (118,796)	2.6 (127,778)	3.1 (135,732)	3.2 (136,696)	3.6 (145,033)	3.6 (160,489)	4.1 (187,961)
CEZ*	8	11.7 (94,875)	12.1 (135,486)	13.1 (152,973)	13.4 (157,849)	14.3 (166,906)	15.2 (170,001)	16.5 (166,842)	18.2 (170,103)	18.8 (183,757)	20.8 (213,723)
CMZ	64	1.9 (85,749)	1.9 (132,163)	1.7 (152,086)	1.5 (159,375)	1.6 (168,787)	1.5 (172,912)	1.5 (173,615)	1.5 (177,579)	1.4 (193,632)	1.5 (225,278)
CTX*	4	8.6 (73,574)	8.0 (107,409)	8.9 (118,057)	8.9 (119,672)	9.4 (122,459)	9.7 (122,241)	11.0 (119,269)	11.7 (117,676)	12.6 (124,914)	13.7 (135,436)
CTRX	4	-	-	-	-	-	-	-	-	-	17.2 (174,183)
CAZ*	16	3.8 (94,878)	4.0 (138,191)	4.6 (155,293)	5.0 (160,619)	5.7 (169,097)	6.9 (173,031)	8.6 (171,425)	9.5 (174,262)	10.3 (189,618)	11.7 (218,048)
CFPM	32	3.5 (66,399)	4.0 (119,563)	4.8 (138,737)	5.1 (145,745)	5.8 (156,485)	6.8 (160,502)	7.7 (160,138)	8.5 (163,139)	9.1 (177,866)	9.7 (207,945)
AZT*	16	5.1 (75,340)	5.3 (110,259)	5.9 (122,600)	6.2 (127,491)	6.7 (133,009)	8.0 (135,631)	9.1 (133,016)	10.2 (134,988)	11.0 (146,557)	12.5 (165,483)
IPM*	4	0.3 (85,253)	0.3 (126,997)	0.2 (143,813)	0.2 (149,546)	0.3 (154,879)	0.2 (155,242)	0.2 (151,882)	0.2 (154,691)	0.1 (165,377)	0.2 (183,217
MEPM*	4	0.6 (73,903)	0.6 (135,930)	0.5 (159.623)	0.4 (166,298)	0.5 (175,408)	0.4 (179,042)	0.4 (178,240)	0.4 (182,018)	0.4 (197,801)	0.3 (229,357)
AMK	64	0.1 (95,643)	0.1 (141,710)	0.1 (159,871)	0.1 (166.081)	0.1 (174,259)	0.1 (176,609)	0.1 (175,742)	0.1 (179,422)	0.1 (194,640)	0.1 (224,579)
LVFX	8	2.4 (92,993)	2.6 (138,428)	2.7 (156,249)	2.8 (163,688)	3.1 (172,010)	3.4 (175,799)	4.2 (175,200)	4.6 (178,138)	5.2 (192,244)	5.7 (223,973)

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.

iii. *Enterobacter* spp.

Table 3. Resistance rates (%) of *Enterobacter cloacae*

	BP (2014-)	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
ABPC	32	79.0 (39,344)	80.2 (55,960)	79.3 (61,667)	79.8 (61,970)	81.2 (64,820)	81.3 (64,723)	81.4 (62,954)	80.4 (62,121)	82.0 (66,059)	82.9 (74,127)
PIPC	128	20.0 (39,636)	19.8 (58,039)	20.1 (63,580)	20.8 (64,217)	21.2 (66,020)	21.7 (62,798)	21.6 (60,369)	21.3 (58,758)	21.7 (61,527)	22.3 (67,672)
TAZ/ PIPC	4/128	8.6 (21,091)	8.9 (40,315)	8.9 (47,390)	9.4 (48,775)	9.8 (52,186)	10.5 (54,305)	10.3 (54,675)	10.1 (56,350)	10.6 (59,998)	10.8 (68,787)
CEZ*	8	98.2 (41,422)	98.3 (58,637)	98.3 (64,634)	98.3 (64,693)	98.3 (68,017)	98.2 (68,074)	98.2 (67,036)	98.2 (66,201)	98.3 (69,693)	98.2 (78,367)
CMZ**	64	83.4 (37,492)	85.4 (56,647)	85.5 (63,331)	86.1 (64,158)	88.0 (68,013)	87.4 (68,727)	88.1 (68,183)	87.9 (67,430)	88.1 (71,629)	87.6 (80,859)
CTX*	4	31.1 (32,718)	31.6 (46,727)	31.2 (50,311)	32.4 (50,022)	32.9 (51,470)	33.7 (50,606)	34.0 (49,402)	34.1 (47,591)	34.9 (48,848)	35.0 (51,214)
CTRX	4	-	-	-	-	-	-	-	-	-	35.8 (63,311)
CAZ*	16	24.7 (41,456)	25.0 (59,533)	24.9 (65,317)	25.8 (65,027)	26.3 (68,737)	26.8 (69,265)	27.4 (67,922)	27.7 (67,174)	28.5 (71,014)	29.0 (79,151)
CFPM	32	4.2 (29,836)	4.2 (52,218)	4.0 (58,298)	4.0 (59,398)	3.9 (64,337)	4.0 (65,211)	3.7 (65,110)	3.5 (64,286)	3.6 (67,964)	3.3 (76,726)
AZT*	16	23.8 (33,551)	24.0 (48,570)	23.9 (52,951)	24.3 (53,374)	24.9 (55,988)	26.1 (56,211)	26.3 (55,380)	26.5 (54,810)	27.4 (58,130)	27.6 (64,318)
IPM*	4	1.6 (37,396)	1.3 (54,926)	1.2 (60,602)	1.1 (60,689)	1.1 (63,611)	1.2 (61,918)	1.0 (61,234)	0.9 (59,721)	0.9 (62,027)	0.8 (66,680)
MEPM*	4	1.3 (32,589)	1.4 (59,009)	1.2 (67,250)	1.1 (67,392)	1.1 (71,119)	0.9 (71,548)	1.0 (70,910)	0.8 (70,077)	0.7 (74,210)	0.6 (83,317)
AMK	64	0.2 (42,005)	0.2 (61,086)	0.1 (67,133)	0.1 (67,125)	0.1 (70,659)	0.1 (70,392)	0.1 (69,812)	0.1 (68,955)	0.1 (73,178)	0.1 (81,661)
LVFX	8	3.5 (40,942)	3.7 (59,393)	3.4 (65,161)	3.5 (65,690)	3.2 (69,392)	3.1 (70,034)	2.9 (69,816)	2.6 (68,752)	2.5 (71,907)	2.3 (80,646)

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.

Table 4. Resistance rates (%) of *Klebsiella* (*Enterobacter*)* *aerogenes*

	BP (2014-)	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
ABPC	32	77.1 (18,385)	78.9 (26,680)	77.9 (29,228)	79.1 (30,844)	80.3 (32,746)	80.5 (33,621)	80.8 (33,862)	79.6 (35,315)	81.0 (38,564)	82.3 (42,088)
PIPC	128	14.5 (18,550)	14.2 (27,189)	15.8 (29,852)	17.1 (31,802)	17.4 (33,048)	18.9 (32,497)	18.6 (32,139)	17.5 (32,962)	17.5 (35,871)	18.4 (38,643)
TAZ/PIPC	4/128	4.9 (9,568)	4.8 (18,731)	4.8 (21,767)	5.7 (24,082)	6.9 (26,272)	6.9 (28,085)	7.2 (29,124)	7.0 (30,954)	7.4 (34,399)	7.6 (38,718)
CEZ**	8	94.0 (19,173)	93.7 (27,526)	94.2 (30,088)	94.5 (31,800)	95.0 (33,996)	94.7 (35,183)	95.1 (35,448)	95.0 (36,851)	94.8 (40,246)	94.8 (44,354)
CMZ	64	84.8 (17,587)	86.8 (26,739)	87.1 (29,681)	88.0 (31,915)	89.1 (34,051)	89.5 (35,408)	89.9 (36,068)	90.0 (37,881)	89.7 (41,502)	89.8 (45,944)
CTX**	4	28.3 (15,173)	30.7 (21,985)	31.1 (23,572)	32.9 (24,195)	33.4 (25,493)	34.2 (26,271)	35.4 (26,655)	35.2 (27,111)	35.9 (28,608)	37.5 (29,469)
CTRX	4	-	-	-	-	-	-	-	-	-	37.5 (35,448)
CAZ**	16	24.3 (19,439)	25.2 (27,886)	25.7 (30,388)	26.7 (32,030)	27.8 (34,142)	28.5 (35,487)	29.6 (35,985)	29.7 (37,638)	30.1 (41,161)	31.2 (45,029)
CFPM	32	1.2 (13,499)	1.1 (24,302)	1.1 (27,146)	1.3 (29.464)	1.4 (32,216)	1.5 (33,583)	1.4 (34,454)	1.5 (36,047)	1.6 (39,114)	1.5 (43,437)
AZT**	16	15.8 (15,846)	17.5 (23,225)	17.5 (25,023)	18.0 (26,772)	19.2 (28,281)	20.2 (29,397)	20.8 (30,056)	20.4 (31,103)	20.8 (34,014)	21.4 (36,517)
IPM**	4	1.7 (17,463)	1.9 (25,690)	1.9 (28,307)	1.9 (29,869)	2.6 (31,288)	2.3 (31,645)	2.2 (32,050)	1.7 (33,173)	1.3 (35,870)	1.4 (38,094)
MEPM**	4	0.9 (15,003)	0.8 (27,560)	0.8 (31,311)	0.8 (33,150)	0.8 (35,448)	0.8 (36,550)	0.9 (37,291)	0.9 (38,989)	0.9 (42,475)	0.7 (46,742)
AMK	64	0.2 (19,492)	0.1 (28,627)	0.1 (31,338)	0.1 (33,074)	0.1 (35,214)	0.1 (36,204)	0.05 (36,866)	0.05 (38,542)	0.04 (41,981)	0.04 (45,882)
LVFX	8	1.0 (19,068)	0.9 (28,012)	1.0 (30,451)	0.9 (32,503)	0.9 (34,383)	0.9 (35,735)	0.9 (36.768)	1.0 (38.092)	0.9 (41,329)	0.9 (45,227)

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.

iv. Pseudomonas aeruginosa

Table 5. Resistance rates (%) of *Pseudomonas aeruginosa*

	BP (2014-)	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
PIPC	128	10.8 (125,242)	10.5 (181,977)	10.5 (201,764)	10.3 (205,165)	10.0 (206,858)	10.3 (214,513)	10.0 (211,455)	9.8 (214,729)	9.7 (223,807)	9.8 (252,866)
TAZ/ PIPC	4/128	8.8 (79,574)	8.8 (132,769)	8.4 (155,724)	8.3 (165,402)	8.1 (172,748)	8.4 (185,720)	7.8 (185,847)	7.8 (191,294)	7.8 (201,973)	8.0 (230,183)
CAZ	32	9.5 (126,718)	8.6 (180,479)	8.7 (199,597)	8.6 (202,025)	8.4 (203,554)	8.7 (210,892)	8.6 (207,738)	8.7 (211,983)	8.7 (221,033)	8.8 (246,519)
CFPM	32	7.5 (113,268)	6.6 (166,096)	6.5 (185,283)	6.3 (191,502)	6.0 (194,385)	5.9 (200,818)	5.7 (198,849)	5.5 (202,904)	5.3 (212,498)	5.0 (238,636)
AZT	32	14.5 (107,167)	14.0 (146,841)	13.8 (158,737)	13.7 (162,952)	13.1 (162,365)	13.3 (167,331)	13.6 (164,518)	13.4 (166,971)	13.0 (176,832)	12.3 (193,248)
IPM*	8	19.9 (119,323)	18.8 (168,471)	17.9 (186,380)	16.9 (188,981)	16.2 (188,778)	16.2 (195,183)	15,9 (191,793)	15,8 (194,826)	14.8 (202,639)	13.9 (225,975)
MEPM*	8	14.4 123,976)	13.1 (180,850)	12.3 (201,991)	11.4 (206,368)	10.9 (209,149)	10.6 (217,161)	10.5 (214,691)	10.3 (218,610)	9.5 (228,253)	8.8 (257,396)
GM	16	5.1 (117,421)	4.5 (165,777)	4.1 (182,343)	3.3 (184,453)	2.9 (184,135)	3.1 (190,296)	3.0 (184,307)	2.8 (184,581)	2.5 (193,104)	2.4 (213,082)
AMK	64	1.9 (128,923)	1.5 (185,327)	1.3 (204,892)	1.1 (208,098)	0.9 (209,413)	0.9 (217,512)	0.8 (214,949)	0.7 (219,053)	0.6 (228,023)	0.6 (255,928)
LVFX	8	13.0 (120,691)	12.0 (174,301)	11.6 (193,366)	10.8 (197,890)	10.2 (199,760)	9.8 (207,963)	9.5 (204,829)	8.9 (207,311)	8.1 (216,226)	7.5 (244,553)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

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

v. *Acinetobacter* spp.

Table 6. Resistance rates (%) of *Acinetobacter* spp.

	BP	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
PIPC	128	12.4 (20,223)	11.5 (27,887)	10.9 (29,776)	10.9 (27,468)	10.3 (27,905)	10.7 (26,237)	10.2 (23,018)	11.0 (22,399)	10.8 (22,002)	10.9 (24,924)
TAZ/ PIPC	4/128	7.8 (5,215)	8.1 (9,058)	8.6 (10,551)	9.0 (10,983)	9.4 (12,171)	9.0 (12,401)	8.2 (11,478)	9.5 (11,275)	9.0 (11,305)	8.2 (13,590)
SBT/ ABPC	16/32	5.2 (6,462)	4.8 (11,356)	5,4 (12,831)	4.7 (12,241)	4.4 (13,111)	4.3 (12,769)	3.4 (12,047)	3.6 (11,982)	4.3 (11,708)	4.2 (13,338)
CAZ	32	9.3 (20,852)	8.0 (28,166)	7.6 (29,844)	7.9 (27,308)	7.6 (28,077)	8.6 (26,614)	8.4 (23,626)	9.1 (23,064)	9.4 (22,645)	9.9 (25,633)
CFPM	32	7.6 (17,424)	7.2 (25,412)	7.4 (27,386)	7.6 (25,631)	6.8 (26,616)	6.8 (25,224)	7.0 (22,400))	7.2 (22,002)	6.9 (21,702)	6.7 (24,660)
IPM	16	3.6 (11,147)	3.2 (13,942)	3.1 (15,147)	2.5 (14,383)	2.0 (16,995)	1.8 (19,645)	1.1 (21,381))	1.1 (21,243)	1.0 (20,627)	0.9 (22,984)
MEPM	16	2.0 (18,859)	1.8 (28,227)	1.9 (30,489)	1.3 (28,064)	1.5 (29,024)	1.4 (27,418)	1.2 (24,163)	1.2 (23,500)	1.3 (23,196)	1.1 (26,234)
GM	16	8.9 (18,832)	8.5 (25,689)	8.5 (27,313)	8.2 (24,887)	7.8 (25,465)	8.0 (23,925)	7.7 (20,853)	8.6 (20,174)	8.1 (19,819)	7.7 (22,064)
AMK	64	3.6 (20,851)	3.1 (28,568)	2.3 (30,279)	2.3 (27,835)	2.0 (28,437)	2.1 (26,917)	2.0 (23,697)	2.4 (23,217)	2.4 (22,835)	1.6 (25,674)
LVFX	8	8.5 (20,047)	7.7 (27,858)	8.2 (29,702)	8.0 (27,360)	7.0 (28,209)	7.5 (26,898)	7.8 (23,650)	8.7 (22,998)	8.6 (22,546)	8.8 (25,676)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

2) Gram-positive bacteria

Source: JANIS

Looking at the recent status of gram-positive bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) accounted for approximately 50% of all *S. aureus*. Although the proportion has been declining over the past few years, it remains higher than that seen in other countries. The proportion was higher among medical institutions with fewer than 200 beds than among those with 200 or more (Table 10). In the case of *enterococci*, rising vancomycin (VCM) resistance was a problem in many countries, but as shown in Tables 11 and 12, levels in Japan were comparatively low, at less than 0.05% in the case of *Enterococcus faecalis* and 1.9% in *Enterococcus faecium*. However, also in 2021, the VCM resistance rate among *E. faecium* significantly increased and widespread, nosocomial outbreaks of VCM-resistant *E. faecium* involving multiple facilities have been observed in some regions. Regional changes in resistance rates will need to be kept under close observation. The proportion of penicillin-resistant *Streptococcus pneumoniae* (PRSP) accounted for approximately 50% of all detected pneumococcus in cerebrospinal fluid (CSF) samples, though the figure varies from year to year, because only around 100 CSF samples were 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. Resistance rates (%) of total *Staphylococcus aureus**

	BP	2018	2019	2020	2021	2022	2023
PCG	0.25	75.4 (287,805)	75.1 (295,031)	74.3 (281,583)	73.3 (277,317)	72.8 (288,253)	72.7 (303,146)
MPIPC	4	47.8 (266,047)	47.7 (265,763)	47.5 (243,162)	46.0 (237,103)	45.5 (243,386)	45.2 (250,974)
CFX	8	46.1 (57,604)	46.0 (64,239)	46.1 (61,811)	45.2 (62,331)	43.6 (65,031)	43.4 (68,107)
CEZ	32	20.7 (360,772)	19.7 (366,803)	19.3 (339,052)	17.8 (334,737)	16.2 (346,659)	16.5 (373,096)
GM	16	30.4 (345,964)	28.9 (350,425)	27.5 (325,197)	26.1 (317,744)	25.1 (330,361)	24.0 (347,757)
EM	8	51.7 (325,918)	51.2 (329,090)	50.5 (302,105)	48.4 (297,317)	46.6 (308,701)	46.7 (328,327)
CLDM	4	22.0 (340,953)	20.4 (350,136)	18.9 (325,568)	17.3 (319,298)	15.7 (331,565)	15.1 (356,345)
MINO	16	12.2 (377,507)	10.5 (385,264)	9.7 (360,076)	8.9 (353,680)	8.0 (365,963)	7.2 (396,719)
VCM	16	0.0 (374,982)	0.0 (382,254)	0.0 (356,747)	0.0 (347,976)	0.0 (358,032)	0.0 (388,557)
TEIC	32	<0.05 (336,502)	＜0.05 (340,855)	＜0.05 (314,742)	＜0.05 (308,176)	＜0.05 (318,317)	＜0.05 (335,414)
LVFX	4	50.4 (358,941)	51.7 (368,676)	52.3 (344,943)	51.3 (339,292)	51.3 (349,500)	52.3 (378,339)
LZD	8	<0.05 (286,366)	＜0.05 (294,735)	<0.05 (276,069)	<0.05 (268,079)	< 0.05 (277,713)	< 0.05 (295,523)
DAP	2	0.3 (72,401)	0.3 (98,366)	0.3 (108,416)	0.3 (116,811)	0.3 (128,962)	0.2 (142,755)

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.

Table 8. Resistance rates (%) of Methicillin-susceptible *Staphylococcus aureus* (MSSA)

	BP	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
PCG	0.25	57.7 (86,314)	56.2 (119,343)	55.0 (126,394)	53.9 (129,943)	52.9 (135,360)	52.1 (138,818)	51.1 (133,767)	50.7 (135,944)	50.2 (143,105)	50.0 (150,674)
CEZ	32	0.2 (103,603)	0.1 (146,254)	<0.05 (157,917)	<0.05 (161,831)	<0.05 (164,909)	＜0.05 (167,084)	<0.05 (155,735)	<0.05 (159,135)	<0.05 (167,376)	<0.05 (179,023)
CVA/ AMPC	4/8	0.2 (11,666)	0.1 (19,163)	0.1 (21,783)	0.1 (24,713)	0.1 (26,376)	0.1 (25,258)	0.1 (24,967)	0.1 (26,846)	0.1 (28,097)	0.1 (29,323)
IPM	16	0.2 (95,951)	<0.05 (136,878)	<0.05 (146,433)	<0.05 (149,014)	<0.05 (149,454)	＜0.05 (150,811)	<0.05 (138,998)	<0.05 (137,863)	<0.05 (141,411)	<0.05 (145,647)
EM	8	23.8 (96,829)	22.9 (136,763)	23.3 (146,280)	23.5 (148,795)	23.1 (150,809)	22.7 (151,577)	22.6 (139,415)	21.5 (142,251)	20.5 (149,705)	20.3 (158,433)
CLDM	4	2.8 (93,467)	2.8 (136,292)	2.9 (148,439)	2.9 (151,841)	2.7 (155,141)	2.9 (157,700)	3.0 (147,257)	2.9 (150,416)	2.8 (158,285)	2.9 (170,182)
MINO	16	0.6 (104,145)	0.6 (151,493)	0.5 (163,214)	0.6 (167,178)	0.6 (169,953)	0.5 (171,857)	0.6 (161,001)	0.6 (164,230)	0.5 (172,471)	0.6 (186,197)
LVFX	4	10.7 (99,898)	11.6 (144,083)	12.3 (154,868)	13.1 (159,066)	13.8 (161,691)	14.7 (164,665)	15.5 (154,754)	15.9 (158,287)	16.4 (165,426)	17.3 (178,202)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

Table 9. Resistance rates (%) of Methicillin-resistant *Staphylococcus aureus* (MRSA)

	BP (2014-)	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
EM	8	86.0 (107,836)	84.1 (149,851)	83.8 (155,587)	82.9 (157,708)	81.7 (159,215)	80.7 (161,613)	79.8 (147,736)	78.6 (140,331)	76.8 (143,415)	76.8 (153,672)
CLDM	4	60.3 (106,910)	56.0 (153,329)	51.6 (160,500)	46.3 (164,301)	41.7 (169,049)	37.9 (175,081)	35.1 (161,937)	33.1 (153,027)	30.2 (156,646)	28.7 (169,312)
MINO	16	35.1 (121,258)	31.7 (173,983)	29.1 (182,306)	27.1 (185,770)	23.7 (189,813)	20.1 (195,422)	18.7 (181,557)	17.7 (172,374)	16.0 (175,443)	14.3 (191,602)
VCM	16	0.0 (120,535)	0.0 (172,083)	0.0 (181,288)	0.0 (185,948)	0.0 (189,853)	0.0 (195,332)	0.0 (181,671)	0.0 (171,879)	0.0 (174,187)	0.0 (190,401)
TEIC	32	<0.05 (113,749)	<0.05 (158,233)	<0.05 (165,213)	<0.05 (167,342)	<0.05 (169,651)	＜0.05 (173,090)	<0.05 (158,930)	<0.05 (150,589)	<0.05 (153,290)	<0.05 (162,828)
LVFX	4	85.4 (115,586)	85.2 (164,734)	85.8 (172,494)	86.5 (176,790)	86.8 (179,731)	87.8 (186,442)	88.5 (173,610)	88.9 (164,814)	89.4 (166,997)	90.0 (182,277)
LZD*	8	<0.05 (88,255)	0.1 (127,278)	<0.05 (136,468)	<0.05 (139,785)	<0.05 (144,332)	＜0.05 (149,340)	<0.05 (137,980)	<0.05 (129,420)	<0.05 (132,000)	<0.05 (141,211)
DAP	2	1.1 (3,078)	0.9 (16,648)	0,8 (23,217)	0.7 (26,874)	0.5 (35,618)	0.4 (47,835)	0.5 (51,671)	0.5 (53,782)	0.5 (58,616)	0.4 (64,996)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

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

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

Table 10-1. All participating medical institutions

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Number of medical institutions	883	1,435	1,653	1,795	1,947	2,075	2,167	2,220	2,289	2,752
Number of patients with MRSA	120,702	169,528	177,768	182,619	185,709	192,320	176,848	167,858	168,718	183,743
Number of patients with *S. aureus*	246,030	349,743	372,787	383,006	391,316	400,094	367,976	360,912	370,067	400,620
MRSA (%)*	49.1	48.5	47.7	47.7	47.5	48.1	48.1	46.5	45.6	45.9

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

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Number of medical institutions	791	1,177	1,269	1,312	1,334	1,357	1,364	1,378	1,386	1,455
Number of patients with MRSA	115,757	157,419	160,060	160,714	159,054	161,159	144,828	135,984	135,670	139,030
Number of patients with *S. aureus*	237,343	328,540	341,822	344,543	344,156	345,447	312,738	305,116	311,251	320,112
MRSA (%)*	48.8	47.9	46.8	46.6	46.2	46.7	46.3	44.6	43.6	43.4

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

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Number of medical institutions	92	258	384	483	613	718	803	842	903	1,297
Number of patients with MRSA	4,945	12,109	17,708	21,905	26,655	31,161	32,020	31,874	33,048	44,713
Number of patients with *S. aureus*	8,687	21,203	30,965	38,463	47,160	54,647	55,238	55,796	58,816	80,508
MRSA (%)*	56.9	57.1	57.2	57.0	56.5	57.0	58.0	57.1	56.2	55.5

Those detected in selective media were also included.

* The number of patients with MRSA / The number of patients with *S. aureus*

ii. *Enterococcus* spp.

Table 11. Resistance rates (%) of *Enterococcus faecalis*

	BP	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
PCG	16	1.6 (67,324)	1.4 (92,132)	1.1 (98,465)	1.0 (98,478)	0.9 (104,023)	0.9 (107,021)	0.9 (111,226)	0.9 (114,014)	0.8 (117,159)	0.8 (124,597)
ABPC	16	0.3 (77,997)	0.3 (107,733)	0.2 (115,548)	0.2 (116,493)	0.2 (119,014)	0.2 (121,530)	0.2 (123,238)	0.2 (125,752)	0.2 (129,563)	0.2 (138,911)
EM	8	55.5 (69,171)	54.8 (95,409)	54.3 (101,036)	53.8 (101,379)	52.7 (102,496)	51.7 (102,871)	50.2 (103,067)	48.2 (105,505)	46.1 (108,619)	45.8 (118,552)
MINO	16	52.1 (81,925)	49.7 (115,648)	48.9 (123,860)	50.3 (125,728)	50.9 (128,160)	47.2 (130,729)	48.1 (133,174)	50.8 (135,820)	51.9 (139,723)	47.0 (153,581)
VCM	32	<0.05 (81,867)	<0.05 (115,100)	<0.05 (124,305)	<0.05 (126,510)	<0.05 (129,545)	< 0.05 (132,526)	<0.05 (135,184)	<0.05 (137,887)	<0.05 (142,316)	<0.05 (156,297)
TEIC	32	<0.05 (76,160)	<0.05 (105,403)	<0.05 (112,636)	<0.05 (113,501)	<0.05 (115,397)	< 0.05 (117,097)	<0.05 (118,367)	<0.05 (120,564)	<0.05 (124,347)	<0.05 (132,251)
LVFX	8	13.7 (77,563)	12.5 (109,160)	11.9 (117,297)	11.2 (120,136)	10.4 (122,551)	10.1 (125,836)	9.5 (128,449)	9.0 (131,088)	8.3 (134,507)	8.7 (147,680)

The unit of BP is μg/mL.

Figures in parentheses indicate the number of bacterial strains that were tested for antimicrobial susceptibility.

Table 12. Resistance rates (%) of *Enterococcus faecium*

	BP	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
PCG	16	86.9 (24,534)	87.6 (34,752)	88.2 (38,060)	87.8 (39,478)	87.5 (42,178)	87.4 (46,021)	86.9 (49,002)	87.1 (50,976)	87.1 (53,508)	87.4 (57,617)
ABPC	16	86.9 (28,564)	87.6 (41,459)	88.0 (45,069)	87.9 (47,046)	87.6 (49,207)	88.0 (52,929)	87.6 (54,632)	87.9 (56,395)	87.7 (59,105)	88.1 (63,880)
EM	8	84.5 (25,922)	84.5 (37,536)	84.0 (40,509)	83.1 (42,259)	83.0 (43,555)	83.1 (45,992)	83.1 (47,133)	80.0 (49,083)	79.5 (51,391)	81.5 (55,915)
MINO	16	32.2 (31,550)	35.1 (46,351)	34.7 (50,325)	36.2 (52,494)	38.3 (54,540)	33.0 (58,314)	31.7 (60,040)	30.2 (62,137)	31.5 (64,243)	28.8 (70,493)
VCM	32	0.7 (30,996)	0.7 (45,514)	0.9 (49,618)	0.8 (52,127)	0.9 (54,279)	1.5 (58,377)	1.4 (60,412)	2.6 (62,811)	2.6 (65,363)	1.9 (71,747)
TEIC	32	0.2 (29,151)	0.3 (41,905)	0.6 (45,388)	0.4 (47,321)	0.6 (48,991)	1.0 (52,502)	0.8 (54,125)	1.4 (55,948)	1.5 (58,342)	1.2 (63,085)
LVFX	8	84.7 (28,448)	85.8 (42,068)	86.6 (45,834)	86.5 (48.995)	86.7 (51,003)	87.6 (55,293)	86.9 (57,199)	87.2 (59,808)	86.9 (62,209)	86.9 (67,816)
LZD	8	0.1 (22,044)	0.1 (33,382)	0.1 (37,099)	<0.05 (39,584)	0.1 (41.596)	0.1 (44,887)	0.1 (46,611)	0.1 (47,809)	0.1 (49,958)	0.1 (55,010)

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. Resistance rates (%) of *Streptococcus pneumoniae* (spinal fluid specimens)

	BP	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
PCG	0.125	47.0 (83)	40.5 (126)	36.4 (140)	29.1 (117)	38.3 (94)	32.0 (100)	33.3 (57)	59.5 (42)	50.9 (57)	50.8 (59)
CTX	2	2.9 (69)	2.0 (100)	1.0 (105)	2.1 (97)	4.5 (88)	1.2 (85)	4.3 (47)	5.6 (36)	4.1 (49)	13.0 (54)
CTRX	2	-	-	-	-	-	-	-	-	-	11.1 (54)
MEPM	1	1.2 (83)	4.2 (119)	0.7 (134)	5.0 (120)	2.1 (95)	1.0 (99)	6.0 (50)	6.8 (44)	8.9 (56)	18.2 (55)
EM	1	92.5 (67)	84.9 (86)	75.5 (98)	82.4 (91)	75.0 (76)	84.8 (79)	76.7 (43)	86.5 (37)	77.8 (45)	70.8 (48)
CLDM	1	65.1 (63)	62.7 83)	61.2 (98)	49.5 (91)	43.7 (71)	64.0 (75)	57.1 (42)	52.8 (36)	57.8 (45)	46.7 (45)
LVFX	8	1.3 (76)	0.0 (105)	0.0 (123)	0.9 (111)	2.3 (88)	0.0 (93)	0.0 (50)	0.0 (40)	1.9 (52)	0.0 (52)
VCM	2	0.0 (82)	0.0 (119)	0.0 (134)	0.0 (116)	0.0 (98)	0.0 (96)	0.0 (56)	0.0 (42)	0.0 (56)	0.0 (57)

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. Resistance rates (other than spinal fluid specimens) (%) of *Streptococcus pneumoniae*

	BP	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
PCG*	4	2.5 (27,206)	2.7 (36,475)	2.1 (35,960)	2.1 (34,415)	2.2 (33,483)	2.2 (31,506)	3.5 (16,056)	3.4 (16,526)	3.8 (14,510)	3.7 (17,727)
CTX	4	1.8 (23,002)	1.6 (30,734)	1.4 (29,405)	1.6 (27,773)	1.4 (27,004)	1.4 (26,040)	2.1 (13,140)	2.1 (13,878)	2.4 (12,372)	2.2 (15,330)
CTRX	4	-	-	-	-	-	-	-	-	-	2.6 (17,144)
MEPM	1	5.4 (25,760)	5.0 (34,461)	5.7 (34,885)	6.0 (34,011)	6.3 (33,115)	6.4 (31,489)	8.9 (16,152)	8.9 (16,479)	8.8 (14,452)	9.6 (17,827)
EM	1	86.7 (22,215)	85.5 (30,501)	84.4 (30,144)	82.4 (28,097)	81.3 (27,154)	81.5 (26,270)	80.4 (13,529)	80.5 (14,352)	82.0 (12,750)	81.4 (16,206)
CLDM	1	57.1 (20,296)	56.1 (27,555)	54.1 (28,541)	50.5 (27,536)	49.9 (26,459)	50.9 (25,404)	49.5 (13,651)	49.5 (14,047)	50.3 (12,386)	49.8 (15,506)
LVFX	8	3.3 (26,236)	3.5 (35,457)	4.1 (35,431)	4.3 (34,241)	4.4 (33,551)	4.7 (32,057)	6.4 (16,499)	6.0 (16,818)	6.4 (14,805)	6.9 (18,402)
VCM	2	0.0 (25,775)	0.0 (33,530)	0.0 (33,670)	0.0 (32,681)	0.0 (31,741)	0.0 (30,250)	0.0 (15,625)	0.0 (16,176)	0.0 (14,140)	0.0 (17,741)

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

The numbers of cases reported under National Epidemiological Surveillance of Infectious Disease each year through 2021 were publicized as confirmed reported data. Cases reported since 2013 are listed below. The scope of reporting was limited to cases where the isolated bacteria was regarded as the cause of an infectious disease, or cases where it was detected from specimens that normally should be aseptic. Colonization was excluded from the scope of reporting.

Among notifiable diseases (diseases that must be reported to the authorities in all cases), there have been around 80 reports of vancomycin-resistant enterococci (VRE) infection per year since 2017, representing a slight rise from the trend of 50 to 60 reports per year between 2013 and 2016. Since 2017, the number of cases has been increasing and in 2022, 133 cases were reported. No case of vancomycin-resistant *Staphylococcus aureus* (VRSA) infection has been reported since November 5, 2003, when this disease became notifiable. Carbapenem-resistant *Enterobacteriales* (CRE) infection became a notifiable disease on September 19, 2014, with 2,015 cases reported in 2022 and generally ranging from 2,000 to 2,300 cases since 2018. Surveillance for multidrug-resistant *Acinetobacter* (MDRA) infection was started in February 2011, with reporting of cases limited at first to designated sentinel sites. It subsequently became a notifiable disease on September 19, 2014, and reports ranged between 20 and 40 cases per year thereafter, with 13 cases reported in 2022.

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 have been using the PCR method to test strains isolated from notified cases of CRE infection for carbapenemase genes and other information. In 2021 results for 1,441 strains were reported. The major carbapenemase gene was detected in 217 (15.1%) isolates, with the IMP form of the domestic carbapenemase gene accounting for the majority, 189 (87.1%). Bacterial species of the strains detected with IMP type and IMP genotypes showed similar regional characteristics since 2017.

Looking at antimicrobial-resistant infections notified by Japan's designated sentinel sites (in principle medical institutions that have 300 or more beds, 500 institutions nationwide), both the number of reports of MRSA infections and the number of reports per sentinel site had decreased since 2011, with 14,694 cases (30.7 cases per designated sentinel site) reported in 2022. Multidrug-resistant *Pseudomonas aeruginosa* (MDRP) infections have generally declined since 2013, with 103 cases (0.22 cases per designated sentinel site) reported in 2022. Penicillin-resistant *Streptococcus pneumoniae* (PRSP) infections continued to decline in both the number of reports and the number of reports per sentinel.

i. Diseases subject to notifiable disease surveillance

Table 15. Number of cases reported for diseases subject to notifiable disease surveillance (2013-2022)

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
VRE	55	56	66	61	83	80	80	136	124	133
VRSA	0	0	0	0	0	0	0	0	0	0
CRE	-	314*	1,671	1,573	1,660	2,289	2,333	1,956	2,066	2,015
MDRA	-	15*	38	33	28	24	24	10	6	13

* 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 (2013-2022)

		2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
PRSP	Total	3,161	2,292	2,057	2,017	2,001	1,895	1,754	879	846	698
	Per site	6.65	4.79	4.29	4.21	4.18	3.94	3.65	1.84	1.77	1.46
MRSA	Total	20,155	18,082	17,057	16,338	16,551	16,311	16,241	14,940	14,516	14,694
	Per site	42.43	37.83	35.61	34.11	34.55	33.91	33.84	31.19	30.30	30.68
MDRA*	Total	8	4	-	-	-	-	-	-	-	-
	Per site	0.02	0.01	-	-	-	-	-	-	-	-
MDRP	Total	319	268	217	157	128	121	127	116	118	103
	Per site	0.67	0.56	0.45	0.33	0.27	0.25	0.26	0.24	0.25	0.22

* 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 137 outbreaks of food-borne illness that occurred in Tokyo in 2022, 29 outbreaks (21.2%) were caused by *Campylobacter* spp., being the largest cause of bacterial food-borne illness since 2005.[1] The strains provided for antimicrobial susceptibility tests were *Campylobacter jejuni* and *Campylobacter coli* isolated from sporadic diarrhea patients in Tokyo. Resistance rates for 2013-2022 are shown in the tables. the number of samples was limited, with only 49 strains of *C. jejuni* and 2 strains of *C. coli*. In 2022, the number of strains tested was very low. The resistance rate of *Campylobacter jejuni* (*C. jejuni*) to ciprofloxacin (CPFX) was 53.1%, which has increased as compared to 2021. The resistance rate of erythromycin (EM) was 0%, and the resistance rate of CPFX to *Campylobacter coli* was 100%, which was the same level as the previous year. In both cases, the resistance rate has remained largely unchanged, although it has increased or decreased from year to year. However, the number of tested strains was smaller for *Campylobacter coli* and this should be taken into consideration upon interpretation of the result.

Table 17. Resistance rates (%) of *Campylobacter jejuni* * from sporadic diarrhea

(Number of samples)	2013 (85)	2014 (125)	2015 (116)	2016 (113)	2017 (115)	2018 (110)	2019 (132)	2020 (86)	2021 (42)	2022 (49)
EM	1.2	0.8	0.9	0.9	1.7	1.8	3.0	0.0	2.4	2.0
NA	50.6	50.4	37.1	53.1	46.1	51.7	54.5	31.4	31.0	53.1
CPFX	50.6	50.4	37.1	52.2	43.5	51.8	54.5	31.4	31.0	53.1

* Strains isolated from diarrhea cases in Tokyo.

Prepared from [5] with partial modification.

Table 18. Resistance rates (%) of *Campylobacter coli* * from sporadic diarrhea

(Number of samples)	2013 (12)	2014 (7)	2015 (8)	2016 (14)	2017 (8)	2018 (8)	2019 (16)	2020 (7)	2021 (3)	2022 (2)
EM	16.7	28.6	0.0	14.3	25.0	62.5	25.0	28.6	33.3	50.0
NA	75.0	57.1	50.0	50.0	62.5	50.0	68.8	57.1	100.0	100.0
CPFX	75.0	57.1	50.0	35.7	62.5	37.5	68.8	57.1	100.0	100.0

* Strains isolated from diarrhea cases in Tokyo.

Prepared from [5] with partial modification.

ii. Non-typhoidal *Salmonella* spp.

Source: Public Health Institutes

The 21-23 Public Health Institutes across Japan conducted research on the multidrug-resistant status of the 3,303 *Salmonella* spp. that were isolated between 2015 and 2023, using standardized methodology.[2] Table 19 lists the key serotypes of human-derived strains and food-derived strains.

In total, 38.7% of the 2,510 human-derived strains (from symptomatic humans) and 90.2% of the 1,173 food-derived strains indicated resistance to one or more of the 17 antimicrobials used in the study (Tables 20 and 21). Although this investigation was not conducted as a routine national surveillance operation, this was nationwide surveillance, and the resistance rates of the strains isolated between 2015 and 2023 are considered to reflect the current status in Japan. In this reporting period (2023), 85 (43.8%) of 194 human-derived strains and 166 (89.2%) of 186 food-derived strains were resistant to one or more agents, which did not differ significantly from the resistance rates of 2,316 human-derived strains (38.3%) and 987 food-derived strains (90.4%), which were isolated between 2015-2022. Over the past nine years, annual trends indicate a slight decrease in human-derived strains between 2021 and 2022, followed by an increase in 2023. In contrast, food-derived strains have remained largely stable during this period. Forty-six (1.8%) among 2,510 human-derived strains, and 68 (5.8%) among 1,173 food-derived strains, indicated multidrug resistance to as many as 6 to 13 agents. In addition, resistant strains to meropenem (MEPM) were detected for the first time in human-derived isolates in 2020 (Table 20). This isolated strain was *S.* Heidelberg, a multidrug-resistant strain resistant to eight agents, including MEPM. On the other hand, no MEPM-resistant strains have been detected in food-derived strains to date.

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, *S.* Schwarzengrund in particular accounted for a higher proportion of isolates in the recent period (2020-2023) than in 2015-2019, but the resistance trends were not significantly different. In human-derived strains, on the other hand, as resistance trends were observed characteristic to each serotype, the resistance rates were compared by stereotype

over time and shown.

Three serotypes (*S*. Schwarzengrund, *S*. Infantis and *S*. Manhattan) were found commonly in both the top 10 human-derived and top 5 food-derived serotypes, and the antimicrobial resistance rates of these three serotypes were compared between human- and food-derived strains (Table 29). Clear similarities were observed in overall resistance trends to various antimicrobials, suggesting a strong association between human-derived resistant strains (approximately 40% of S. Infantis and the majority of *S*. Schwarzengrund and *S*. Manhattan) and food-derived resistant strains.

In addition to antimicrobial susceptibility tests, strains isolated between 2015 and 2022 (2,316 human-derived strains, 987 food-derived strains) that demonstrated resistance to one or more of the agents cefotaxime (CTX), ceftazidime (CAZ), and cefoxitin (CFX) (46 human-derived strains and 8 food-derived strains) underwent testing to detect extended-spectrum β-lactamase (ESBL) and AmpC β-lactamase (AmpC)

producing genes. The CTX-M-1 group was the most common genotype among the ESBL producing genes in human-derived and food-derived strains alike, followed by TEM. CIT was the most common genotype among the AmpC producing genes in human-derived and food-derived strains alike, followed by TEM. These results showed similarities in trends toward the detection of ESBL and AmpC producing genes in both human-derived and food-derived strains, while the CTX-M-9 group (ESBL-producing genes) was detected only in human-derived strains, and the EBC-type (AmpC genes) was detected only in food-derived strains. Strain characteristic detections were also observed.

Furthermore, to conduct detailed phylogenetic analysis between human-derived and food-derived strains, as well as to examine the genetic content of each strain, a total of 1,265 *Salmonella* strains (683 human-derived and 582 food-derived) isolated from 2015 to 2022 at regional public health institutes were subjected to whole genome sequencing using next-generation sequencing technologies in collaboration with the Antimicrobial Resistance Clinical Reference Center of the National Institute of Infectious Diseases.

Table 19. Serotypes of human- and food-derived non-typhoidal *Salmonella* spp. (2015-2023)

Human-derived strains (n= 2,510)	%	Food-derived strains (n= 1,173)	%
Enteritidis	14.0	Schwarzengrund	58.8
4:i:-	11.6	Infantis	18.7
Infantis	8.4	Manhattan	7.2
Thompson	8.1	Agona	1.7
Typhimurium	6.1	Heidelberg	1.5
Saintpaul	5.5	Others	12.0
Schwarzengrund	5.5	Total	100.0
Stanley	3.5		
Newport	3.1		
Manhatten	2.2		
Others	32.0		
Total	100.0		

Table 20. Resistance rates of human-derived non-typhoidal *Salmonella* spp. (2015-2023)

	2015 (n=387)	2016 (n=360)	2017 (n=393)	2018 (n=315)	2019 (n=265)	2020 (n=211)	2021 (n=146)	2022 (n=239)	2023 (n=194)	SUM (n=2510)
ABPC	17.3	18.1	16.0	19.4	14.7	14.7	12.3	14.2	19.1	16.5
GM	0.3	0.6	0.8	0.6	1.5	0.5	0.7	0.4	0.5	0.6
KM	5.9	11.7	7.4	8.3	6.4	6.2	7.5	4.6	5.2	7.3
SM	27.4	30.0	26.2	29.2	23.8	25.6	21.9	19.2	22.2	25.8
TC	32.6	29.2	27.5	25.4	22.6	26.1	21.9	18.4	21.1	25.9
ST	4.4	6.7	8.1	6.3	3.4	9.0	4.8	2.9	8.8	6.1
CP	2.3	6.4	5.3	6.0	5.3	5.2	5.5	4.2	6.7	5.1
CTX	0.3	2.5	3.3	3.2	1.5	0.9	2.1	1.3	1.5	1.9
CAZ	0.3	2.2	1.8	1.9	0.8	0.9	1.4	0.8	1.0	1.3
CFX	0.0	1.4	0.5	0.6	0.0	0.9	1.4	0.8	0.5	0.6
FOM	0.0	0.3	0.3	0.3	0.4	0.5	0.0	0.0	0.0	0.2
NA	7.0	8.1	8.9	5.7	4.2	5.2	5.5	13.4	17.5	8.2
CPFX	0.3	0.8	1.8	0.3	0.4	0.0	1.4	0.8	0.0	0.5
NFLX	0.3	0.8	0.5	0.0	0.8	0.0	0.0	0.8	0.0	0.4
AMK	0.0	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.5	0.0	0.0	0.0	0.0
Number resistant to one or more antimicrobials	164	161	147	125	89	83	46	73	85	972
Proportion resistant to one or more antimicrobials	42.4	44.7	37.4	39.7	33.6	39.3	31.5	30.5	43.8	38.7

Table 21. Resistance rates of food-derived non-typhoidal *Salmonella* spp.* (2015-2023) (%)

	2015 (n=156)	2016 (n=110)	2017 (n=86)	2018 (n=108)	2019 (n=126)	2020 (n=129)	2021 (n=140)	2022 (n=132)	2023 (n=186)	SUM (n=1173)
ABPC	17.9	13.6	11.6	12.0	11.1	12.4	5.0	2.3	6.5	10.1
GM	0.0	0.9	1.2	0.0	0.0	0.0	0.7	0.0	0.5	0.3
KM	48.1	47.3	45.3	50.0	57.1	65.9	62.9	59.1	67.7	57.0
SM	82.7	70.9	69.8	77.8	64.3	70.5	71.4	81.1	69.9	73.3
TC	85.9	76.4	73.3	78.7	70.6	82.9	80.7	81.8	74.7	78.6
ST	19.9	16.4	12.8	38.0	25.4	24.8	14.3	22.0	47.3	25.7
CP	7.1	10.0	2.3	8.3	4.0	7.0	4.3	4.5	5.9	6.0
CTX	5.1	5.5	8.1	6.5	6.3	4.7	1.4	0.0	3.2	4.2
CAZ	4.5	6.4	8.1	6.5	4.8	3.9	0.0	0.0	2.7	3.7
CFX	2.6	3.6	8.1	4.6	5.6	5.4	1.4	0.0	2.2	3.3
FOM	0.0	0.9	1.2	0.0	0.0	0.0	0.0	0.0	0.5	0.2
NA	18.6	18.2	14.0	16.7	27.0	23.3	20.0	22.0	15.1	19.4
CPFX	0.0	0.9	1.2	0.0	0.0	0.0	0.0	0.0	0.5	0.3
NFLX	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.5	0.1
AMK	0.0	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Number resistant to one or more antimicrobials	143	96	77	98	113	124	121	120	166	1058
Proportion resistant to one or more antimicrobials	91.7	87.3	89.5	90.7	89.7	96.1	86.4	90.9	89.2	90.2

Table 22. Resistance rates of food-derived *S*. Infantis (2015-2023) (%)

	2015 (n=65)	2016 (n=33)	2017 (n=19)	2018 (n=27)	2019 (n=24)	2020 (n=8)	2021 (n=20)	2022 (n=10)	2023 (n=13)	SUM (n=219)
ABPC	10.8	12.1	5.3	14.8	8.3	37.5	10.0	0.0	30.8	12.3
GM	0.0	3.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.5
KM	46.2	42.4	15.8	33.3	37.5	62.5	35.0	60.0	23.1	39.3
SM	81.5	72.7	68.4	85.2	58.3	50.0	60.0	100.0	46.2	72.6
TC	89.2	81.8	68.4	85.2	58.3	37.5	70.0	100.0	53.8	77.2
ST	18.5	30.3	0.0	44.4	12.5	0.0	30.0	30.0	38.5	23.3
CP	3.1	3.0	0.0	0.0	0.0	12.5	5.0	0.0	0.0	2.3
CTX	4.6	6.1	5.3	11.1	8.3	12.5	0.0	0.0	23.1	6.8
CAZ	3.1	9.1	5.3	11.1	0.0	12.5	0.0	0.0	15.4	5.5
CFX	4.6	9.1	5.3	14.8	8.3	25.0	5.0	0.0	23.1	8.7
FOM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NA	3.1	9.1	0.0	3.7	16.7	0.0	15.0	0.0	0.0	5.9
CPFX	0.0	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 23. Resistance rates of food-derived *S*. Schwarzengrund (2015-2023) (%)

	2015 (n=47)	2016 (n=38)	2017 (n=45)	2018 (n=51)	2019 (n=66)	2020 (n=95)	2021 (n=107)	2022 (n=94)	2023 (n=147)	SUM (n=690)
ABPC	17.0	5.3	0.0	7.8	3.0	5.3	1.9	0.0	2.7	3.9
GM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
KM	85.1	86.8	77.8	80.4	92.4	73.7	72.0	71.3	79.6	78.4
SM	93.6	78.9	82.2	76.5	74.2	80.0	73.8	80.9	72.1	77.7
TC	95.7	84.2	80.0	86.3	81.8	93.7	83.2	85.1	78.2	84.6
ST	36.2	18.4	24.4	56.9	43.9	30.5	12.1	21.3	49.0	32.9
CP	19.1	13.2	4.4	9.8	6.1	5.3	4.7	6.4	4.8	7.0
CTX	0.0	0.0	2.2	0.0	0.0	1.1	0.9	0.0	0.7	0.4
CAZ	0.0	0.0	2.2	0.0	0.0	0.0	0.0	0.0	0.7	0.1
CFX	0.0	0.0	2.2	0.0	0.0	1.1	0.0	0.0	0.0	0.1
FOM	0.0	2.6	2.2	0.0	0.0	0.0	0.0	0.0	0.0	0.1
NA	25.5	21.1	6.7	23.5	27.3	20.0	18.7	22.3	13.6	19.3
CPFX	0.0	2.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1
NFLX	0.0	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0

Table 24. Resistance rates of human-derived *S*. Infantis (2015-2023) (%)

	2015 (n=34)	2016 (n=48)	2017 (n=47)	2018 (n=22)	2019 (n=16)	2020 (n=19)	2021 (n=9)	2022 (n=5)	2023 (n=10)	SUM (n=210)
ABPC	0.0	2.1	0.0	9.1	6.3	5.3	0.0	0.0	0.0	2.4
GM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
KM	20.6	14.6	6.4	22.7	12.5	5.3	11.1	0.0	0.0	12.4
SM	29.4	33.3	19.1	50.0	31.3	26.3	22.2	0.0	10.0	28.1
TC	47.1	33.3	21.3	54.5	37.5	47.4	22.2	20.0	0.0	34.3
ST	14.7	14.6	2.1	18.2	0.0	21.1	0.0	0.0	20.0	11.0
CP	0.0	0.0	0.0	9.1	6.3	5.3	0.0	0.0	0.0 0.0	1.9
CTX	0.0	0.0	0.0	4.5	6.3	5.3	0.0	0.0	0.0	1.4
CAZ	0.0	0.0	0.0	0.0	0.0	5.3	0.0	0.0	0.0	0.5
CFX	0.0	2.1	0.0	0.0	0.0	5.3	0.0	0.0	0.0	1.0
FOM	0.0	0.0	0.0	0.0	6.3	0.0	0.0	0.0	0.0	0.5
NA	8.8	4.2	8.5	0.0	12.5	5.3	11.1	0.0	0.0	6.2
CPFX	0.0	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 25. Resistance rates of human-derived *S*. Enteritidis (2015-2023) (%)

	2015 (n=39)	2016 (n=41)	2017 (n=47)	2018 (n=43)	2019 (n=37)	2020 (n=35)	2021 (n=20)	2022 (n=47)	2023 (n=43)	SUM (n=352)
ABPC	5.1	19.5	4.3	7.0	5.4	0.0	0.0	23.4	2.3	8.2
GM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
KM	2.6	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.6
SM	12.8	12.2	10.6	14.0	5.4	2.9	0.0	23.4	0.0	9.9
TC	10.3	2.4	4.3	9.3	5.4	2.9	0.0	6.4	0.0	4.8
ST	5.1	0.0	0.0	0.0	0.0	5.7	0.0	0.0	4.7	1.7
CP	2.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3
CTX	0.0	2.4	0.0	0.0	0.0	0.0	5.0	0.0	0.0	0.3
CAZ	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3
CFX	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
FOM	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.0
NA	10.3	26.8	12.8	25.6	10.8	14.3	15.0	44.7	55.8	25.3
CPFX	0.0	0.0	0.0	0.0	0.0	0.0	5.0	0.0	0.0	0.0
NFLX	0.0	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0

Table 26. Resistance rates of human-derived *S*. Saintpaul (2015-2023) (%)

	2015 (n=27)	2016 (n=26)	2017 (n=41)	2018 (n=10)	2019 (n=8)	2020 (n=12)	2021 (n=7)	2022 (n=4)	2023 (n=2)	SUM (n=137)
ABPC	7.4	7.7	14.6	10.0	0.0	8.3	0.0	0.0	0.0	8.8
GM	0.0	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.7
KM	0.0	3.8	4.9	0.0	0.0	0.0	0.0	0.0	0.0	2.2
SM	3.7	3.8	12.2	0.0	0.0	8.3	0.0	0.0	0.0	5.8
TC	40.7	15.4	22.0	10.0	12.5	25.0	14.3	25.0	0.0	22.6
ST	0.0	11.5	17.1	10.0	12.5	8.3	0.0	0.0	0.0	9.5
CP	3.7	0.0	14.6	0.0	12.5	0.0	0.0	0.0	0.0	5.8
CTX	0.0	0.0	12.2	0.0	0.0	0.0	0.0	0.0	0.0	3.6
CAZ	0.0	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.7
CFX	0.0	3.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.7
FOM	0.0	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.7
NA	7.4	3.8	19.5	0.0	0.0	0.0	0.0	25.0	0.0	8.8
CPFX	3.7	0.0	9.8	0.0	0.0	0.0	0.0	0.0	0.0	1.5
NFLX	3.7	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0
IPM	0.0	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0

Table 27. Resistance rates of human-derived *S*. 4: i:- (2015-2023) (%)

	2015 (n=60)	2016 (n=37)	2017 (n=36)	2018 (n=36)	2019 (n=23)	2020 (n=24)	2021 (n=17)	2022 (n=21)	2023 (n=36)	SUM (n=290)
ABPC	71.7	64.9	77.8	86.1	82.6	79.2	76.5	71.4	66.7	74.5
GM	1.7	0.0	2.8	0.0	0.0	0.0	0.0	0.0	0.0	0.7
KM	3.3	5.4	2.8	8.3	4.3	4.2	11.8	0.0	5.6	4.8
SM	73.3	70.3	80.6	91.7	82.6	70.8	70.6	66.7	69.4	75.5
TC	85.0	62.2	77.8	80.6	65.2	50.0	76.5	66.7	61.1	71.4
ST	5.0	10.8	5.6	8.3	8.7	0.0	5.9	9.5	13.9	7.6
CP	3.3	10.8	8.3	13.9	8.7	4.2	11.8	9.5	13.9	9.0
CTX	0.0	2.7	2.8	2.8	0.0	0.0	0.0	0.0	0.0	1.0
CAZ	0.0	2.7	2.8	0.0	0.0	0.0	0.0	0.0	0.0	0.7
CFX	0.0	0.0	2.8	0.0	0.0	0.0	0.0	0.0	0.0	0.3
FOM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NA	1.7	2.7	5.6	0.0	0.0	0.0	0.0	0.0	8.3	2.4
CPFX	0.0	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0
AMK	0.0	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 28. Resistance rates of human-derived *S*. Thompson (2015-2023) (%)

	2015 (n=28)	2016 (n=28)	2017 (n=29)	2018 (n=29)	2019 (n=27)	2020 (n=11)	2021 (n=14)	2022 (n=21)	2023 (n=17)	SUM (n=204)
ABPC	0.0	10.7	0.0	0.0	7.4	0.0	0.0	0.0	0.0	2.5
GM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
KM	7.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
SM	7.1	7.1	3.4	6.9	0.0	0.0	7.1	0.0	0.0	3.9
TC	3.6	7.1	6.9	0.0	0.0	0.0	0.0	0.0	0.0	2.5
ST	0.0	7.1	0.0	0.0	0.0	0.0	0.0	0.0	11.8	2.0
CP	0.0	7.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
CTX	0.0	10.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.5
CAZ	0.0	7.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
CFX	0.0	7.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
FOM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NA	0.0	0.0	0.0	3.4	0.0	0.0	0.0	0.0	0.0	0.5
CPFX	0.0	7.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
NFLX	0.0	7.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
AMK	0.0	0.0	0.0	0.0	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	0.0	0.0	0.0	0.0
MEPM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 29. Resistance rates of *S.* Infantis, *S.* Schwarzengrund, and *S.* Manhattan detected in humans and food (2015-2023) (%)

	Infantis		Schwarzengrund		Manhattan	
	Human (n=210)	Food (n=219)	Human (n=139)	Food (n=690)	Human (n=54)	Food (n=85)
ABPC	2.4	12.3	2.9	3.9	1.9	14.1
GM	0.0	0.5	0.7	0.0	0.0	0.0
KM	12.4	39.3	61.9	78.4	0.0	0.0
SM	28.1	72.6	64.7	77.7	90.7	96.5
TC	34.3	77.2	64.7	84.6	87.0	80.0
ST	11.0	23.3	23.0	32.9	0.0	7.1
CP	1.9	2.3	3.6	7.0	0.0	0.0
CTX	1.4	6.8	2.9	0.4	0.0	8.2
CAZ	0.5	5.5	2.2	0.1	0.0	8.2
CFX	1.0	8.7	0.0	0.1	0.0	1.2
FOM	0.5	0.0	0.0	0.1	0.0	0.0
NA	6.2	5.9	14.4	19.3	9.3	17.6
CPFX	0.0	0.0	0.0	0.1	0.0	1.2
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, 1,167, and 1,023, 825, 698, 950 and 1,134 *Neisseria gonorrhoeae* strains that were respectively isolated between 2015 and 2023 were tested for antimicrobial susceptibility (based on EUCAST breakpoints; Table 30). Ceftriaxone (CTRX)-resistant strains respectively accounted for 6.2%, 4.3%, 4.3%, 3.5%, 5.4%, 2.7%, 0.7, 1.9% and 1.8% since 2015. Strains assessed as resistant based on the CLSI Criteria (MIC ≥ 0.5 μg/mL) accounted for 0.6%, 0.4%, 0.5%, 0.3%, 0.4%, 0%, 0%, 0.1% and 0.1% since 2015. No spectinomycin (SPCM)-resistant strains were present. On the other hand, the resistance rate of azithromycin (AZM) was 13.0% in 2015 and shifted between 33% and 43.9% from 2016 to 2020, with 11.6%, 18.4% and 34.0% in 2021, 2022 and 2023, respectively.

The CLSI Criteria do not provide a resistance breakpoint for AZM, but, using the azithromycin (AZM) 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." When we investigated the resistance rate (see Reference (8)), albeit as a reference, we found that, between 2015 and 2023, 3.2%, 4.0%, 4.0%, 6.3%, 7.5%, 7.0%, 6.7, 9.8% and 13.1% of strains, respectively, had a MIC of 2 μg/mL or higher, indicating an upward trend. According to clinical assessments in Japan, strains indicating an AZM 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 11.0%, 9.3%, 11.2%, 15.9%, 14.9%, 14.3%, 11.5%, 18.2% and 34.0% of strains respectively between 2015 and 2023. Among the other three antimicrobials, the proportion of cefixime (CFIX)- resistant strains accounted for approximately 20-40%, and that of CPFX-resistant strains accounted for approximately 60-80%. Benzylpenicillin (PCG) would not have a therapeutic effect on more than 80% of strains.

Table 30. Resistance rates of *Neisseria gonorrhoeae* (%)

	2015 (618 strains)	2016 (675 strains)	2017 (982 strains)	2018 (1167 strains)	2019 (1023 strains)	2020 (825 strains)	2021 (698 strains)	2022 (950 strains)	2023 (1134 strains)
PCG*	38.4 (96.6)	36.3 (96.9)	37.8 (99.0)	31.7 (82.5)	35.8 (88.5)	37.1 (98.9)	23.5 (92.7)	22.3 (98.7)	39.8 (99.4)
CFIX	36.2	43.2	31.0	28.4	33.4	33.1	21.9	25.9	22.2
CTRX	6.2	4.3	4.3	3.5	5.4	2.7	0.7	1.9	1.8
SPCM	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
AZM	13.0	33.5	42.6	43.9	40.1	40.2	11.6	18.4	34.0
CPFX	79.5	78.0	75.8	66.9	64.6	71.2	75.6	83.4	80.4

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), PCG (> 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 14-46 *Salmonella* Typhi strains that were isolated between 2015 and 2023 were tested for antimicrobial susceptibility (Excluding the year 2021, which is estimated to have been significantly affected by the novel coronavirus pandemic. The same applies to *Salmonella* Paratyphi A and *Shigella* spp.). Ciprofloxacin (CPFX)-non-susceptible strains accounted for 60.7-83.9%, while strains with advanced resistance (MIC ≥ 4 μg/mL) to ciprofloxacin accounted for 5.9-42.9%. During this period, 23 strains of multidrug-resistant *Salmonella* Typhi that indicated resistance to ampicillin (ABPC), chloramphenicol (CP) and sulfamethoxazole-trimethoprim (ST) were isolated, along with nine strains of cefotaxime（CTX)-resistant *Salmonella* Typhi.

The 5-30 *S.* Paratyphi A strains isolated between 2015 and 2023 were tested for antimicrobial susceptibility. CPFX non-susceptible strains accounted for 76.9-100%. No strains with advanced CPFX or CTX resistance were isolated among the *Salmonella* Paratyphi A.

The 14-156 *Shigella* spp. strains that were isolated between 2015 and 2023 were tested for antimicrobial susceptibility. ST-resistant strains accounted for 71.4-91.9%; CPFX-resistant strains for 7.1-45.7%; and CTX-resistant strains for 0.0-27.0%.

Table 31. Resistance rates of *Salmonella* Typhi (%)

	2015 (32 strains)	2016 (46 strains)	2017 (31 strains)	2018 (34 strains)	2019 (28 strains)	2020 (20 strains)	2021 (3 strains)	2022 (14 strains)	2023 (40 strains)
ABPC	5.7	2.2	12.9	2.9	10.7	20.0	0.0	14.3	20.0
CP	5.7	2.2	12.9	5.9	10.7	25.0	0.0	14.3	15.0
ST	5.7	2.2	12.9	5.9	10.7	25.0	0.0	21.4	20.0
NA	68.8	63.0	83.9	61.7	57.1	55.0	66.7	57.1	82.5
CPFX	68.8(12.5*)	63.0(23.9*)	83.9(16.1*)	61.7(5.9*)	60.7(10.7*)	65.0(25.0*)	100.0(0.0*)	64.3 (42.9)	82.5 (22.5)
CTX	0.0	0.0	0.0	2.9	3.6	15.0	0.0	0.0	5.0

*Advanced resistance to fluoroquinolone

Table 32. Resistance rates of *Salmonella* Paratyphi A (%)

	2015 (30 strains)	2016 (20 strains)	2017 (13 strains)	2018 (21 strains)	2019 (16 strains)	2020 (5 strains)	2021 (0 strains)	2022 (10 strains)	2023 (4 strains)
ABPC	0.0	0.0	0.0	0.0	0.0	0.0	-	10.0	0.0
CP	0.0	0.0	0.0	0.0	0.0	0.0	-	0.0	0.0
ST	0.0	0.0	0.0	0.0	0.0	0.0	-	0.0	0.0
NA	80.0	80.0	76.9	100.0	87.5	100.0	-	70.0	75.0
CPFX	83.3	83.3	76.9	100.0	87.5	100.0	-	100.0	100.0
CTX	0.0	0.0	0.0	0.0	0.0	0.0	-	0.0	0.0

Table 33. Resistance rates of *Shigella* spp. (%)

	2015 (105 strains)	2016 (73 strains)	2017 (91 strains)	2018 (156 strains)	2019 (91 strains)	2020 (74 strains)	2021 (2 strains)	2022 (14 strains)	2023 (32 strains)
ABPC	21.9	42.5	31.9	19.2	14.3	41.9	50.0	14.3	56.3
CP	11.4	24.7	26.4	9.0	6.6	4.1	50.0	7.1	34.4
ST	81.0	80.8	73.6	76.9	76.9	91.9	50.0	71.4	84.4
NA	63.8	52.1	52.8	45.5	33.0	83.8	50.0	7.1	34.4
CPFX	45.7	35.6	35.2	21.2	14.3	35.1	0.0	7.1	28.1
CTX	5.7	16.4	13.2	5.1	3.3	27.0	0.0	0.0	12.5

5) Candida auris

The first case of invasive *Candida auris* bloodstream infection was reported in 2022, and surveillance commenced in December 2023. In addition to collecting bacterial strains through domestic medical institutions, public health centers, and local public health institutes, bacterial strains were also obtained in the form of isolated strains from three domestic clinical laboratories.

As of December 2024, 73 cases had been confirmed, the majority of which were clade II strains derived from otorrhea. Although a few cases of colonization in the respiratory tract and wound sites were observed, no cases of invasive infections were identified.

However, a clade I strain derived from otorrhea was confirmed in one case, suggesting the need for caution regarding future isolation trends.

In terms of drug susceptibility, resistance to fluconazole was observed in nearly 20% of cases, while no resistance was detected to echinocandin or polyene antifungal agents.

6) Mycobacterium tuberculosis

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

Looking at major antituberculosis antibiotics—isoniazid (INH), rifampicin (RFP), and ethambutol (EB)—among patients with culture-positive pulmonary tuberculosis who were newly notified between 2012 and 2022, resistance to INH has been on the rise in recent years, while RFP and EB resistance rates have remained mostly at the same level. Although a rise of up to 1.1 percentage points was seen in streptomycin (SM) resistance in 2017, it has mostly remained at the same level since 2018. 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 40 to 60 (0.4-0.9%) per year, decreasing to 26 by 2022.

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

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Culture-positive patients, N	10,259	10,035	9,878	9,580	9,016	8,110	6,645	5,902	5,231	5,515
INH-resistant, n (%)*	349 (4.6)	372 (4.9)	369 (4.8)	383 (4.9)	377 (5.0)	359 (5.4)	297 (5.7)	221 (4.9)	200 (4.9)	254 (5.6)
RFP-resistant, n (%)*	76 (1.0)	77 (1.0)	74 (1.0)	80 (1.0)	87 (1.1)	65 (1.0)	60 (1.2)	56 (1.2)	41 (1.0)	52 (1.1)
INH & RFP-resistant†, n (%)*	56 (0.5)	48 (0.5)	49 (0.6)	52 (0.7)	55 (0.6)	44 (0.7)	46 (0.9)	41 (0.9)	26 (0.6)	35 (0.8)
SM-resistant, n (%)§	469 (6.2)	476 (6.3)	461 (6.0)	557 (7.1)	471 (6.3)	428 (6.5)	356 (6.9)	287 (6.4)	272 (6.7)	304 (6.7)
EB-resistant, n (%)¶	130 (1.7)	129 (1.7)	100 (1.3)	106 (1.3)	130 (1.7)	126 (1.9)	78 (1.5)	79 (1.9)	59 (1.4)	66 (1.5)

* The denominator was defined as the number of patients with recorded INH- and RFP-susceptibility testing results among all culture- positive patients: 8,046 patients in 2011, 8,347 in 2012, 7,701 in 2013, 7,645 in 2014, 7,630 in 2015, 7,732 in 2016, 7,891 in 2017, 7,570 in 2018, 6,658 in 2019, 5,209 in 2020, 4,551 in 2021, 4,086 in 2022, and 4,526 in 2023.

† INH- and RFP- resistant tuberculosis 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 in 2013, 52 in 2014, 48 in 2015, 47 in 2016, 51 in 2017, 47 in 2018, 41 in 2019, 38 in 2020, 36 in 2021, 23 in 2022 and 77 in 2023.

¶ 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 patients in 2012, 13 in 2013, 13 in 2014, 19 in 2015, 17 in 2016, 14 in 2017, 13 in 2018, 8 in 2019, 14 in 2020, 9 in 2021, 11 in 2022, and 18 in 2023).

7) *Clostridioides difficile* infection

Clostridioides difficile infection (CDI) is a spore-forming gram-positive anaerobic bacillus that colonizes the intestines of about 10% of healthy adults.[3] 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]

Existing 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 particularly high risk in ICU wards.[6] Comparison of prevalence rates among hospitals and with other countries should take into account the influence of specimen collection wards, testing methods, definition of relapse, differences in average length of hospital stay, and other factors.

Since 2019, the AMR Clinical Reference Centre (AMRCRC) has been operating the J-SIPHE, preparing annual reports, and started investigating CDI trends. The number of CDI outbreaks per 10,000 patient hospital days (n in the table is the number of facilities, and the distribution of occurrences per facility (number of occurrences/total number of patients in hospital x 10,000) is shown) showed a decreasing trend: in 2019, 1.38 (IQR: 0.56-2.43) in 276 facilities; in 2020, 1.20 (IQR: 0.45-2.13) in 347 facilities; in 2021, 0.96 (IQR: 0.32-1.97) in 470 facilities; in 2022, 0.82 (IQR: 0.14-1.66) in 1,241 facilities; in 2023, 0.72 (IQR: 0.00-1.64) in 1,796 facilities. The impact of changes in population characteristics with the increase in the number of participating facilities should be considered.

Table 35. Distribution of *Clostridioides difficile* outbreaks in hospitals (outbreaks per 10,000 patient hospital days)

	2019 (n=276)*	2020 (n=347)**	2021 (n=470) **	2022 (n=1,241)**	2023 (n=1,796)**
C. difficile (IQR)	1.38 (0.56-2.43)	1.20 (0.45-2.13)	0.96 (0.32-1.97)	0.82 (0.14-1.66)	0.72 (0.00-1.64)

n in the table indicates the number of facilities and the distribution of the number of occurrences per facility (number of occurrences/total number of patients in hospital x 10,000)

*2019 included 253 facilities for toxin testing using immunochromatography, 3 facilities for testing using NAAT, and 20 other facilities.

**2020: Only toxin is confirmed by immunochromatography and judged as CDI when positive, and the test is terminated when negative. 81 facilities in 2020, 65 in 2021, 194 in 2022, and 246 in 2023. If the test is negative, the test is terminated. 8 facilities in 2020, 2 in 2021, 5 in 2022, and 6 in 2023. Immunochromatography to confirm both GDH and toxin and determine CDI if GDH-positive and toxin-positive; if GDH-positive and toxin-negative, the test is completed without determining CDI. 115 facilities in 2020, 203 in 2021, 500 in 2022, and 793 in 2023. If both GDH and toxin are confirmed by immunochromatography and both GDH-positive and toxin-positive, the test is determined as CDI; if GDH-positive and toxin-negative, the test is determined for toxin using culture colonies and if both are negative, the test is terminated. 104 facilities in 2020, 110 in 2021, 226 in 2022, and 262 in 2023. Immunochromatography confirms both GDH and toxin and determines CDI if GDH positive and toxin positive; if GDH positive and toxin negative, determines toxin by toxin gene test in faces; if negative, test terminated. 36 facilities in 2020, 59 in 2021, 177 in 2022, and 288 in 2023. If the test is negative, the test is terminated. 3 facilities in 2020, 1 in 2021, 29 in 2022, and 41 in 2023. Others (other than above): 38 facilities in 2020, 45 in 2021, 136 in 2022, and 175 in 2023.

8) 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 10 years. In 2023 among 348,567 surgical operations undertaken at 825 institutions, SSI were reported in 14,033 cases (4.0%). The incidence of SSI, which had been declining since 2011, stabilized in 2022 but again decreased in 2023.

In the intensive care unit (ICU) division of JANIS, the incidence of ventilator-associated pneumonia has been 1.2-1.8 per 1,000 days of ICU stay over the past 10 years, with a rate of 1.4 per 1,000 days of ICU stay recorded in 2023. While the incidence of urinary tract infection was around 0.5-0.8 per 1,000 days of ICU stay, the incidence of catheter related bloodstream infection was around 0.6-0.8 per 1,000 days of ICU stay. Both of these rates have been fluctuating slightly. JANIS monitors cases of infections that occurred between 48 hours after admission to ICU and discharge from ICU.

i. Surgical site infection

Table 36. The trend (%) of reported SSI cases

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Total SSI cases per total surgical operations (%)*	6.0	5.8	5.7	5.4	5.1	4.6	4.4	4.2	4.2	4.0
Participated medical institutions	552	671	730	772	802	785	786	768	814	825
Total surgical operations	207,244	251,832	274,132	292,031	305,960	307,052	290,795	291,958	313,110	348,567
Total SSI cases	12,508	14,701	15,674	15,889	15,566	14,226	12,696	12,227	12,998	14,033

*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) x100

Prepared from annual reports of the SSI division, JANIS.[7]

ii. Infections at Intensive Care Unit (ICU)

Table 37. Incidence rates of infection at ICU

		2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Ventilator-associated pneumonia	Total infection incidence rate*	1.4	1.5	1.5	1.3	1.3	1.3	1.2	1.8	1.4	1.4
	Total infections at monitored medical institutions	395	522	499	405	409	387	333	508	421	417
Urinary tract infection	Total infection incidence rate*	0.5	0.5	0.6	0.7	0.8	0.6	0.7	0.5	0.6	0.7
	Total infections at monitored medical institutions	148	190	219	213	244	174	183	157	184	211
Catheter-related bloodstream infection	Total infection incidence rate*	0.7	0.7	0.8	0.7	0.6	0.6	0.7	0.7	0.8	0.7
	Total infections at monitored medical institutions	205	240	263	213	190	177	193	214	229	224

*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) x1,000

Prepared from annual reports of the ICU division, JANIS.[8]

9) Survey of infection treatment and control and the disease burden at hospitals

Source: J-SIPHE, AMR Clinical Reference Center (AMRCRC)

The AMR Clinical Reference Center (AMRCRC) operates the J-SIPHE system, which can be used for AMR measures at hospitals as well as for promoting regional cooperation. The J-SIPHE 2023 Annual Report covers a total of 2,534 participating medical institutions (1,057 institutions calculating Infection Prevention and Control Premium 1, 668 calculating Premium 2, 751 calculating Premium 3, and 58 calculating no premium). Registration information was optional for each participating facility. The median number of blood cultures submitted at hospitals (n=1,520) was 18.3/1,000 patient days (IQR: 4.7-35.3), while the median rate of multiple sets (n=1,407, counting facilities submitting 20 or more) for patients aged 15 and older was 95.7 %（IQR: 90.6-97.8). The median positive rate (n=1,407, counting facilities submitting 20 or more) was 16.3% (IRQ: 13.1-21.6).

In 2023, the number of outbreaks of bacteria detected in blood samples per 10,000 patient days was the highest for *Escherichia coli* with a median of 2.0 (IQR: 0.9-3.2), followed by *Staphylococcus aureus* with 1.4 (IQR: 0.5-2.2), *Klebsiella pneumoniae* at 0.7 (IQR: 0.2-1.3), showing a slight decrease compared to the previous year. On the other hand, the incidences of drug-resistant *S. aureus* and *E. coli* have declined, while the incidence of drug-resistant *Klebsiella pneumoniae* has remained unchanged.

The overall hand hygiene compliance rate (n=126) was 66.5%, while the breakdown of the figures by ward function showed that wards categorized in "others" (n=68) had a higher rate of compliance, at 69.1% compared to the other wards.

The amount of hand sanitizer consumed per 1,000 patient days for the period 2019–2021 represents a combined figure of both usage and dispensing, whereas from 2022 onward, due to differing trends, the dispensing quantity is treated separately, and only the usage amount is presented here. In 2023, the total usage across all units (n=1,055) was 10.4 L (IQR: 6.4-15.5), with the critical care wards (n=382) using 42.1 L (IQR: 26.7-66.1), which was higher compared to general wards. The use of hand hygiene products had been on an increasing trend from 2019 to 2022; however, it then exhibited a slight downward trend in 2023.

The estimated number of deaths in patients with bloodstream infections was also published after a study of JANIS data carried out with a Health, Labour and Welfare Policy Research Grants. The number of deaths due to MRSA has shown declining or unchanged trends, while the number of deaths due to fluoroquinolone-resistant *E. coli* has remained on the rise and was estimated at 3,915 in 2017. Until 2022, the number of deaths attributable to MRSA had shown a decreasing trend, followed by stabilization. The number of deaths associated with fluoroquinolone-resistant *E. coli* had been increasing annually, but in recent years, it has leveled off. The number of deaths associated with *K. pneumoniae* or *Pseudomonas aeruginosa* remained stable; however, the number of deaths attributable to *Streptococcus pneumoniae* significantly decreased from 2020 to 2022, in contrast to previous years.

DALYs, an indicator of burden of disease that includes losses due to factors other than death (e.g. sequelae), were published. Some of the parameters used in the estimation were borrowed from previous studies overseas.

Table 38. Basic information on medical institutions participating in J-SIPHE for annual report

	2019	2020	2021	2022	2023
Number of participating facilities	581	778	818	1,876	2,534
(Premium 1)	(449)	(539)	(547)	(868)	(1,057)
(Premium 2)	(127)	(232)	(263)	(493)	(668)
(Premium 3)	-	-	-	(487)	(751)
(without Premium)	(5)	(7)	(8)	(28)	(58)
Number of beds, median (IQR)	340.5(221.3-525.3)	308.1(196.0-498.3)	301 (184-480)	214 (129.8-382.2)	199 (120.8-356.2)
Average hospital days, median (IQR)	13.6(11.7-17.1)	14.4(12.0-19.0)	14.0 (11.8-19.7)	16.9 (12.3-34.7)	19.7 (12.7-43.1)

IQR (Interquartile range)

*Premium 3 was newly established in April 2022.

Table 39. Distribution of multiple sets of blood culture at hospitals (%)

	2019	2020	2021	2022	2023
All patients, median (IQR)	90.6(83.6-95.4) (n=276)	92.8(87.9-96.1) (n=326)	93.1(88.0-96.7) (n=401)	93.1 (87.1-96.4) (n=960)	92.8(86.1-96.6) (n=1,408)
Patients aged 15 years and older, median (IQR)	95.0(90.8-97.2) (n=276)	95.7(92.3-97.5) (n=326)	96.0(92.8-97.7) (n=401)	95.6 (91.2-97.6) (n=960)	95.7(90.6-97.8) (n=1,407)
Patients aged under 15 years, median (IQR)	4.9(0.9-16.8) (n=178)	5.2(0.0-21.7) (n=211)	7.9(1.4-26.7) (n=261)	7.6 (0.7-22.5) (n=510)	6.2(2.0-18.4) (n=559)

*Share of submissions of 2 sets or more of blood culture among blood culture submissions

2020: Data from facilities with 20 or more blood culture submissions during the period of interest.

(n in the table indicates the number of facilities, the distribution of blood culture set rates per facility)

Table 40. Distribution of occurrences of bloodstream infections at hospitals (total number per 10,000 patient days)

	Median (IQR)*				
	2019 (n=253)	2020 (n=329)	2021 (n=329)	2022 (n=1.030)	2023 (n=1,520)
S. aureus	1.61 (0.86-2.17)	1.38 (0.75-2.21)	1.53 (0.80-2.27)	1.50 (0.63-2.27)	1.38 (0.48-2.21)
Enterococcus faecalis)	0.37 (0.12-0.65)	0.38 (0.07-0.65)	0.39 (0.12-0.67)	0.31 (0.00-0.59)	0.29 (0.00-0.58)
Escherichia coli	2.20 (1.40-3.37)	2.13 (1.23-3.26)	2.21 (1.42-3.25)	2.07 (1.01-3.14)	2.00 (0.89-3.16)
Klebsiella pneumoniae	0.83 (0.43-1.29)	0.77 (0.32-1.26)	0.83 (0.36-1.29)	0.72 (0.22-1.27)	0.69 (0.20-1.31)
Klebsiella aerogenes†	-	-	-	0.00 (0.00-0.20)	0.00 (0.00-0.21)
Enterobacter spp.	0.32 (0.08-0.61)	0.31 (0.00-0.67)	0.34 (0.03-0.67)	-	-
Enterobacter cloacae complex†	-	-	-	0.15 (0.00-0.40)	0.10 (0.00-0.37)
Streptococcus pneumoniae	0.00 (0.00-0.15)	0.00 (0.00-0.08)	0.00 (0.00-0.07)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
MRSA	0.59 (0.26-0.94)	0.56 (0.24-0.89)	0.56 (0.26-0.96)	0.56 (0.15-0.97)	0.50 (0.14-0.95)
3CREC	0.42 (0.16-0.84)	0.50 (0.14-0.83)	0.49 (0.21-0.85)	0.46 (0.00-0.81)	0.00 (0.00-0.84)
FQREC	0.64 (0.27-1.18)	0.66 (0.28-1.11)	0.69 (0.35-1.13)	0.64 (0.18-1.07)	0.55 (0.09-1.06)
3CRKP	0.00 (0.00-0.09)	0.00 (0.00-0.12)	0.00 (0.00-0.11)	0.00 (0.00-0.12)	0.00 (0.00-0.15)
PRSP	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)

MRSA; methicillin resistant S. aureus, 3 CREC; 3rd generation Cephalosporine resistant *E. coli*, FQREC; fluoroquinolone resistant *E coli*, 3CRKP; 3rd generation Cephalosporine resistant *K. pneumoniae*, PRSP; penicillin resistant *S. pneumoniae*

* The tabulation includes MRSA for S. aureus, FQREC or 3CREC for *E. coli*, 3CRKP for *Klebsiella pneumoniae*, and PRSP for S. pneumoniae.

† *Enterobacter* spp. are counted by dividing them into *Enterobacter cloacae* complex and *Klebsiella aerogenes* starting in January 2022.

(n in the table indicates the maximum number of facilities that participated in the tally by bacterium, the distribution of bloodstream infections per facility)

Table 41. Distribution of hand hygiene compliance rate at hospitals (%)

	Median (IQR)				
	2019	2020	2021	2022	2023
Overall	57.5(45.0-68.3) (n=45)	62.6(50.3-75.1) (n=47)	68.4(50.9-78.0) (n=50)	67.0（49.0-78.9) (n=110)	66.5(49.9-77.1) (n=126)
Critical Care Area	67.0(55.8-75.2) (n=22)	68.9(52.9-78.3) (n=22)	75.6(51.6-83.4) (n=26)	72.2（57.8-81.6） (n=45)	67.8(57.5-77.4) (n=49)
General wards	56.9(42.6-68.0) (n=44)	62.8(48.4-75.1) (n=41)	67.9(48.4-78.6) (n=48)	67.6（47.2-77.2） (n=93)	66.2(49.5-76.7) (n=111)
Other wards	59.1(39.0-75.2) (n=22)	68.3(42.6-82.6) (n=26)	64.0(52.0-75.4) (n=26)	65.0（49.8-79.7） (n=55)	69.1(53.5-82.5) (n=68)

(n in the table indicates the number of facilities, the distribution of hygiene compliance rate per facility)

Table 42. Distribution of total amount of hand sanitizer consumed at hospitals (L/1,000 patient days)

		Median (IQR)				
		2019	2020	2021	2022	2023
Overall		7.41 (4.21-11.42) (n=198)	9.63 (5.69-14.48) (n=245)	10.39 (6.66-16.50) (n=321)	11.31 (7.05-17.19) (n=677)	10.41(6.36-15.48) (n=1,055)
Category of addition	Premium 1			12.06(7.85-18.91) (n=239)	14.04 (9.68-20.58) (n=371)	13.26(9.35-19.30) (n=483)
	Premium 2			6.32(3.71-10.51) (n=79)	8.27 (5.52-12.34) (n=214)	8.81(5.31-12.99) (n=269)
	Premium 3				8.06 (4.55-12.80) (n=185)	7.35(4.60-11.10) (n=314)
Ward function	Critical Care Area	33.61 (18.51-58.52) (n=111)	41.15 (28.67-76.19) (n=120)	52.43 (28.85-86.57) (n=159)	46.55 (28.40-73.69) (n=272)	42.10(26.73-66.10) (n=382)
	General wards	7.35 (4.71-12.16) (n=184)	9.12 (6.36-14.83) (n=219)	9.85 (6.70-15.58) (n=290)	11.20 (7.46-16.42) (n=576)	10.17(6.66-15.01) (n=879)
	Other wards	6.31 (3.98-12.84) (n=125)	8.95 (4.91-15.57) (n=168)	10.12 (5.71-17.53) (n=227)	10.50 (6.23-17.40) (n=496)	9.30(5.69-15.44) (n=784)

(n in the table indicates the number of facilities, the distribution of hand sanitizer consumed per facility)

Table 43. Estimated number of deaths from bloodstream infection (patients)

	Patients (95% CI) *								
	2015	2016	2017	2018	2019	2020	2021	2022	2023
*S. aureus**	7,372 (5,721-9,047)	7,935 (6,172-9,725)	8,070 (6,271-9,885)	8,187 (6,361-10,034)	8,732 (6,793-10,693)	7,510 (5,399-9,624)	8,039 (5,776-10,316)	9,528 (7,387-11,620)	10,439 (8,097-12,770)
MRSA	3,608 (2,357-4,873)	3,758 (2,453-5,078)	3,716 (2,428-5,029)	3,690 (2,411-4,979)	3,966 (2,590-5,363)	3,633 (2,516-4,901)	3,917 (2,715-5,288)	3,938 (2,602-5,386)	4,505 (2,952-6,266)
*S. pneumoniae**	480 (160-879)	430 (144-787)	447 (149-818)	463 (154-846)	410 (137-750)	247 (82-453)	204 (68-374)	198 (66-363)	220 (73-370)
PRSP	126 (42-231)	108 (36-198)	94 (31-173)	113 (38-206)	106 (35-194)	77 (26-141)	74 (25-136)	60 (20-101]	99 (33-168)
*E. coli**	7,130 (5,701-8,643)	7,636 (6,111-9,251)	8,001 (6,404-9,688)	8,154 (6,523-9,890)	8,666 (6,921-10,506)	8,527 (6,829-10,240)	8,713 (6,983-10,481)	8,542 (6,843-10,311)	9,992 (7,937-12,006)
FQREC	2,889 (2,715-3,071)	3,310 (3,113-3,528)	3,376 (3,173-3,591)	3,753 (3,534-3,994)	4,201 (3,955-4,467)	4,118 (3,876-4,394)	4,170 (3,920-4,445)	4,172 (3,930-4,434)	4,827 (4,530-5,145)
3CREC	2,146 (1,155-3,300)	2,252 (1,212-3,462)	2,377 (1,280-3,660)	2,647 (1,425-4,074)	3,009 (1,620-4,625)	2,890 (1,559-4245)	3,028 (1,635-4,445)	2,970 (1,601-4,565)	3,810 (2,048-5,590)
*Klebsiella pneumoniae**	4,167 (3,171-5,276)	4,218 (3,207-5,318)	4,311 (3,275-5,437)	4,561 (3,466-5,755)	4,506 (3,424-5,704)	4,484 (3,405-5,668)	4,529 (3,444-5,727)	4,659 (3,453-5,840)	5,640 (4,268-7,188)
3CRKP	474 (344-608)	492 (359-633)	461 (334-592)	533 (386-685)	530 (385-680)	597 (432-761)	682 (495-870)	762 (572-974)	1,120 (838-1,427)
*Pseudomonas aeruginosa**	2,036 (1,320-2,855)	2,109 (1,369-2,957)	2,074 (1,345-2,909)	2,188 (1,418-3,069)	2,243 (1,455-3,148)	2,139 (1,385-2,996)	2,344 (1,516-3,282)	2,282 (1,373-3,197)	2,598 (1,563-3,637)
CRPA	343 (296-388)	369 (318-418)	303 (263-343)	318 (275-360)	324 (280-367)	344 (297-388)	399 (345-448)	323 (281-366)	294 (257-334)

MRSA; methicillin resistant S. *aureus*, PRSP; penicillin resistant *S. pneumoniae*, FQREC; fluoroquinolone resistant *E. Coli*, 3CREC; 3rd generation Cephalosporine resistant *E. coli*, 3CRKP; 3rd generation Cephalosporine resistant *K. pneumoniae*, CRPA; Carbapenem resistant *P. aeruginosa*,

†The method for calculating the estimated number of deaths followed that reported by Tsuzuki et al (Tsuzuki S et al. IJID 2021. DOI: 10.1016/j.ijid.2021.05.018). The total number of bacteremia cases was estimated from the number of beds at participating facilities and the actual number of beds in each year based on JANIS data. The estimated number of deaths was then multiplied by the mortality rate per microorganism obtained from previous studies. Mortality rates due to bacteremia per microorganism are in the appendix to the above literature (https://www.ijidonline.com/article/S1201-9712(21)00419-7/fulltext#supplementaryMaterial).

**S. aureus* includes MRSA, *S. pneumoniae* includes PRSP, *E. coli* includes FQREC or 3CREC (FQREC and 3CREC are calculated independently for bacteria that are resistant to each drug), *K. pneumoniae* includes 3CRKP, and *P. aeruginosa* includes CRPA. Figures in parentheses represent 95% confidence intervals.

10) Survey of infections and antimicrobial use at facilities for the elderly

Source: AMRCRC

Funded by a Health and Labor Sciences Research Grant and Health, Labour and Welfare Policy Research Grants, the AMRCRC conducted a survey of healthcare- associated infections and antimicrobial use at facilities for the elderly. [9-11]

i Medical long-term care wards/hospitals

A Point Prevalence Survey (PPS) was conducted by randomly selecting 1,175 facilities with medical long-term care wards from members of the Japan Association of Medical and Care Facilities (January 2020 survey). Eighty facilities (7.8% response rate) responded. The median patient age was 84.0 years (78, 90). The median age of male patients was 82.0 years (75, 87.8) and that of female patients was 87.0 years (80.8, 92). The top infectious foci were ”pneumonia” in 199 patients (39.5%), ”urinary tract infection” in 135 patients (26.8%), and ”bronchitis” in 19 patients (3.8%). The main antimicrobial agents used were injectable third generation cephalosporins, penicillin beta-lactamase inhibitor combinations, and carbapenems.

ii Long-term care facilities for the elderly

The center randomly selected facilities from among the members of the Japan Association of Geriatric Health Services Facilities and conducted a PPS. In the 1st PPS (conducted in February 2019, 1,500 facilities), responses were received from 134 facilities (a response rate of 8.9%), in the 2nd PPS (conducted in February 2022, 1,000 facilities), responses were received from 100 facilities (a response rate of 10.0%)

The antimicrobial use rate in the 1st PPS was 1.7% (172 antimicrobial users, total 10,148 residents). 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 focus of infection were urinary tract infections, affecting 70 people (46.1%); pneumonia, affecting 29 people (19.1%); and upper respiratory tract infections, affecting 11 people (7.2%). The main antimicrobials used to treat urinary tract infections were fluoroquinolones, while the antimicrobials primarily used for pneumonia were injectable third generation cephalosporins.

The antimicrobial use rate in the 2nd PPS was 1.3% (110 antimicrobial users, total 8,291 residents). The median age of the patients was 89.0 years (IQR: 84-93), while the median age of male patients was 85.0 years (IQR: 80.5-89.5) and that of female patients was 89.0 years (IQR: 86.5-94.0). The top focus of infection were urinary tract infections, affecting 47 people (51.6%); pneumonia, affecting 14 people (15.4%); and cellulitis, affecting 7 people (7.7%). The main antimicrobials used to treat urinary tract infections and were fluoroquinolones while the antimicrobials primarily used for pneumonia were injectable third generation cephalosporins.

iii Welfare facilities for the elderly requiring long-term care (special nursing homes for the aged)

The center randomly selected 1,500 welfare facilities for the elderly requiring long-term care from among the members of the Japanese Council of Senior Citizens Welfare Service and conducted a point prevalence survey (PPS). Responses were received from 139 facilities (a response rate of 9.3%). The median age of the patients was 90.0 years (IQR: 85, 93), while the median age of male patients was 80.5 years (IQR: 76, 90) and that of female patients was 92.0 years (IQR: 87, 93).

The top focuses of infection were urinary tract infections, affecting 23 people (31.5%); pneumonia, affecting 11 people (15.1 %); and upper respiratory tract infections, affecting 9 people (12.3%). The main antimicrobials used to treat urinary tract infections were fluoroquinolones, while the main ones used for pneumonia were injectable third generation cephalosporins.

Table 44. Use of antimicrobial agents in long-term care wards/hospitals and elderly care facilities

facility [Number of facilities responding]	Antimicrobial use rate (Antimicrobial users/residents on survey date)	Major infections for which antimicrobial agents were used	Major antimicrobial classes (All infectious diseases)
Medical long-term care (Medical institutions) [82]	9.4% (630/6,729)	Pneumonia (39.5%) Urinary tract infections (26.8%) Bronchitis (3.8%)	Injectable 3rd gen cephalosporins Combinations of penicillins, including beta lactamase inhibitors Carbapenems
Medical and rehabilitation facilities (Geriatric health care) 1st PPS [126]	1.7% (172/10,148)	Urinary tract infection (46.1%) Pneumonia (19.1%) Upper respiratory tract infections (7.2%)	Fluoroquinolones Third generation cephalosporins Combinations of penicillins, including beta lactamase inhibitors
2nd PPS [98]	1.3% (110/8,291)	Urinary tract infection (51.6%) Pneumonia (15.4%) Cellulitis (7.7%)	Fluoroquinolones 3rd gen cephalosporins Oral fluoroquinolones Broad-spectrum penicillins
Nursing care and welfare (Special nursing homes) [137]	1.0% (94/9,044)	Urinary tract infection (31.1%) Pneumonia (14.9%) Upper respiratory tract infection (12.2%)	Fluoroquinolones 3rd generation cephalosporins Macrolide

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(2) Animals

1) Bacteria derived from food-producing animals

Source: Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

Under the JVARM, antimicrobial susceptibility tests were performed using the broth microdilution method according to the CLSI guidelines to determine the MICs of antimicrobial agents for various strains collected. For agents with a breakpoint (BP) established by the CLSI, susceptibility was interpreted using the CLSI Criteria. The BPs of the other antimicrobial agents used EUCAST values (ECOFF) or were determined microbiologically (intermediate value of a bimodal MIC distribution). Agents for which BPs could not be established using these methods were not listed in the table as it was not possible to calculate the resistance rate.

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. With regard to the site of bacterial isolation, *Salmonella* spp. were mainly isolated from feces, gastrointestinal tract and liver, *Staphylococcus* spp. mainly from milk and udder, and *Escherichia coli* mainly from feces, gastrointestinal tract and lungs.

i. *Salmonella* spp.

Monitoring of antimicrobial resistance had been carried out on 11 agents until 2018, and from 2019 onward, 12 agents were surveyed with meropenem (MEPM) added. For resistance rates in cattle- and swine-derived strains were collected in 2022, more than 50% were resistant to tetracycline (TC). In contrast, the resistance rates of cefotaxime (CTX) and ciprofloxacin (CPFX), important antimicrobial agents in human medicine, were less than 5% in swine-derived strains, 16.9% for CTX and 8.4% for CPFX in cattle-derived strains, and 0.0% for MEPM in both cattle, swine and chicken. It must be noted that the BPs of cefazolin (CEZ), and colistin (CL), and it is important to note that since 2018, CPFX has been adjusted to the lower breakpoint (BP) following the changes made by CLSI.

The most common *Salmonella* serotypes isolated from diseased food-producing animals from 2013 to 2022 were *S*. Typhimurium and its monophasic variant *S*. 4: i:- among cattle-derived strains; *S*. Typhimurium, *S.* 4:i:-, and *S.* Choleraesuis among swine-derived strains; and *S.* Schwarzengrund, *S.* Infantis, and *S*. Enteritidis among chicken-derived strains. In the strains collected in 2022, the isolation rate of *S*. Dublin increased in cattle, all of which were CTX and CL resistant. Regarding the resistance rates by serotype, *S.* Choleraesuis from swine exhibited high resistance, with 56.3% resistance to Ampicillin (ABPC) and 65.0% resistance to TC. Resistance greater than 70% was observed for ABPC and TC in cattle- and swine-derived *S*. 4: i:-, for TC in chicken-derived *S*. Infantis, and for kanamycin (KM) and TC in chicken-derived *S*. Schwarzengrund. On the other hand, the resistance rates to CTX and CPFX, important antimicrobial agents in human medicine, were less than 10% for both serotypes.

Table 45. The resistance rates (%) of *Salmonella* spp. isolated from diseased animals

Agent	BP	Animal species	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
ABPC	32*	Cattle	60.7	61.9	56.6	50.0	40.7	36.8	56.1	39.2	42.9	55.4
		Swine	45.0	41.4	46.9	41.1	40.9	50.0	50.7	37.7	25.8	51.7
		Chickens	4.0	3.9	14.3	-	-	4.5	18.8	0.0	0.0	16.7
CEZ	8* (~2015: 32*)	Cattle	8.9	7.9	7.9	22.9	5.1	3.5	19.3	19.6	30.6	21.7
		Swine	0.0	0.0	6.1	23.2	6.8	9.4	18.8	13.2	0.0	20.7
		Chickens	4.0	0.0	0.0	-	-	0.0	0.0	0.0	0.0	16.7
CTX	4*	Cattle	8.9	7.9	7.9	4.3	1.7	0.0	1.8	0.0	26.5	16.9
		Swine	0.0	0.0	4.1	0.0	0.0	0.0	0.0	1.9	0.0	3.4
		Chickens	4.0	0.0	0.0	-	-	0.0	0.0	0.0	0.0	16.7
MEPM	4*	Cattle	-	-	-	-	-	-	0.0	0.0	0.0	0.0
		Swine	-	-	-	-	-	-	0.0	0.0	0.0	0.0
		Chickens	-	-	-	-	-	-	0.0	0.0	0.0	0.0
GM	16*	Cattle	0.0	3.2	7.9	4.3	1.7	1.8	1.8	17.6	14.3	12.0
		Swine	15.0	15.5	8.2	17.9	15.9	4.7	7.2	15.1	0.0	6.9
		Chickens	2.0	0.0	0.0	-	-	0.0	18.8	0.0	0.0	0.0
KM	64*	Cattle	25.0	14.3	21.1	25.7	5.1	0.0	8.8	3.9	4.1	10.8
		Swine	6.7	8.6	6.1	10.7	13.6	4.7	18.8	13.2	3.2	10.5
		Chickens	22.0	29.4	42.9	-	-	63.6	62.5	37.5	57.1	50.0
TC	16*	Cattle	66.1	50.8	55.3	42.9	39.0	33.3	56.1	43.1	44.9	53.0
		Swine	66.7	60.3	61.2	58.9	50.0	50.0	44.9	43.4	48.4	51.7
		Chickens	30.0	39.2	42.9	-	-	77.3	68.8	81.3	71.4	50.0
NA	32*	Cattle	1.8	3.2	11.8	5.7	5.1	1.8	1.8	25.5	38.8	21.7
		Swine	5.0	15.5	6.1	7.1	9.1	20.3	24.6	20,8	16.1	17.2
		Chickens	8.0	3.9	28.6	-	-	0.0	43.8	31.3	42.9	16.7
CPFX	1* (~2017 : 4*)	Cattle	0.0	0.0	0.0	0.0	1.7	1.8	1.8	0.0	2.0	8.4
		Swine	0.0	0.0	0.0	3.6	4.5	4.7	1.4	0.0	3.2	3.4
		Chickens	0.0	0.0	0.0	-	-	0.0	18.8	0.0	0.0	0.0
CL	4* (~2015: 16*)	Cattle	0.0	0.0	0.0	1.4	5.1	0.0	1.8	0.0	26.5	7.2
		Swine	1.7	0.0	0.0	3.6	4.5	6.3	8.7	5.7	3.2	10.3
		Chickens	2.0	0.0	0.0	-	-	18.2	18.8	0.0	28.6	0.0
CP	32*	Cattle	10.7	17.5	22.4	12.9	3.4	3.5	28.1	2.0	26.5	41.0
		Swine	11.7	25.9	12.2	8.9	18.2	21.9	10.1	17.0	9.7	0.0
		Chickens	6.0	3.9	14.3	-	-	0.0	0.0	0.0	0.0	0.0
ST (TMP from 2012 to 2016)	76/4* (TMP: 16*)	Cattle	1.8	6.3	13.2	4.3	3.4	1.8	24.6	3.9	2.7	2.7
		Swine	36.7	32.8	22.4	21.4	25.0	12.5	24.6	20.8	3.2	6.9
		Chickens	14.0	29.4	42.9	-	-	59.1	50.0	37.5	14.3	0.0
Number of isolates tested (n)		Cattle	56	63	76	70	59	57	57	51	49	83
		Swine	60	58	49	56	44	64	69	53	31	29
		Chickens	50	51	7	-	-	22	16	16	7	6

The unit of BP is μg/mL.

The results are publicly available on the website of the National Veterinary Assay Laboratory (https://www.maff.go.jp/nval/yakuzai/yakuzai_AMR_2.html).

* BP follows CLSI Criteria.

-: Not under surveillance

Table 46. Number of strains of *Salmonella* spp. isolated from diseased food-producing animals by serotype (2013-2022)

Serotypes	Cattle	Swine	Chickens	Total	(%)
Typhimurium	205	268	4	484	29.3
4:i:-	225	125	0	350	21.2
Choleraesuis	3	123	2	128	7.8
Schwarzengrund	6	3	65	73	4.4
Derby	2	31	0	33	2.0
Infantis	20	12	42	74	4.5
Braenderup	6	2	10	18	1.1
Newport	25	7	5	37	2.2
Mbandaka	12	1	12	25	1.5
Thompson	27	2	7	36	2.2
Enteritidis	2	1	16	19	1.2
Dublin	27	0	0	27	1.6
Rissen	21	16	0	37	2.2
Stanley	30	3	0	33	2.0
Tennessee	0	0	8	8	0.5
Others	144	65	59	268	16.2
Total	755	659	230	1650	100.0

Table 47. Resistance rates (%) of *Salmonella* spp. from diseased animals by serotype (2013-2022)

Agents	BP	Typhimurium		4: i:-		Choleraesuis	Infantis	Schwarzengrund
		Cattle (n=205)	Swine (n=268)	Cattle (n=225)	Swine (n=125)	Swine (n=123)	Chickens (n=42)	Chickens (n=65)
ABPC	32*	46.3	26.1	92.9	72.8	48.0	7.1	4.6
CEZ	8*	11.7	5.6	21.8	18.4	4.9	2.4	0.0
CTX	4*	5.4	0	3.6	0.8	1.6	2.4	0.0
GM	16*	1.0	4.1	11.6	12.0	25.2	0.0	0.0
KM	64*	26.3	4.9	6.2	6.4	27.6	45.2	78.5
TC	16*	40.5	41	91.1	84.8	69.1	78.6	93.8
NA	32*	8.3	10.4	14.2	15.2	31.7	11.9	23.1
CPFX	1*	0.0	2.6	4.0	2.4	0.0	0.0	0.0
CL	4*	0.5	3.7	2.2	8.0	0.0	4.8	3.1
CP	32*	18.5	20.5	19.6	12.8	10.6	2.4	3.1
ST （TMP）**	76/4* （TMP is 16）	4.4	19.4	17.3	7.2	48.0	42.9	63.1

The unit of BP is μg/mL.* BP follows CLSI Criteria. ** TMP from 2012 to 2016.

ii. Staphylococcus aureus

Monitoring of antimicrobial resistance was carried out on 7 agents until 2018. Starting from 2019, 8 agents were surveyed, including Oxacillin (MPIPC). Although caution is required when comparing resistance rates due to the small number of strains derived from swine and chickens, resistance rates to TC in swine-derived strains were observed to exceed 60% in 2022. Resistance rates to all antimicrobials, except GM, were observed to be higher in swine-derived strains than in those derived from cattle and chickens. Resistance to CPFX, which is a critically important antimicrobial for human medicine was less than 1% in strains isolated from cattle and chickens, while in strain from swine was 31.3%.

Table 48. Resistance rates (%) of *Staphylococcus aureus* isolated from disease appraisal samples

Agents*.	BP	Animal species	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
ABPC (PCG since 2019)	0.5 (ABPC) 0.25 (PCG)	Cattle	11.0	11.1	21.3	7.8	7.4	9.3	6.4	7.0	2.0	9.1
		Swine	-	-	-	75.6	71.4	82.4	87.5	81.0	81.8	81.3
		Chickens	0.0	15.4	50.0	3.7	22.6	8.0	0.0	12.5	0.0	0.0
MPIPC	4†	Cattle	-	-	-	-	-	-	2.4	0.8	0.0	0.0
		Swine	-	-	-	-	-	-	15.0	4.8	0.0	12.5
		Chickens	-	-	-	-	-	-	0.0	0.0	0.0	0.0
SM	64	Cattle	2.8	1.1	2.7	1.4	3.4	5.8	8.0	4.7	5.9	4.0
		Swine	-	-	-	33.3	20.4	39.2	17.5	19.0	31.8	25.0
		Chickens	0.0	7.7	16.7	3.7	0.0	0.0	0.0	0.0	15.0	14.3
GM	16†	Cattle	1.8	0.0	1.3	0.0	0.6	0.0	0.0	0.8	0.0	2.0
		Swine	-	-	-	2.2	14.3	11.8	7.5	4.8	4.5	0.0
		Chickens	0.0	0.0	0.0	3.7	9.7	4.0	0.0	0.0	0.0	9.5
EM	8†	Cattle	5.5	0.0	6.7	2.8	1.7	5.8	4.8	3.9	1.0	3.0
		Swine	-	-	-	37.8	38.8	52.9	52.5	33.3	18.2	56.3
		Chickens	0.0	15.4	16.7	22.2	6.5	4.0	17.6	4.2	5.0	4.8
TC	16†	Cattle	8.3	5.5	6.7	0.0	0.0	0.6	2.4	0.8	2.0	5.1
		Swine	-	-	-	57.8	53.1	60.8	77.5	57.1	54.5	68.8
		Chickens	0.0	16.7	16.7	33.3	19.4	20.0	17.6	20.8	5.0	9.5
CP	32†	Cattle	0.9	0.0	1.3	0.0	0.6	0.6	1.6	0.0	5.9	2.0
		Swine	-	-	-	22.2	30.6	43.1	37.5	28.6	22.7	37.5
		Chickens	0.0	15.4	33.3	3.7	3.2	8.0	0.0	12.5	5.0	4.8
CPFX	4†	Cattle	0.9	0.0	1.3	0.7	0.6	0.0	1.6	1.6	1.0	3.0
		Swine	-	-	-	11.1	8.2	23.5	5.0	23.8	13.6	31.3
		Chickens	4.2	15.4	33.3	3.7	3.2	2.8	0.0	16.7	0.0	0.0
Number of isolates tested (n)		Cattle	109	91	75	141	175	172	125	128	101	99
		Swine	-	-	-	45	49	51	40	21	22	16
		Chickens	24	12	6	27	31	25	17	24	20	21

Units of BP are in μg/ml. -: Swine-derived strains up to 2015 are not shown because the number of isolates was less than 5 in each year.

* NA is also included in the survey, but its resistance rates are not listed as BPs cannot be set. † BP follows CLSI Criteria.

iii. *Escherichia coli*

Monitoring of antimicrobial resistance was carried out on 12 agents until 2018 and on 13 agents from 2019 onward. In 2022, an antimicrobial resistance rate exceeding 50% was observed to ABPC and TC in cattle, swine and chickens, in chloramphenicol (CP) in cattle and swine, and in ST among swine. Resistance rates to 6 out of 13 antimicrobials were observed to be higher in strains isolated from swine than in those derived from cattle and chickens. Resistance to CTX, CPFX, and CL, which are critically important antimicrobials for human medicine, was in the ranges 6.0 to 17.6%, 10.2 to 31.4%, and 0.0 to 16.0%, respectively, while the resistance rate to MEPM was 0.0% in any livestock species. It must be noted that the BPs of CEZ and CL since 2016 and CPFX since 2019 were the CLSI's revised figures. For CL, in 2018 its designation as a feed additive was revoked and its use was prohibited, and it was positioned as a second-line agents for veterinary use and its use is restricted. The resistance rate to CL showed more than 50% for swine-derived strains in 2017, but it decreased to 16.0% in 2022. It will be necessary to continue to monitor future trends in the resistance rate due to the strengthening of these risk management measures.

Table 49. Resistance rates (%) of *Escherichia coli* isolated from disease appraisal material

Agent	BP	Animal species	2013†	2014†	2015	2016	2017	2018	2019	2020	2021	2022
ABPC	32*	Cattle	61.4	57.8	57.7	37.7	50.0	51.7	62.8	63.8	52.8	50.0
		Swine	65.2	50.4	56.9	74.5	70.7	62.8	67.6	61.2	63.6	76.0
		Chickens	54.2	-	60.4	43.5	33.3	52.9	47.5	56.8	55.0	61.2
CEZ	8*(~2015: BP 32)	Cattle	21.1	6.7	13.5	15.6	15.6	17.2	28.7	27.7	18.5	28.4
		Swine	10.1	6.1	9.2	34.3	35.0	21.5	23.5	17.6	21.6	28.0
		Chickens	16.7	-	14.6	15.2	11.1	17.6	20.0	13.5	13.3	20.4
CTX	4*	Cattle	10.5	6.7	7.7	7.8	8.9	9.2	14.9	22.3	13.9	17.6
		Swine	2.5	0.0	3.7	2.9	3.3	3.3	4.9	2.4	8.0	6.0
		Chickens	14.6	-	10.4	6.5	5.6	11.8	7.5	8.1	11.7	6.1
SM	32	Cattle	-	68.9	71.2	49.4	61.1	57.5	63.8	63.8	61.1	61.8
		Swine	-	64.3	66.1	74.5	72.4	54.5	64.7	61.2	62.5	72.0
		Chickens	-	-	60.4	56.5	38.9	51.0	65.0	67.6	61.7	40.8
GM	16*	Cattle	17.5	6.7	11.5	10.4	8.9	10.3	8.5	11.7	7.4	8.8
		Swine	24.1	8.7	19.3	21.6	22.8	13.2	12.7	14.1	22.7	20.0
		Chickens	3.1	-	2.1	10.9	5.6	2.0	5.0	10.8	0.0	4.1
KM	64*	Cattle	38.6	26.7	26.9	16.9	26.7	28.7	31.9	29.8	22.2	27.5
		Swine	34.2	33.9	31.2	46.1	39.0	32.2	27.5	24.7	25.0	20.0
		Chickens	35.4	-	39.6	50.0	36.1	27.5	25.0	37.8	33.3	38.8
TC	16*	Cattle	50.9	66.7	59.6	54.5	62.2	58.6	66.0	66.0	63.0	66.7
		Swine	79.1	75.7	75.2	87.3	78.9	70.2	68.6	69.4	80.7	72.0
		Chickens	61.5	-	70.8	78.3	55.6	72.5	60.0	70.3	63.3	57.1
MEPM	4*	Cattle	-	-	-	-	-	-	0.0	0.0	0.0	0.0
		Swine	-	-	-	-	-	-	0.0	0.0	0.0	0.0
		Chickens	-	-	-	-	-	-	0.0	0.0	0.0	0.0
NA	32*	Cattle	29.8	33.3	32.7	18.2	33.3	33.3	36.2	34.0	28.7	38.2
		Swine	60.1	52.2	49.5	48.0	50.4	33.1	27.5	32.9	38.6	38.0
		Chickens	59.4	-	52.1	56.5	55.6	35.3	60.0	32.4	61.7	28.6
CPFX	1*(~2018: BP 4*)	Cattle	19.3	24.4	30.8	11.7	17.8	21.8	28.7	28.7	25.0	31.4
		Swine	36.1	23.5	32.1	24.5	28.5	11.6	15.7	20.0	21.6	18.0
		Chickens	25.0	-	8.3	8.7	11.1	5.9	35.0§1	18.9	31.7	10.2
CL	4*(~2015: BP16*)	Cattle	5.3	6.7	0.0	10.4	20.0	11.5	11.7	1.1	0.9	1.0
		Swine	3.2§2	0.0§2	2.8	56.9	52.0	35.5	27.5	27.1	23.9	16.0
		Chickens	1.0	-	0.0	8.7	0.0	2.0	10.0	0.0	0.0	0.0
CP	32*	Cattle	21.1	28.9	42.3	19.5	28.9	31.0	38.3	40.4	35.2	51.0
		Swine	64.6	64.3	60.6	69.6	59.3	57.0	54.9	57.6	61.4	50.0
		Chickens	25.0	-	16.7	21.7	11.1	21.6	15.0	32.4	18.3	24.5
ST (TMP from 2012 to 2017)	76/4* (TMP: 16*)	Cattle	22.8	33.3	40.4	23.4	35.6	42.5	41.5	40.4	33.3	32.4
		Swine	49.4	59.1	64.2	62.7	56.9	52.9	56.9	51.8	53.4	50.0
		Chickens	33.3	-	33.3	23.9	13.9	19.6	35.0	24.3	31.7	32.7
Strains tested (n)		Cattle	57	45	52	77	90	87	94	94	108	102
		Swine	158	115	109	102	123	121	102	85	88	50
		Chickens	96	-	48	46	36	51	40	37	60	49

The unit of BP is μg/mL. The results are publicly available on the website of the National Veterinary Assay Laboratory (https://www.maff.go.jp/nval/yakuzai/yakuzai_AMR_2.html).

* BP follows CLSI Criteria. Resistance rates for years prior to the change are based on BP before the change.

-: Not under surveillance.

§1 The resistance rate to CPFX in chicken-derived strains for 2019 was 22.5% when adopting the pre-2018 BP:4.

§2 The resistance rates to CL in swine-derived strains for 2013, 2014, and 2015 were 42.4%, 44.3%, and 62.0%, respectively, when adopting the post-2016 BP:4 μg/mL.

Bacteria derived from healthy food-producing animals

Surveillance of food-borne pathogenic bacteria and indicator bacteria from healthy food-producing animals was carried out using samples of feces collected at animal and poultry slaughterhouses. When JVARM first began, surveillance was carried out using samples of feces from food-producing animals collected at farms by livestock hygiene service centers. Surveillance at animal and poultry slaughterhouses was parallelly launched in FY2012, as this facilitated more intensive sampling at a stage closer to the final food product. In FY2016, there was confirmed to be no major difference in the findings of both surveys, so JVARM shifted to surveillance at animal and poultry slaughterhouses for bacteria derived from healthy food-producing animals.

i. *Escherichia coli*

Monitoring of antimicrobial resistance was carried out on 12 agents until 2017, and on 13 agents adding MEPM from 2018 onward. In 2022, resistance to TC in swine- and chicken-derived strains, SM and KM in chicken-derived strains was observed to exceed 40%. The rates of resistance to critically important antimicrobials for human medicine CTX, CPFX, and CL were less than 1%, less than 15%, and less than 5%, respectively, while the resistance rate to MEPM was 0.0%, in any livestock species.

Table 50. Resistance rates (%) of *Escherichia coli* from animal slaughterhouses and poultry slaughterhouses

Agent	BP	Animal species	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
ABPC	32*	Cattle	6.5	3.2	5.5	7.4	4.8	11.6	6.3	5.1	5.0	7.3
		Swine	26.0	40.9	34.4	36.7	33.7	34.9	32.5	44.1	33.3	37.5
		Chickens	35.5	40.1	43.5	35.4	39.3	36.1	36.7	30.6	40.7	23.9
CEZ	8* (~2015:32*)	Cattle	0.3	0.0	0.0	1.9	0.8	0.5	1.0	0.4	1.1	0.3
		Swine	0.8	1.1	1.0	6.7	1.2	2.4	3.8	1.1	2.0	1.5
		Chickens	7.8	5.8	3.8	10.1[§1]	6.7[§1]	7.7[§1]	4.7[§1]	6.6	3.4	2.1
CTX	4*	Cattle	0.0	0.0	0.0	0.4	0.4	0.0	0.7	0.0	0.0	0.0
		Swine	0.0	0.0	0.0	1.1	1.2	0.0	2.5	0.0	2.0	0.7
		Chickens	4.8	4.1	2.2	5.1	4.7	3.2	3.1	4.1	2.1	0.7
MEPM	4*	Cattle	—	—	—	—	—	0.0	0.0	0.0	0.0	0.0
		Swine	—	—	—	—	—	0.0	0.0	0.0	0.0	0.0
		Chickens	—	—	—	—	—	0.0	0.0	0.0	0.0	0.0
SM	32	Cattle	12.3	16.7	12.4	22.1	19.0	18.5	19.7	14.6	18.0	18.5
		Swine	44.9	51.1	39.6	50.0	41.0	49.4	41.3	45.2	24.5	31.6
		Chickens	38.6	44.8	41.8	51.3	41.3	48.4	40.6	47.1	48.3	45.8
GM	16*	Cattle	0.3	0.0	0.0	0.8	0.0	0.0	0.0	0.4	0.4	0.3
		Swine	2.4	6.8	2.1	3.3	3.6	3.6	2.5	1.1	1.0	2.9
		Chickens	1.8	2.9	2.2	5.1	6.0	5.2	6.3	3.3	1.4	2.1
KM	64*	Cattle	1.5	0.4	0.7	4.3	1.2	0.0	0.7	0.4	0.8	1.4
		Swine	7.9	10.2	8.3	10.0	10.8	8.4	10.0	5.4	8.8	5.9
		Chickens	24.1	33.1	37.5	43.0	36.7	43.9	37.5	31.4	44.8	44.4
TC	16*	Cattle	16.4	19.0	18.6	29.8	21.0	26.5	22.9	19.8	23.8	23.4
		Swine	62.2	58.0	45.8	56.7	55.4	55.4	47.5	62.4	52.0	55.1
		Chickens	44.0	43.6	54.9	56.3	46.0	49.0	62.5	52.9	46.2	43.0
NA	32*	Cattle	1.8	2.4	2.6	2.3	2.0	2.1	1.4	3.2	1.9	2.1
		Swine	11.0	9.1	5.2	15.6	12.0	12.0	11.3	8.6	9.8	8.1
		Chickens	36.1	45.3	35.9	35.4	39.3	40.6	36.7	48.8	37.2	33.1
CPFX	1* (~2018:4*)	Cattle	0.6	0.8	0.0	0.4	0.0	0.5	0.3	0.4	0.0	1.0
		Swine	0.8	2.3	3.1	4.4	0.0	1.2	2.5	2.2	2.0	3.7
		Chickens	5.4	9.9	4.9	9.5	12.0	12.3	12.5	18.2	14.5	14.8
CL	4* (~2015:16*)	Cattle	0.0	0.8	0.0	0.4	1.2	0.0	0.3	0.0	0.0	0.0
		Swine	0.0	0.0	0.0	4.4[§2]	2.4[§2]	6.0[§2]	2.5[§2]	4.3	2.0	2.2
		Chickens	0.6	0.0	0.5	1.9	3.3	0.0	0.0	0.8	0.0	0.0
CP	32*	Cattle	2.3	3.6	2.9	2.3	2.8	4.8	4.2	5.9	6.5	7.3
		Swine	23.6	34.1	25.0	25.6	21.7	25.3	22.5	30.1	26.5	33.1
		Chickens	11.4	15.1	9.8	19.6	11.3	17.4	15.6	20.7	9.7	12.0
ST	76/4*	Cattle	2.9	5.2	2.9	0.4	2.0	5.3	2.8	2.8	3.4	3.8
		Swine	26.8	34.1	30.2	4.4	26.5	32.5	23.8	25.8	30.4	30.1
		Chickens	31.9	30.2	28.3	27.8	34.7	33.5	30.5	22.3	23.4	19.7
Number of isolates tested (n)		Cattle	341	252	274	258	252	189	288	253	261	286
		Swine	127	88	96	90	83	83	80	93	102	136
		Chickens	166	172	184	158	150	155	128	121	145	142

The unit of BP is μg/mL. The results are publicly available on the website of the National Veterinary Assay Laboratory (https://www.maff.go.jp/nval/yakuzai/yakuzai_AMR_2.html).

* BP follows CLSI Criteria. Resistance rates for years prior to the change are based on BP before the change.

[§1] If the BP of 32 μg/mL used until 2015 is applied, CEZ resistance rate in chicken-derived strains was 7.0% in 2016, 4.7% in 2017, 3.2% in 2018, and 3.5% in 2019.

[§2] If the BP of 16 μg/mL used until 2015 is applied, CL resistance rate in swine-derived strains was 1.1% in 2016, 0.0% in 2017, 0.0% in 2018, and 0.0% in 2019.

ii. *Campylobacter jejuni*

Monitoring of antimicrobial resistance was carried out on 7 agents until 2016, and on 8 agents, adding azithromycin (AZM) from 2017onward. In 2022, resistance to NA, and CPFX in cattle- and chicken-derived strains and TC in cattle-derived strain exceeded 30%. On the other hand, resistance to SM, EM, and CP were less than 5% in each case. Resistance to CPFX and AZM, which are critically important antimicrobials for human medicine, were 54.3% and 1.6% in cattle-derived strains, respectively, and 34.0% and 0.0% in chicken-derived strains, respectively.

Table 51. Resistance rates (%) of *Campylobacter jejuni* from animal and poultry slaughterhouses

Agents*	BP	Animal species	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
ABPC	32	Cattle	9.1	12.9	8.9	7.4	8.2	8.6	11.4	8.2	10.5	10.1
		Chickens	19.8	17.5	18.6	16.2	28.4	14.9	14.3	22.4	15.3	22.0
SM	16	Cattle	3.5	3.8	3.2	6.2	4.1	8.6	1.8	3.6	4.4	3.9
		Chickens	0.0	3.5	2.1	8.8	1.5	0.0	0.0	2.0	0.0	0.0
EM	32 †	Cattle	0.7	0.0	1.3	0.0	0.0	5.7	0.0	2.7	0.9	1.6
		Chickens	0.0	0.0	0.0	0.0	1.5	0.0	0.0	4.1	0.0	0.0
AZM	4	Cattle	—	—	—	—	0.0	5.7	0.0	2.7	0.9	1.6
		Chickens	—	—	—	—	1.5	0.0	0.0	4.1	0.0	0.0
TC	16 †	Cattle	52.4	49.2	52.2	63.0	72.2	65.7	67.5	70.9	62.3	65.1
		Chickens	44.4	38.6	27.8	33.8	46.3	23.4	34.3	22.4	28.8	20.0
CP	16	Cattle	6.3	0.0	1.3	1.2	6.2	2.9	6.1	0.9	6.1	0.8
		Chickens	0.0	1.8	0.0	2.9	0.0	2.1	0.0	0.0	0.0	0.0
NA	16	Cattle	33.6	50.8	42.7	44.4	48.5	31.4	60.5	62.7	64.9	57.4
		Chickens	48.1	29.8	27.8	57.4	46.3	31.9	37.1	32.7	44.1	34.0
CPFX	4 †	Cattle	29.4	49.2	40.8	44.4	50.5	31.4	59.6	62.7	60.5	54.3
		Chickens	39.5	29.8	25.8	51.5	44.8	29.8	34.3	32.7	33.9	34.0
Strains tested (n)		Cattle	143	132	157	81	97	35	114	110	114	114
		Chickens	81	57	94	68	67	47	35	49	59	50

The unit of BP is μg/mL. The results are publicly available on the website of the National Veterinary Assay Laboratory (https://www.maff.go.jp/nval/yakuzai/yakuzai_AMR_2.html).

While GM were also included in the scope of monitoring, the proportion of GM-resistant strains were not listed because BP could not be established.

† BP follows CLSICriteria. Resistance rates for years prior to the change are based on BP before the change.

iii. *Campylobacter coli*

Monitoring of antimicrobial resistance was carried out on 7 agents until 2016, and on 8 agents, adding AZM from 2017 onward. In 2022, swine-derived strains exhibited resistance rates exceeding 60% to SM and TC, and over 50% to CPFX. On the other hand, CP resistance was less than 3%. Resistance to CPFX, which is a critically important antimicrobial for human medicine, was 50.6%, while the AZM resistance rate was 20.5%.

Table 52. Resistance rates (%) of slaughterhouse-derived *Campylobacter coli*

Agent*	BP	Animal species	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
ABPC	32	Swine	25.5	36.6	24.6	15.4	29.5	17.2	26.7	21.4	23.9	13.3
SM	32	Swine	78.3	69.9	72.3	64.1	68.9	69.0	68.3	71.4	64.8	62.7
EM	32†	Swine	44.3	43.0	26.2	38.5	31.1	20.7	33.3	21.4	33.8	20.5
AZM	4	Swine	—	—	—	—	31.1	20.7	31.7	21.4	33.8	20.5
TC	16†	Swine	93.4	80.6	87.7	89.7	83.6	86.2	78.3	73.8	76.1	65.1
CP	16	Swine	3.8	7.5	9.2	15.4	1.6	3.4	3.3	2.4	2.8	2.4
NA	32	Swine	53.8	52.7	47.7	61.5	50.8	58.6	45.0	52.4	54.9	49.4
CPFX	4†	Swine	46.2	50.5	47.7	59.0	54.1	58.6	40.0	50.0	54.9	50.6
Strains tested (n)		Swine	106	93	65	39	61	29	60	42	71	83

The unit of BP is μg/mL. The results are publicly available on the website of the National Veterinary Assay Laboratory (https://www.maff.go.jp/nval/yakuzai/yakuzai_AMR_2.html).

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

† BP follows CLSI Criteria.

iv. *Enterococcus* spp.

Monitoring of antimicrobial resistance was carried out on 10 agents until 2014, and 11 agents from 2015 onward with vancomycin (VCM) added. From 2018, dihydrostreptomycin (DSM), oxytetracycline (OTC) and enrofloxacin (ERFX) were changed to SM, TC and CPFX, respectively, of which resistance rates were investigated for 10 agents excepting SM as no BPs were established for it. In 2022, the resistance rate of *Enterococcus* spp. exceeded 40% to KM in chicken-derived strains and to TC in both swine- and chicken-derived strains. In contrast, resistance rates to ABPC were less than 1% in any livestock species. Resistance rates to CPFX, which belongs to the fluoroquinolone class of antibiotics important in human medicine, ranged from 0.3 to 11.7%. The resistance rate to VCM, which is an important antibiotic agent in human medicine, was 0.0%.

In 2022, among *Enterococcus* spp., *E. faecalis* ranged from 4.9% (14 out of 288) of cattle-derived strains to 33.3% (77 out of 231) of chicken-derived strains, and *E. faecium* ranged from 1.7% (5 out of 288) of cattle-derived strains to 11.7% (27 out of 231) of swine-derived strains. Resistance to CPFX -one of the fluoroquinolones which are critically important antimicrobials for human medicine-in *E. faecalis* was 0.0% (cattle-derived) to 5.2% (chicken-derived), and in *E. faecium* was 20.0%, 35.0% and 63.0% in cattle-, swine- and chicken-derived strains, respectively, with higher rates among *E. faecium* from chicken.

Table 53. Resistance rates (%) of *Enterococcus* spp. from animal and poultry slaughterhouses

Agent*	BP	Animal species	2014†	2015	2016	2017	2018	2019	2020	2021	2022
ABPC	16§	Cattle	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Swine	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Chickens	0.6	0.0	0.0	0.0	0.0	0.8	0.5	0.5	0.9
DSM	128	Cattle	31.2	14.9	2.9	0.8	-	-	-	-	-
		Swine	55.7	34.4	29.7	28.0	-	-	-	-	-
		Chickens	30.9	49.2	30.6	27.0	-	-	-	-	-
GM	32	Cattle	4.2	2.2	0.8	0.0	13.5	3.1	8.6	2.2	2.1
		Swine	3.4	3.1	4.4	1.2	19.0	10.0	6.5	2.6	2.8
		Chickens	5.5	9.4	4.5	3.4	12.6	9.5	6.2	3.2	6.1
KM	128	Cattle	5.0	4.1	1.3	0.8	15.9	6.3	15.7	13.9	12.2
		Swine	20.5	31.3	17.6	22.0	35.4	21.3	33.1	19.7	
		Chickens	37.0	47.0	41.4	41.9	61.6	49.2	48.2	40.6	45.9
OTC	16	Cattle	21.2	27.1	27.6	26.4	-	-	-	-	-
		Swine	54.5	59.4	64.8	58.5	-	-	-	-	-
		Chickens	58.0	63.0	66.2	52.0	-	-	-	-	-
TC	16§	Cattle	-	-	-	-	24.7	24.3	20.6	25.1	26.0
		Swine	-	-	-	-	58.2	55.0	59.7	48.7	63.3
		Chickens	-	-	-	-	64.2	54.8	59.6	41.9	48.5
CP	32§	Cattle	0.0	0.0	0.4	0.4	0.6	0.4	0.4	0.4	0.0
		Swine	17.0	10.4	15.4	14.6	15.2	11.3	16.1	10.3	14.1
		Chickens	8.8	7.2	10.2	8.8	9.3	12.7	9.8	6.9	7.8
EM	8§	Cattle	3.8	1.5	2.5	2.1	1.8	2.4	3.7	4.3	2.1
		Swine	28.4	30.2	34.1	26.8	27.8	23.8	31.5	22.2	30.5
		Chickens	43.1	42.5	45.2	41.2	36.4	34.9	36.8	26.3	25.1
LCM	128	Cattle	3.1	0.7	2.5	2.1	1.8	2.0	2.2	3.9	1.7
		Swine	50.0	34.4	37.4	35.4	36.7	41.3	39.5	29.1	39.0
		Chickens	34.3	43.1	47.1	40.5	37.7	41.3	40.9	34.6	32.5
ERFX	4	Cattle	1.2	0.4	0.8	0.0	-	-	-	-	-
		Swine	9.1	2.1	1.1	3.7	-	-	-	-	-
		Chickens	3.9	13.3	3.8	2.7	-	-	-	-	-
CPFX	4§	Cattle	-	-	-	-	2.4	1.6	0.4	1.3	0.3
		Swine	-	-	-	-	17.7	7.5	4.8	5.1	8.5
		Chickens	-	-	-	-	6.6	11.1	7.3	8.8	11.7
TS.	64	Cattle	2.3	0.7	2.1	2.5	1.8	2.4	2.2	4.3	1.4
		Swine	21.6	19.8	28.6	24.4	26.6	23.8	29.8	17.9	24.3
		Chickens	42.0	35.9	42.7	41.2	34.4	34.1	30.6	24.0	19.0
VCM	32	Cattle	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Swine	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Chickens	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Number of isolates tested (n)		Cattle	260	269	289	242	170	255	267	231	
		Swine	88	96	91	82	79	80	124	117	
		Chickens	181	181	157	148	151	126	193	217	

The unit of BP is μg/mL.

* While AZM, SM, NA, BC and SNM were also included in the scope of the survey, the resistance rates were not listed because BP could not be established.

† The monitoring was not conducted on *Enterococcus* spp. derived from animal slaughterhouses in 2013.

§ BP follows CLSI Criteria.

-: Not under surveillance.

Table 54. Resistance rates (%) of *Enterococcus faecalis* from animal and poultry slaughterhouses

Agent*	BP	Animal species	2014 †	2015	2016	2017	2018	2019	2020	2021	2022
ABPC	16 §	Cattle	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Swine	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Chickens	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
DSM	128	Cattle	36.4	35.7	12.5	0.0	-	-	-	-	-
		Swine	62.5	100.0	43.5	38.5	-	-	-	-	-
		Chickens	53.8	72.4	40.6	38.8	-	-	-	-	-
GM	32	Cattle	27.3	0.0	0.0	0.0	40.0	0.0	16.7	20.0	0.0
		Swine	12.5	15.4	8.7	7.7	31.0	35.7	17.9	4.2	9.8
		Chickens	9.9	14.3	6.3	3.5	15.1	15.0	7.0	4.9	9.1
KM	128	Cattle	9.1	14.3	0.0	0.0	46.7	0.0	25.0	40.0	0.0
		Swine	12.5	69.2	30.4	30.8	51.7	42.9	53.8	20.8	36.6
		Chickens	57.1	66.3	55.2	58.8	66.0	51.7	47.7	51.9	57.1
OTC	16	Cattle	27.3	28.6	37.5	10.0	-	-	-	-	-
		Swine	87.5	92.3	73.9	84.6	-	-	-	-	-
		Chickens	67.0	70.4	83.3	65.9	-	-	-	-	-
TC	16 §	Cattle	-	-	-	-	26.7	25.0	12.5	100.0	14.3
		Swine	-	-	-	-	65.5	57.1	66.7	54.2	82.9
		Chickens	-	-	-	-	70.8	66.7	77.9	59.3	64.9
CP	32 §	Cattle	0.0	0.0	12.5	10.0	6.7	25.0	4.2	20.0	0.0
		Swine	62.5	53.8	39.1	38.5	27.6	35.7	41.0	20.8	43.9
		Chickens	13.2	9.2	15.6	12.9	11.3	20.0	14.0	12.3	14.3
EM	8 §	Cattle	9.1	0.0	0.0	10.0	0.0	25.0	8.3	60.0	0.0
		Swine	62.5	69.2	52.2	61.5	44.8	50.0	56.4	37.5	51.2
		Chickens	64.8	60.2	59.4	58.8	43.4	53.3	44.2	40.7	33.8
LCM	128	Cattle	9.1	0.0	0.0	10.0	0.0	25.0	4.2	60.0	0.0
		Swine	75.0	92.3	56.5	61.5	51.7	50.0	59.0	37.5	51.2
		Chickens	45.1	54.1	59.4	55.3	43.4	55.0	43.0	40.7	35.1
ERFX	4	Cattle	0.0	0.0	0.0	0.0	-	-	-	-	-
		Swine	0.0	7.7	0.0	0.0	-	-	-	-	-
		Chickens	1.1	0.0	2.1	0.0	-	-	-	-	-
CPFX	4 §	Cattle	-	-	-	-	0.0	0.0	0.0	0.0	0.0
		Swine	-	-	-	-	3.4	7.1	5.1	8.3	4.9
		Chickens	-	-	-	-	2.8	3.3	0.0	4.9	5.2
TS.	64	Cattle	0.0	0.0	0.0	10.0	0.0	25.0	4.2	60.0	0.0
		Swine	62.4	69.2	52.2	61.5	44.8	50.0	56.4	37.5	48.8
		Chickens	65.9	53.1	59.4	60.0	43.4	55.0	44.2	40.7	29.9
VCM	32	Cattle	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Swine	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Chickens	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Strains tested (n)		Cattle	11	14	8	10	15	4	24	5	14
		Swine	8	13	23	13	29	14	39	24	41
		Chickens	91	98	96	85	106	60	86	81	77

The unit of BP is μg/mL.

* While AZM, SM, NA, BC and SNM were also included in the scope of the survey, the resistance rates were not listed because BP could not be established.

† The monitoring was not conducted on *Enterococcus* spp. derived from animal slaughterhouses in 2013.

§ BP follows CLSI Criteria.

-: Not under surveillance.

Table 55. Resistance rates (%) of *Enterococcus faecium* from animal and poultry slaughterhouses

Agent*	BP	Animal species	2014[†]	2015	2016	2017	2018	2019	2020	2021	2022
ABPC	16[§]	Cattle	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0	0.0
		Swine	0.0	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
		Chickens	0.0	0.0	0.0	0.0	0.0	0.0	4.5	0.0	3.7
DSM	128	Cattle	33.3	0.0	25.0	0.0	-	-	-	-	-
		Swine	58.3	0.0	28.6	27.3	-	-	-	-	-
		Chickens	13.9	16.1	30.0	18.2	-	-	-	-	-
GM	32	Cattle	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0	0.0
		Swine	0.0	0.0	0.0	0.0	50.0	-	0.0	7.7	0.0
		Chickens	2.8	3.2	10.0	9.1	0.0	0.0	4.5	0.0	7.4
KM	128	Cattle	33.3	16.7	0.0	50.0	-	0.0	16.7	100.0	20.0
		Swine	25.0	72.7	28.6	72.7	100.0	-	57.1	76.9	65.0
		Chickens	33.3	35.5	40.0	45.5	90.0	85.7	100.0	87.0	85.2
OTC	16	Cattle	0.0	16.7	0.0	0.0	-	-	-	-	-
		Swine	41.7	9.1	42.9	54.5	-	-	-	-	-
		Chickens	58.3	64.5	60.0	31.8	-	-	-	-	-
TC	16[§]	Cattle	-	-	-	-	-	0.0	0.0	0.0	40.0
		Swine	-	-	-	-	50.0	-	28.6	46.2	40.0
		Chickens	-	-	-	-	60.0	57.1	72.7	26.1	59.3
CP	32[§]	Cattle	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0	0.0
		Swine	25.0	0.0	0.0	9.1	0.0	-	0.0	23.1	0.0
		Chickens	8.3	6.5	0.0	9.1	10.0	28.6	4.5	4.3	14.8
EM	8[§]	Cattle	0.0	33.3	25.0	0.0	-	0.0	33.3	0.0	20.0
		Swine	58.3	54.5	57.1	45.5	0.0	-	14.3	46.2	40.0
		Chickens	30.6	35.5	20.0	27.3	40.0	28.6	50.0	30.4	40.7
LCM	128	Cattle	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0	20.0
		Swine	50.0	9.1	28.6	27.3	0.0	-	14.3	30.8	35.0
		Chickens	19.4	29.0	20.0	27.3	20.0	28.6	40.9	30.4	48.1
ERFX	4	Cattle	0.0	16.7	25.0	0.0	-	-	-	-	-
		Swine	25.0	0.0	0.0	27.3	-	-	-	-	-
		Chickens	13.9	71.0	30.0	18.2	-	-	-	-	-
CPFX	4[§]	Cattle	-	-	-	-	-	0.0	0.0	33.3	20.0
		Swine	-	-	-	-	0.0	-	28.6	23.1	35.0
		Chickens	-	-	-	-	20.0	42.9	36.4	34.8	63.0
TS.	64	Cattle	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0	0.0
		Swine	16.7	0.0	28.6	18.2	0.0	-	0.0	15.4	10.0
		Chickens	19.4	22.6	20.0	27.3	20.0	28.6	18.2	21.7	33.3
VCM	32	Cattle	-	0.0	0.0	0.0	-	0.0	0.0	0.0	0.0
		Swine	-	0.0	0.0	0.0	0.0	-	0.0	0.0	0.0
		Chickens	-	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Strains tested (n)		Cattle	6	6	4	4	0	1	6	3	5
		Swine	12	11	7	11	2	0	7	13	20
		Chickens	36	31	10	22	10	7	22	23	27

The unit of BP is μg/mL.

* While AZM, SM, NA, BC and SNM were also included in the scope of the survey, the resistance rates were not listed because BP could not be established.

[†] The monitoring was not conducted on *Enterococcus* spp. derived from animal slaughterhouses in 2013.

[§] BP follows CLSI Criteria.

-: Not under surveillance.

v. *Salmonella* spp.

Monitoring of 12 agents in chicken-derived strains was carried out until 2017, and on 13 agents adding MEPM from 2018 onward. Among chicken-derived strains in 2022 resistance to KM exceeding 70%, resistance to TC exceeding 60%, and resistance to SM exceeding 40% were observed. On the other hand, resistance to CEZ was less than 1% and no resistance to gentamicin (GM) was observed. In the realm of critically important antimicrobials for human medicine, the rate of resistance to CTX and CPFX was less than 1% and resistance to CL or MEPM was 0.0%.

The *Salmonella* serotypes most commonly isolated from poultry slaughterhouses from 2015 to 2022 were *S.* Schwarzengrund and *S.* Infantis. In comparison of *Salmonella* serotypes isolated from poultry slaughterhouses with those isolated from food and from humans (source: Nippon AMR One Health Report 2023: Table 19) (Table 58, Figure 1), the same trends were observed in *Salmonella* serotypes isolated from poultry slaughterhouses as in those isolated from food. The top two serotypes isolated from poultry slaughterhouses were the same as those isolated from food, respectively accounting for 89.1% and 75.9% 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 two serotypes isolated from poultry slaughterhouses accounting for 14.0% of human-derived strains, which suggested the possibility that there are variety of origin other than poultry or their food products.\ Comparison of the resistance rates of the top two serotypes *S.* Schwarzengrund and *S.* Infantis, which account for the majority of the poultry slaughterhouse-derived strains, between poultry slaughterhouse-derived and food-derived strains and human strains (Table 59, Fig. 2) (source: Nippon AMR One Health Report 2023: Table 29)showed that KM, SM, and TC resistance rates were similar between food- and poultry slaughterhouse-derived strains.

In *S.* Schwarzengrund, similarities were observed in the resistance rates of human-derived strains as well as those of poultry slaughterhouse- and food-derived strains. On the other hand, the human-derived *S.* Infantis strains showed different resistance rates compared to the strains other isolates, suggesting that the human-derived *S.* Infantis may have originated from sources other than chickens and foods.

Table 56. Resistance rates (%) of *Salmonella* spp. from poultry slaughterhouses

Agent	BP	Animal species	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
ABPC	32*	Chickens	22.9	17.2	13.0	13.5	8.0	6.8	5.6	1.8	11.9	0.7
CEZ	8*(~2015: 32*)	Chickens	5.9	3.1	1.6	7.7	3.6	3.4	3.7	1.8	3.8	0.7
CTX	4*	Chickens	5.1	2.3	1.6	1.9	1.8	2.6	1.9	0.9	2.5	0.7
MEPM	4*	Chickens	—	—	—	—	—	0.0	0.0	0.0	0.0	0.0
SM	32	Chickens	84.7	85.9	76.4	77.9	60.7	72.6	33.6	48.6	69.9	49.3
GM	16*	Chickens	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
KM	64*	Chickens	42.4	57.8	69.1	72.1	73.2	68.4	75.7	68.8	63.2	73.5
TC	16*	Chickens	82.2	85.2	83.7	82.7	77.7	76.9	69.2	73.4	78.3	64.0
CP	32*	Chickens	0.8	1.6	1.6	0.0	0.9	1.7	0.9	0.0	0.0	0.0
CL	4*(~2015: 16*)	Chickens	0.0	0.0	0.0	0.0	0.0	0.9	1.9	0.0	0.0	0.0
NA	32*	Chickens	19.5	17.2	15.4	12.5	17.0	18.8	8.4	11.9	19.4	14.7
CPFX	1*(~2017: 4*)	Chickens	0.0	0.0	0.0	0.0	0.0	0.9	0.9	0.9	0.8	0.7
ST	76/4*	Chickens	48.3	51.6	57.7	56.7	55.4	53.0	52.3	45.9	49.5	39.0
Strains tested (n)		Chickens	118	128	123	104	112	117	107	109	129	136

The unit of BP is μg/mL.

* BP follows CLSI Criteria.

The results are publicly available on the website of the National Veterinary Assay Laboratory (https://www.maff.go.jp/nval/yakuzai/yakuzai_AMR_2.html).

Table 57. Serotypes of *Salmonella* spp. derived from poultry slaughterhouses (2015-2022)

Serotypes	Number of strains isolated	(%)
Schwarzengrund	661	70.5
Infantis	174	18.6
Typhimurium	35	3.7
Agona	13	1.4
Manhattan	32	3.4
Others	22	2.3
Total	937	100.0

Table 58. Serotypes of *Salmonella* spp. derived from poultry slaughterhouses, food, and humans (2015-2022)

From poultry slaughterhouses (n=937)	%
Schwarzengrund	70.5
Infantis	18.6
Typhimurium	3.7
Manhattan	1.4
Agona	3.4
Others	2.3
Total	100.0

From food (n=987)*	%
Schwarzengrund	55.0
Infantis	20.9
Manhattan	8.0
Heidelberg	1.8
Enteritidis	1.8
Others	12.5
Total	100.0

From humans (n=2,316)*	%
Schwarzengrund	5.4
Infantis	8.6
Enteritidis	13.3
4:i:-	10.8
Thompson	8.1
Typhimurium	6.3
Saintpaul	5.8
Stanley	3.5
Newport	2.9
Manhattan	2.2
Others	33.1
Total	100.0

*Source: Nippon AMR One Health Report 2023: Table 19

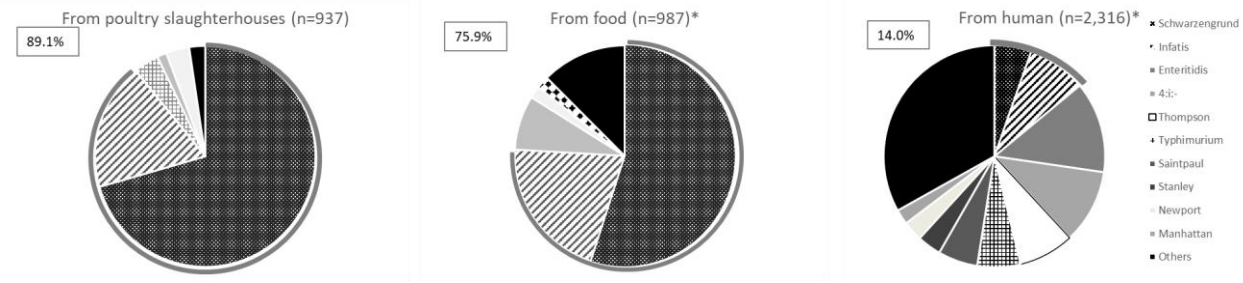

Figure 1. Proportions of the top 2 serotypes of *Salmonella* spp. derived from poultry slaughterhouses isolated in food and humans (2015-2022)
(figures for proportions in human-derived and food-derived strains are quoted from Nippon AMR One Health Report 2023: Table 19)

Table 59. Resistance rates (%) of *S*. Infantis and *S*. Schwarzengrund strains isolated from poultry slaughterhouses (chickens), food, and humans (2015-2022)

	Infantis			Schwarzengrund		
	Chicken (n=174)	Food (n=206)*	Humans (n=200)*	Chicken (n=661)	Food (n=543)*	Humans (n=125)*
ABPC	6.3	11.2	2.5	0.9	4.2	2.4
GM	0.0	0.5	0.0	0.0	0.0	0.0
KM	48.3	40.3	13.0	84.9	78.1	63.2
SM	65.5	74.3	29.0	59.9	79.2	65.6
TC	76.4	78.6	36.0	76.2	86.4	65.6
CP	1.1	2.4	2.0	0.6	7.6	2.4
CTX	4.6	5.8	1.5	0.6	0.6	2.4
NA	6.3	6.3	6.5	14.7	20.8	14.4
CPFX	0.0	0.0	0.0	0.8	0.2	0.0

*Source: Nippon AMR One Health Report 2023: Table 29

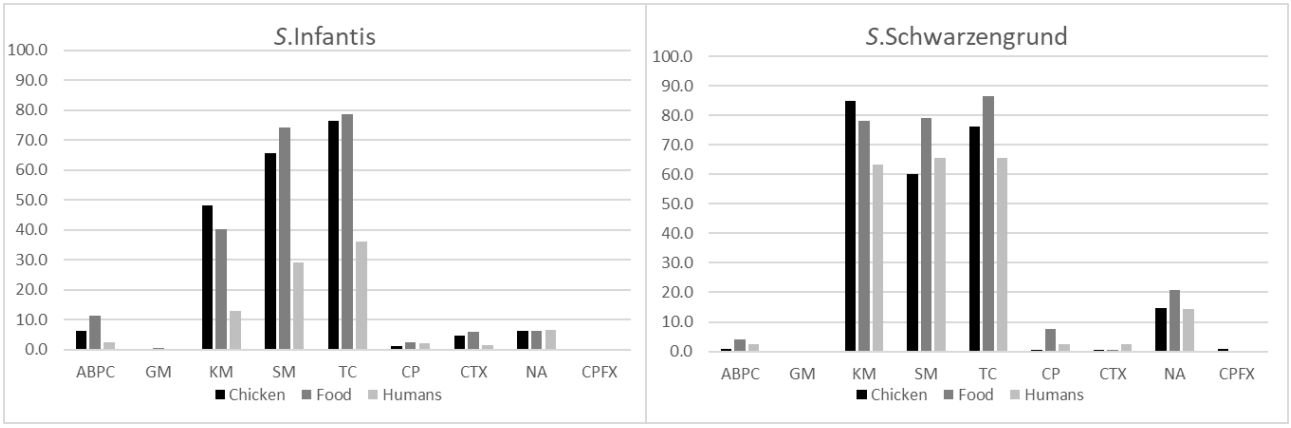

Figure 2. Resistance rates of *S*. Infantis and *S*. Schwarzengrund strains derived from humans, food, and poultry slaughterhouses (2015-2022)
(figures for resistance rates in human-derived and food-derived strains are quoted from Nippon AMR One Health Report 2023: Table 29)

2) Aquatic animal farming

Source: Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

For the monitoring and surveillance of antimicrobial resistance in marine aquaculture sector under the JVARM, antimicrobial susceptibility monitoring was conducted focusing on α-hemolytic *streptococci**, *Photobacterium damselae* subsp. *Piscicida* and *Vibrio* spp. that were derived from diseased fish and on *Vibrio parahaemolyticus* that was 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 4 to 6 prefectures per year, increasing to 8 in 2017, 10 to 12 from 2018 to 2022.

To further enhanced surveillance of trends in antimicrobial resistance in marine aquaculture sector, the scope of surveillance was expanded to all farmed fishes in 2017 and antimicrobial susceptibility monitoring of α-hemolytic *streptococci* and *Vibrio* spp. is now being carried out.

Additionally, since 2021, a pilot study has been conducted on the antimicrobial susceptibility of α-hemolytic *streptococci* and *Vibrio* spp. derived from healthy fish (yellowtail), and healthy fish samples have been provided from five prefectures. In antimicrobial susceptibility tests, MIC values were measured using a broth microdilution method or an agar plate dilution method compliant with the CLSI Guidelines. For antimicrobial agents with a BP established by the CLSI, susceptibility was interpreted using the CLSI Criteria. The BPs of the other antimicrobial agents were determined microbiologically (intermediate value of a bimodal MIC distribution).

* The pathogenic bacterium of α-hemolytic streptococcal infection was previously identified as *Lactococcus garvieae*; however, a strain with a different serotype, distinct from the conventional serotype (serotype I), emerged. This strain, previously classified as serotype II, was reclassified in 2023 as *Lactococcus formosensis* (hereafter referred to as serotype II for convenience). Furthermore, since 2020, another serotype (serotype III) of α-hemolytic *streptococci* has also been identified.

Diseased fish-derived bacteria

i. α-hemolytic *streptococci* derived from diseased fish

The monitoring of antimicrobial resistance was conducted from 2011 to 2022 on four agents that had been approved as a fisheries medicine for α-hemolytic streptococcal infection. As an overall trend, the resistance rate of LCM exhibits significant fluctuations compared to the relatively stable resistance rates of EM and OTC, suggesting the potential influence of serotypes II and III. In 2022, resistance rate to LCM was 82.3% (43.5% for serotype I, 90.8% for serotype II, and 98.7% for serotype III (In 2021, 24.6% for serotype I, 85.7% for serotype II, and 50.0% for serotype III)). In 2022, the resistance rate to EM was 5.2% (0% for serotype I, 10.8% for serotype II, and 0% for serotype III), a significant decrease compared to the previous year's rate of 14.5% (1.5% for serotype I, 20.0% for serotype II, and 50.0% for serotype III). The resistance rate to OTC was maintained at a low level of 0% (0% for serotype I, 0% for serotype II, 0% for serotype III [in 2021, 1.5% for serotype I, 0% for serotype II, 0% for serotype III]). As the MIC distribution of florfenicol (FF) was not bimodal, the BP could not be established, and the resistance rate could therefore not be calculated. However, all strains had low MICs (≤4 μg/mL) (Table 60).

Table 60. Resistance rates (%) of α-hemolytic *streptococci in the past 10 years*

Agent*[1]	BP (-2019)	BP (2020-)	2013	2014	2015	2016	2017*[2]*[3]	2018	2019	2020	2021	2022
EM	8	16	0.0	0.0	2.2	1.7	1.9	0.0	3.1	0.6	14.5	5.2
LCM	8	16	68.2	40.0	53.3	58.3	61.0	31.5	54.6	53.8	66.2	82.3
OTC	8	16	0.0	0.0	2.2	1.7	0.0	0.0	2.6	0.6	1.0	0.0
Strains tested (n)			22	25	45	60	105	149	194	158	207	271

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.

*[3]: An agar plate dilution method was used in monitoring until 2016, but the broth microdilution method has been used since 2017.

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

The monitoring of antimicrobial resistance from 2011 to 2016 was conducted on five agents that had been approved as a fisheries medicine against pseudotuberculosis. 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 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 FF resistant strains was not calculated given that no bimodal MIC distribution was observed, MICs were low (MIC ≤ 1μg/mL) in all strains, suggesting that the susceptibility was maintained. The strains tested in 2015 showed low MICs to all the tested agents (Table 61).

Table 61. Resistance rates (%) of 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.

No strains were isolated at all in 2016.

iii. *Vibrio* spp.

Monitoring of four agents that had been approved as a fisheries medicine against vibriosis has been carried out since 2017 in respect of strains derived from diseased fish. In 2022, resistance to OTC was 7.4%. FF was not bimodal and almost all bacterial strains showed low MICs (MIC ≤ 4μg/ml). Although the MIC distribution of OA was not bimodal, all strains showed low MICs (MIC ≤ 0.5μg/ml), which suggested that susceptibility to these agents was maintained. Sulfamonomethoxine (SMMX), however, did not show clear bimodal MIC distribution, so the resistance rate could not be calculated (Table 62).

Table 62. Trends in resistance rates among *Vibrio* spp. (%)

Agent*	BP (-2019)	BP (2020-)	2017	2018	2019	2020	2021	2022
OTC	8	16	12.8	15.7	0.0	11.9	4.2	7.4
Strains tested (n)			39	51	40	42	71	79

The unit of BP is μg/mL.

* While FF, OA and SMMX were also included in the scope of survey, their resistance proportion were not listed because BP cannot be established.

iv. *Vibrio parahaemolyticus* derived from aquaculture environment

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

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 (EM MIC: ≤ 2μg/mL、OTC and FF MIC: ≤ 1μg/mL, OA MIC: ≤ 0.5μg/mL) in all strains, excluding lincomycin (LCM MIC: 32 - 256μg/mL), which suggested that the susceptibility was maintained to these agents.

Healthy fish-derived bacteria

Monitoring of healthy fish-derived bacteria (α-hemolytic *streptococci* and *Vibrio spp*.) was initiated in 2021 on a trial basis. The number of fish farms sampled was 10 in 5 prefectures, and each farm sampled 10 fish. The protocol will undergo continuous review and revision as necessary, in parallel with the ongoing accumulation of data.

Furthermore, due to the limited number of isolated samples, calculating the resistance rates proved challenging, and as a result, the resistance rate is not provided.

i. Pathogenic strains of *α-hemolytic streptococcus* from healthy cultured yellowtail

The investigation was conducted on the healthy cultured yellowtail-derived strains caught in 2022. Although this organism is pathogenic and its life cycle in seawater is unknown, based on the results of this survey, the isolation rate was 8% and strains were isolated in 2 of the 10 farms in 5 prefectures. Strains isolated from one facility exhibited EM sensitivity (≤0.125 μg/mL), LCM resistance (64 μg/mL), and OTC resistance (64 μg/mL), and those from another facility showed EM sensitivity (≤0.125 μg/mL), LCM resistance (128 μg/mL), and OTC sensitivity (≤0.125 μg/mL).

ii. *Vibrio* spp. from healthy cultured yellowtail

The investigation of the strains derived from healthy cultured yellowtail caught in 2022 were piloted for four agents approved for use in fisheries against Vibrio disease.

The results of the investigation showed an isolation rate of 60%, with bacteria isolated from 8 farms in 4 prefectures out of 10 farms in 5 prefectures. Since the bacteria are endemic to marine environments, it is expected that they would be isolated with a high probability.

In 2022, among the isolates, one strain demonstrated resistance to OTC (64 μg/mL), and two strains exhibited resistance to SMMX (>128 μg/mL). For other agents, the strains showed low MIC values for FFC (0.5-1 μg/mL) and OA (≤0.125-0.5 μg/mL).

3) Companion animals

Source: Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

Routine monitoring of antimicrobial resistance in bacteria derived from diseased dogs and cats was launched in 2017, as part of efforts to strengthen monitoring under the AMR Action Plan. Monitoring of antimicrobial resistance in bacteria derived from diseased animals, unlikely from healthy animals, has the potential to be affected using 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.

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 (ECOFF) or were determined microbiologically (intermediate value of a bimodal MIC distribution).

Bacterial strains from diseased dogs and cats

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.

Samples of *Escherichia coli* and *Klebsiella* spp. were collected from urine and reproductive organs, samples of coagulase-positive *Staphylococcus* spp. from urine and skin, and samples of *Enterococcus* spp. from urine and ears.

i. *Escherichia coli*

In 2023, as in the years before, the rates of resistance to ABPC and NA were high, ranging from 48.3 to 58.4% among the agents surveyed. On the other hand, the rates of resistance to GM, KM and CP, and to SM and ST in strains isolated from dogs were less than 20%. The rates of resistance to critically important antimicrobials for human medicine in dog- and cat-derived strains respectively were as follows: 26.8% and 27.7% to CTX, 38.3% and 34.3% to CPFX, 0.0% and 0.7% to CL, and both 0.0% to MEPM.

Table 63. Resistance rates (%) of *Escherichia coli* derived from diseased dogs and cats

Agent	BP	Animal species	2017	2018	2019	2020	2021	2022	2023
ABPC	32*	Dog	55.3	63.0	51.1	50.3	54.4	53.5	48.3
		Cat	64.0	65.6	60.2	56.5	59.4	47.9	56.2
CEZ	32*	Dog	31.2	44.2	30.3	31.1	32.8	30.3	30.2
		Cat	37.5	49.5	32.0	29.8	33.5	32.0	38.0
CEX	32†	Dog	31.7	42.9	31.5	32.8	32.8	32.4	29.5
		Cat	41.9	47.3	31.3	31.7	37.1	32.5	39.4
CTX	4*	Dog	26.1	41.6	26.4	27.1	27.8	25.9	26.8
		Cat	33.8	39.8	26.6	26.1	29.4	24.3	27.7
MEPM	4*	Dog	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		Cat	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SM	32†	Dog	29.6	29.9	20.2	27.1	25.6	20.5	16.8
		Cat	32.4	34.4	28.9	19.3	23.5	17.8	21.9
GM	16*	Dog	14.1	18.8	12.9	13.0	12.2	11.9	10.1
		Cat	12.5	15.1	9.4	9.9	17.1	10.7	13.1
KM	64*	Dog	6.5	7.8	5.1	5.6	5.6	7.6	4.7
		Cat	8.1	12.9	7.0	3.7	6.5	4.1	5.1
TC	16*	Dog	28.1	27.9	21.3	23.2	20.6	20.0	18.1
		Cat	24.3	28.0	26.6	16.8	24.1	23.1	23.4
CP	32*	Dog	12.6	16.2	11.8	7.9	12.8	5.4	9.4
		Cat	13.2	15.1	7.8	5.0	8.2	8.3	12.4
CL	4*	Dog	1.0	0.0	0.0	0.0	0.0	0.0	0.0
		Cat	0.0	1.1	0.0	0.6	0.6	0.0	0.7
NA	32*	Dog	61.8	72.7	56.2	58.8	56.1	55.1	51.0
		Cat	58.8	68.8	46.9	55.9	54.7	53.3	58.4
CPFX	4* (1*since 2018)	Dog	43.2	55.2	38.8	42.4	40.6	37.3	38.3
		Cat	39.0	50.5	37.5	38.5	41.2	29.6	34.3
ST	76/4*	Dog	24.6	27.9	17.4	19.2	18.3	24.3	18.8
		Cat	22.1	34.4	22.7	14.3	21.8	16.0	21.2
Strains tested (n)		Dog	199	154	178	177	180	185	149
		Cat	136	93	128	161	170	169	137

The unit of BP is μg/mL.

* BP follows CLSI Criteria.

† BP follows EUCAST Criteria.

ii. *Klebsiella* spp.

Of the *Klebsiella* spp., *K. pneumoniae* was the most commonly collected, and *K. oxytoca* and *K. aerogenes* were also collected. In 2023, resistance exceeding 40% was observed to CEZ, cephalexin (CEX), CTX, SM, TC, NA, CPFX and ST in cat-derived strains. On the other hand, resistance to KM was below 20% in strains derived from both dogs and cats. Looking at rates of resistance in dog- and cat-derived strains to critically important antimicrobials for human medicine, resistance to CTX was 23.5% and 65.4%, respectively, resistance to CPFX was 24.7% and 59.6%, respectively, and resistance to CL was 4.9% and 0.0%, respectively. Resistance to MEPM was 1.2% and 0.0%.

Table 64. Trends in resistance rates (%) of *Klebsiella* spp. derived from diseased dogs and cats

Agent	BP	Animal species	2017	2018	2019	2020	2021	2022	2023
CEZ	32*	Dog	49.3	48.0	42.0	45.8	44.0	39.3	30.9
		Cat	85.2	90.0	67.6	61.3	69.3	68.1	69.2
CEX	32†	Dog	46.7	48.0	42.0	45.8	44.0	36.0	32.1
		Cat	85.2	80.0	62.2	58.1	64.0	68.1	69.2
CTX	4*	Dog	41.3	40.0	34.6	34.9	37.4	33.7	23.5
		Cat	77.8	80.0	56.8	48.4	56.0	62.3	65.4
MEPM	4*	Dog	0.0	0.0	0.0	0.0	0.0	0.0	1.2
		Cat	0.0	0.0	0.0	0.0	0.0	0.0	0.0
SM	32†	Dog	25.3	34.0	29.6	31.3	30.8	32.6	19.8
		Cat	55.6	55.0	59.5	41.9	52.0	46.4	42.3
GM	16*	Dog	25.3	28.0	21.0	28.9	24.2	30.3	14.8
		Cat	59.3	55.0	40.5	33.9	44.0	49.3	32.7
KM	64*	Dog	8.0	12.0	6.2	10.8	9.9	9.0	3.7
		Cat	22.2	20.0	13.5	12.9	9.3	18.8	11.5
TC	16*	Dog	32.0	44.0	30.9	33.7	26.4	30.3	19.8
		Cat	55.6	65.0	48.6	40.3	56.0	52.2	44.2
CP	32*	Dog	24.0	32.0	19.8	25.3	20.9	21.3	19.8
		Cat	25.9	45.0	16.2	25.8	26.7	27.5	13.5
CL	4*	Dog	1.3	0.0	0.0	0.0	0.0	0.0	4.9
		Cat	3.7	0.0	0.0	1.6	4.0	2.9	0.0
NA	32*	Dog	49.3	60.0	46.9	48.2	54.9	48.3	29.6
		Cat	81.5	95.0	81.1	54.8	77.3	79.7	59.6
CPFX	1*(-2018:4*)	Dog	42.7	56.0	46.9	44.6	49.5	43.8	24.7
		Cat	81.5	90.0	75.7	56.5	73.3	72.5	59.6
ST	76/4*	Dog	40.0	46.0	37.0	39.8	38.5	37.1	27.2
		Cat	74.1	70.0	56.8	43.5	54.7	60.9	57.7
Strains tested (n)		Dog	75	50	81	83	91	89	81
		Cat	27	20	37	62	75	69	52

The unit of BP is μg/mL.

* BP follows CLSI Criteria.

† The ECOFF values defined by EUCAST were used.

iii. Coagulase-positive *Staphylococcus* spp.

The most common coagulase-positive *Staphylococcus* spp. in both dogs and cats was *S. pseudintermedius*. *S. aureus was* also collected.

For *S. pseudintermedius*, dog- and cat-derived strains have shown resistance rates exceeding 50% to all agents except GM and CP since the start of the surveillance in 2017 and except GM in 2023. More than 70% of strains isolated from both dogs and 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 benzylpenicillin (PCG), AZM, and CPFX was observed to exceed 50% in 2023. On the other hand, the resistance rate to SM was low (6.5%) and that to CP was 0.0%. Rates of resistance to AZM, and CPFX, which are critically important antimicrobials for human medicine, were observed to be more than 50%.

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

Agent*	BP	Animal species	2017	2018	2019	2020	2021	2022	2023
PCG	0.25†	Dog	-	-	97.4	95.9	97.4	98.9	92.6
		Cat	-	-	97.6	98.0	98.4	95.7	96.3
MPIPC	0.5†	Dog	58.2	56.6	62.8	51.4	56.6	60.2	50.6
		Cat	68.6	81.8	81.0	77.6	78.7	76.1	81.5
GM	16†	Dog	26.2	54.2	64.1	25.7	40.8	44.3	45.7
		Cat	13.7	63.6	52.4	44.9	50.8	63.0	48.1
TC	16†	Dog	62.3	67.5	66.7	73.0	71.1	65.9	84.0
		Cat	52.9	81.8	85.7	71.4	85.2	73.9	66.7
CP	32†	Dog	43.4	49.4	60.3	58.1	55.3	59.1	65.4
		Cat	64.7	72.7	83.3	67.3	82.0	65.2	66.7
EM	8†	Dog	67.2	74.7	79.5	77.0	71.1	77.3	82.7
		Cat	70.6	86.4	95.2	79.6	91.8	89.1	88.9
AZM	8†	Dog	67.2	74.7	79.5	77.0	71.1	77.3	81.5
		Cat	66.7	86.4	95.2	79.6	91.8	91.3	88.9
CPFX	4†	Dog	64.8	75.9	75.6	74.3	73.7	79.5	77.8
		Cat	88.2	100.0	97.6	93.9	91.8	97.8	100.0
Strains tested (n)		Dog	122	83	78	74	76	88	81
		Cat	51	22	42	49	61	46	27

The unit of BP is μg/mL.

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

Table 66. Resistance rates (%) of *Staphylococcus aureus* derived from diseased cats

Agent	BP	Animal species	2017	2018	2019	2020	2021	2022	2023
PCG	0.25	Cat	-	-	90.0	84.6	96.3	81.0	71.0
MPIPC	4 †	Cat	61.9	70.6	70.0	65.4	51.9	50.0	35.5
CEZ	4 $	Cat	61.9	64.7	66.7	57.7	44.4	47.6	38.7
CEX	16 $	Cat	61.9	70.6	70.0	61.5	59.3	52.4	38.7
CFX	8 $	Cat	61.9	64.7	70.0	61.5	51.9	50.0	41.9
CTX	8 $	Cat	61.9	64.7	70.0	61.5	55.6	47.6	38.7
SM	32 $	Cat	4.8	5.9	0.0	3.8	3.7	4.8	6.5
GM	16 †	Cat	47.6	58.8	36.7	57.7	22.2	31.0	22.6
TC	16 †	Cat	14.3	41.2	43.3	38.5	14.8	21.4	16.1
CP	32 †	Cat	0.0	0.0	0.0	0.0	3.7	0.0	0.0
EM	8 †	Cat	66.7	76.5	70.0	61.5	70.4	52.4	48.4
AZM	8 †	Cat	66.7	76.5	70.0	61.5	70.4	52.4	51.6
CPFX	4 †	Cat	61.9	76.5	83.3	73.1	63.0	59.5	58.1
Strains tested (n)		Cat	21	17	30	26	27	42	31

The unit of BP is μg/mL.

† BP follows CLSI Criteria. $ Uses EUCAST's ECOFF value.

* While ABPC and CMZ were also included in the scope of monitoring, the proportion of ABPC- and CMZ-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 2023, rates of resistance to TC were the highest in both dog- and cat-derived strains (59.2% in dogs and 73.2% in cats), followed by EM (37.7% in dogs and 50.0% in cats), and the resistance rates to ABPC and GM in dog-derived strains and to CP in dog- and cat-derived strains were less than 20%. For CPFX, an important antimicrobial agent in human medicine, 28.5% and 43.8% of dog- and cat-derived strains were found to be resistant, respectively. As to the measurement of VCM which began in 2019 as a test agent, the resistance rates of both dog- and cat-derived strains were 0.0%.

Table 67. Resistance rates (%) of *Enterococcus* spp. derived from diseased dogs and cats

Agent*	BP	Animal species	2017	2018	2019	2020	2021	2022	2023
ABPC	16†	Dog	26.7	20.5	20.0	14.6	13.3	14.8	16.2
		Cat	17.3	31.6	33.0	26.4	24.1	24.5	30.4
GM	32	Dog	22.9	15.4	25.2	25.7	27.8	33.0	18.5
		Cat	19.4	24.6	25.2	25.7	27.1	20.9	33.0
TC	16†	Dog	65.6	67.9	68.9	64.9	63.9	65.9	59.2
		Cat	70.4	73.7	64.1	68.2	65.9	66.9	73.2
CP	32†	Dog	20.6	14.1	18.5	14.6	13.3	14.8	14.6
		Cat	20.4	15.8	8.7	18.2	15.3	12.3	17.0
EM	8†	Dog	61.8	39.7	43.0	45.0	46.1	43.4	37.7
		Cat	41.8	54.4	39.8	48.0	45.9	38.0	50.0
CPFX	4†	Dog	42.7	28.2	31.1	25.1	27.8	34.1	28.5
		Cat	34.7	49.1	43.7	40.5	40.6	40.5	43.8
VCM	32†	Dog	-	-	0.0	0.0	0.0	0.0	0.0
		Cat	-	-	0.0	0.0	0.0	0.0	0.0
Strain tested (n)		Dog	131	78	135	171	180	182	130
		Cat	98	57	103	148	170	163	112

The unit of BP is μg/mL.

* While AZM was also included in the scope of monitoring, the proportion of AZM-resistant strains were not listed because BP could not be established.

† BP follows CLSI Criteria.

Bacterial strains from healthy dogs and cats

Bacterial strains from healthy dogs and cats were collected from veterinary clinics across the country with the cooperation of the Japan Veterinary Medical Association, with the number of strains allocated on the basis of the number of notifications of veterinary clinic (small animals and other animals) establishment received by each prefecture. Rectal swabs were taken from healthy dogs and cats brought to veterinary clinics for health checkups and vaccination. *Escherichia coli* and *Enterococcus* spp. were then isolated from the samples, identified, and ant performed antimicrobial susceptibility tests.

i. *Escherichia coli*

In 2023, healthy dog- and cat-derived strains, as in previous surveys, showed a trend toward higher resistance rates to ABPC and NA among the agents surveyed than to the other agents, while resistance rates to the other agents (see Table 68) were all less than 20%. The rates of resistance to critically important antimicrobials for human medicine in dog- and cat-derived strains were as follows: 11.2% and 3.7% to CTX, and 5.6% and 7.5% to CPFX, while the resistance rates to CL and MEPM were both 0.0%. In all agents which resistant strains had been found, resistance rates of *Escherichia coli* derived from healthy dogs and cats were lower than that from diseased dogs and cats collected in same year.

Table 68. Resistance rates (%) of *Escherichia coli* derived from healthy dogs and cats

Agent	BP	Animal species	2018	2019	2020	2021	2022	2023
ABPC	32*	Dog	33.8	22.9	29.5	17.5	28.1	21.5
		Cat	28.5	27.1	18.5	21.7	25.4	20.6
CEZ	32*	Dog	17.2	13.0	17.8	10.4	14.6	14.0
		Cat	17.1	13.3	7.5	9.9	13.6	11.2
CEX	32†	Dog	17.9	10.9	17.1	9.7	14.0	14.0
		Cat	18.4	13.3	8.9	10.6	14.8	11.2
CTX	4*	Dog	13.2	8.9	13.0	7.8	8.8	11.2
		Cat	10.8	6.4	2.7	7.5	7.1	3.7
MEPM	4*	Dog	0.0	0.0	0.0	0.0	0.0	0.0
		Cat	0.0	0.0	0.0	0.0	0.0	0.0
SM	32†	Dog	19.2	13.0	14.4	8.4	13.5	10.3
		Cat	11.4	11.7	8.9	11.2	7.7	5.6
GM	16*	Dog	3.3	2.6	8.2	1.9	3.5	1.9
		Cat	2.5	4.3	3.4	4.3	2.4	0.9
KM	64*	Dog	5.3	3.6	4.1	2.6	2.9	3.7
		Cat	1.9	3.2	3.4	3.1	2.4	2.8
TC	16*	Dog	16.6	13.0	12.3	8.4	11.1	9.3
		Cat	10.8	10.1	8.2	8.1	3.6	4.7
CP	32*	Dog	4.6	5.7	5.5	3.2	4.7	1.9
		Cat	1.3	3.7	1.4	2.5	1.2	3.7
CL	4*	Dog	0.0	0.5	0.0	0.0	0.0	0.0
		Cat	0.0	0.0	0.0	0.0	0.6	0.0
NA	32*	Dog	27.8	20.8	22.6	10.4	19.3	14.0
		Cat	24.7	28.7	17.8	17.4	20.1	23.4
CPFX	1*	Dog	18.5	8.9	12.3	7.1	10.5	5.6
		Cat	12.0	13.3	4.8	7.5	7.1	7.5
ST	76/4*	Dog	13.2	7.8	11.6	5.8	11.1	3.7
		Cat	12.0	9.6	5.5	7.5	6.5	5.6
Strains tested (n)		Dog	151	192	146	154	171	107
		Cat	158	188	146	161	169	107

The unit of BP is μg/mL.

*BP follows CLSI Criteria.

†BP follows EUCAST Criteria.

ii. *Enterococcus* spp.

The most common *Enterococcus* spp. in both dogs and cats were *E. faecalis*. *E. faecium*, *E. gallinarum*, *E. durans*, *E. hirae*, *E. avium*, and *E. casseliflavus* were also collected. In strains isolated from dogs and cats in 2023, the highest rate of resistance was to TC, followed by EM, while rates of resistance to the other antimicrobials were all less than 20%. The rates of resistance to critically important antimicrobial for human medicine CPFX in dog- and cat-derived strains were 8.9 and 8.8%, and both 0.0% to VCM.

Table 69. Resistance rates (%) of *Enterococcus* spp. derived from healthy dogs and cats

Agent*	BP	Animal species	2018	2019	2020	2021	2022	2023
ABPC	16†	Dog	6.9	1.9	5.4	0.0	2.3	3.3
		Cat	2.2	3.4	1.3	1.2	3.4	0.0
GM	32	Dog	12.4	7.0	14.0	10.2	9.9	6.7
		Cat	11.1	15.7	22.1	11.9	6.9	12.3
TC	16†	Dog	55.9	41.8	43.4	47.7	45.6	45.6
		Cat	48.9	61.8	44.2	58.3	45.7	49.1
CP	32†	Dog	15.9	10.1	10.1	11.7	11.1	6.7
		Cat	11.1	14.6	14.3	15.5	6.0	8.8
EM	8†	Dog	32.4	23.4	27.9	23.4	27.8	27.8
		Cat	34.4	34.8	32.5	38.1	29.3	29.8
CPFX	4†	Dog	13.8	5.7	10.1	5.5	15.8	8.9
		Cat	14.4	13.5	10.4	4.8	8.6	8.8
VCM	32†	Dog	0.0	0.0	0.0	0.0	0.0	0.0
		Cat	0.0	0.0	0.0	0.0	0.0	0.0
Strains tested (n)		Dog	145	158	129	128	171	90
		Cat	90	89	77	84	116	57

The unit of BP is μg/mL.

* While AZM was also included in the scope of monitoring, the proportion of AZM-resistant strains were not listed because BP could not be established.

† BP follows CLSI Criteria.

4) Wild animals

Antimicrobial susceptibility tests were conducted on 963 strains of *Escherichia coli* isolated from 475 wild animals (525 strains from 242 deer; 224 strains from 112 wild boar; 199 strains from 113 small mammals (including brown rats, black rats, large Japanese field mice, and Japanese shrew moles); 10 strains from 4 badgers; 3 strains from 2 feral cattle ((Japanese native cattle *Tokara-Ushi*); and 2 strains from 2 Amami rabbits) within Japan between 2013 and 2017 (Table 70). Strains isolated from deer and wild boar demonstrated resistance to eight agents, while those isolated from small mammals showed resistance to 10 agents. Resistant *E.coli* were observed in 5.9% of strains isolated from deer, with resistance to tetracycline (TC, 4.4%) highest, followed by colistin (1.5%), ABPC, and sulfamethoxazole-trimethoprim (ST, 0.8%). Resistance was observed in 8.0% of strains isolated from wild boar, with resistance to TC (4.0%) highest, followed by ABPC (3.6%), and CP (1.8%). Resistant strains accounted for 18.1% of strains isolated from small mammals, with resistance to ABPC and TC (12.6% in both cases) highest, followed by ST (11.6%). In particular, in the case of small mammals, most of antimicrobial- resistant strains were observed in strains from facilities related to food-producing animals, with resistance to ABPC, ST, TC, and NA observed to be in excess of 10%. However, resistance to only two agents (TC and ST) was found in strains isolated from urban areas and no resistance to any of the 12 agents monitored was found in strains isolated from mountainous areas. Bacteria producing extended-spectrum β-lactamase (ESBL) were observed in 1 strain isolated from small mammals (livestock facility) and the ESBL was found to be CTX-M-1.

While the effects of antimicrobial-resistant bacteria contamination of habitats can be seen in the distribution of resistant bacteria in land-dwelling wild animals, the rates are low compared with food-producing animals and companion animals. 848 *E. coli* isolates from wild deer from 2016 to 2019 also showed a low rate of agent-resistance (9 isolates, 1.1%), although the antimicrobials tested varied (Table 71). Thus, antimicrobial-resistant bacterial contamination of the mountainous areas that form the main habitat of the deer and wild boar covered by this study appeared to be low.

In addition, 135 strains of *E. coli* from the Amami rabbit inhabiting a remote island (Amami Oshima) from 2017 to 2020 were susceptible to the antimicrobials tested. Future research is expected to determine whether Amami rabbit, which mainly feeds on grasses and trees, has less opportunity to receive resistant bacteria from humans, domestic animals, and even other wildlife.

Among 144 *E. coli* strains isolated from common cormorants caught in Gunma, Gifu, Shiga, and Oita prefectures from 2018 to 2019, 5.6% were resistant, and resistance were observed to ABPC (3.5%), TC (2.8%), NA (1.4%), CPFX (0.7%), CL (0.7%), CP (1.4%), and ST (1.4%) (Table 71). In 110 *E. coli* isolates from white-fronted goose feces collected in Miyajima-numa (Hokkaido, Japan) in 2019, one (0.9%) was resistant (ABPC-CEZ resistant) and carried a plasmid-mediated AmpC β-lactamase gene (bla_{ACC}) (Table 72). Although it must be taken into account that the fact that the common cormorant is a resident bird and the white-fronted goose is a migratory bird affects the distribution of resistant strains, attention must be paid to the spread of resistant bacteria and contamination of the aquatic environment through wild waterfowl, as fluoroquinolone-resistant and transmissible *β*-lactamase-producing strains were isolated from wild waterfowl.

Seven-hundred fifty *E. coli* strains isolated from the feces of 274 (75%) of 366 wild animals in Japan between 2018 and 2021 (517 isolates from 189 of 243 deer, 33 isolates from 12 of 43 nutria, 61 isolates from 22 of 22 masked palm civets, 54 isolates from 18 of 18 wild boars, 24 isolates from 8 of 8 raccoon dogs, 9 isolates from 5 of 5 badgers, 11 isolates from 4 of 4 weasels, 11 isolates from 4 of 4 foxes, 7 isolates from 4 of 4 small Japanese field mouse, 9 isolates from 3 of 3 Japanese macaques, 2 isolates from of 1 of 2 raccoons, 6 isolates from 2 of 2 wild cats, 3 isolates from 1 of 1 bear, 3 isolates from 1 of 1 marten) were tested for drug susceptibility.

Antimicrobial resistance was found in *E. coli* from deer (5.4%, 28/517), masked palm civet (1.6%, 1/61), wild boar (7.4%, 4/54), badger (11%, 1/9), fox (9.1%, 1/11), Japanese monkey (11.1%, 1/9) and raccoon (50%, 1/2). Resistance was observed to five agents in the fox-derived strain, four drugs in the deer-derived strain and one drug in the masked palm civet, wild boar, Japanese macaque and common raccoon-derived strains (Table 73). Overall, tetracycline (TC, 5.4%) resistance was the highest, and resistance to six other drugs was observed. The CIP-resistant strains found in foxes were multidrug-resistant strains to ABPC, TC and CP.

CTX-resistant and quinolone-resistant *E. coli* were isolated on DHL agar medium containing antimicrobials (Table 73). CTX-resistant *E. coli* isolated on cephalosporin (CEZ, cephalexin or CTX)-containing media were isolated from 5 of 366 (1.4%, 14 strains). Isolates were from 2 of 243 deer (0.8%, 6 strains), 1 of 6 badgers (16.7%, 2 strains), 1 of 4 foxes (25%, 3 strains) and 1 of 2 raccoons (50%, 2 strains). One strain from foxes was a AmpC β-lactamase-producing strain (CMY-2), while the others were ESBL-producing strains (CTX-M-27, CTX-M-55 and CTX-M-1). Thirty-five strains of quinolone-resistant *E. coli* were isolated from 17 of 366 (4.6%) specimens on NA-containing media and the animals were deer (10, 4.1%), masked palm civet (1, 13.6%), raccoon dog (1, 12.5%), fox (2, 50%) and raccoon (1, 50%). Quinolone-resistant strains showed mutations in the quinolone resistance-determining region (QRDR) of DNA gyrase or topoisomerase IV, and some strains (1 deer, 2 foxes) carried a plasmid mediated quinolone resistance gene (qnrB19).

Recently, a study using an antimicrobial-containing isolation medium for wildlife in urban areas was reported (Table 73): 20 strains of CTX-resistant *E.coli* were isolated on CTX-containing medium from 20 of 80 (25%)

raccoon dogs captured in Kanagawa Prefecture in 2016-2017. The breakdown of β-lactamases produced was 18 isolates had CMY-2 (n=7), CTX-M-14 (n=5), CTX-M-2 (n=2), CTX-M-1 (n=1), CTX-M-55 (n=1), DHA-1 (n=1), 1 isolate had CMY-2 and CTX-M-14, and 1 was unknown. In 2018, quinolone-resistant *E. coli* were isolated using NA-containing media from deer faecal samples in urban areas, mainly in Nara Park. NA-resistant *E. coli* were isolated from 41 of 59 (69.5%) deer, and NA-resistant *E. coli* isolated from 22 of them were also resistant to fluoroquinolones. In this area, antimicrobial-resistant *E.coli* with similar genotypes were observed in several deer species, suggesting a high distribution rate of resistant bacteria through deer-deer transmission (intra-species transmission). Resistant *E. coli* were also isolated from deer feces collected in urban areas, primarily Nara Park in 2019-2020, rural area neighboring Nara Park around urban areas in 2018-2021, and mountainous areas in the prefecture in 2019, using cephalexin-containing and NA-containing media. CTX-resistant *E. coli* were isolated from deer in urban areas (24.3%, 35/ 144) and deer in rural area (4.3%, 1/23), but not from deer in mountainous areas (0/30). Regarding quinolone-resistant *E. coli*, CPFX-resistant *E. coli* were isolated from deer in urban areas (11.1%, 16/144) and rural area (4.3%, 1/23), but not from deer in mountain areas (0/30). The genotypes of resistant *E. coli* carried by multiple deer in urban areas and deer in rural earea were different, and no dissemination of resistant *E. coli* from deer in urban area to those in rural area was observed.

Genetic analysis of resistant *E. coli* isolated from wildlife in Japan has revealed the distribution of the pandemic clone ST131 [1-3]. Phylogenetic analysis using whole genome data from these wildlife-derived strains, as well as from aquatic environments and human patients, showed the following: (i) Domestic ST131 strains have low genetic similarity to ST131 strains foreign obtained from public databases, (ii) ST131 strains isolated from domestic wildlife can be classified into a common cluster based on the accessory genome of human-derived domestic strains, and (iii) Core genome SNP analysis indicates that some wildlife-derived ST131 strains are genetically similar to human-derived ST131 strains. These findings suggest that domestic ST131 has spread from human society into natural environments, including wildlife [4].

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Table 70. Resistance rates (%) of *Escherichia coli* derived from wild animals from 2013 to 2017

Agent (BP)	Deer				Wild boar	Small mammals				Other		
	Mountains	Shrines	Parks	Subtotal	Mountains	Livestock facilities	Urban areas	Mountains	Subtotal	Badgers	Kuchinoshima cattle	Amami rabbits
Number of strains	327	102	96	525	224	106	47	46	199	10	3	2
Number of resistant	15	5	11	31	18	30	6	0	36	4	2	1
Resistance rate (%)	4.6	4.9	11.5	5.9	8.0	28.3	14.0	0.0	18.1	40.0	66.7	50.0
ABPC (32)	0.6	2.0	0.0	0.8	3.6	23.6	0.0	0.0	12.6	10.0	0.0	0.0
CEZ (32)	0.0	0.0	0.0	0.0	0.0	2.8	0.0	0.0	1.5	0.0	0.0	0.0
CTX (4)	0.0	0.0	0.0	0.0	0.0	1.9	0.0	0.0	1.0	0.0	0.0	0.0
MEPM (2)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
GM (16)	0.3	0.0	0.0	0.2	0.4	2.8	0.0	0.0	1.5	0.0	0.0	0.0
KM (64)	0.9	0.0	0.0	0.6	1.3	5.7	0.0	0.0	3.0	20.0	0.0	0.0
TC (16)	3.1	2.0	11.5	4.4	4.0	17.9	12.8	0.0	12.6	20.0	33.3	0.0
NA (32)	0.9	0.0	0.0	0.6	0.9	11.3	0.0	0.0	6.0	0.0	0.0	0.0
CPFX (2)	0.3	0.0	0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
CL (4)	1.2	2.9	1.0	1.5	1.3	3.8	0.0	0.0	2.0	10.0	33.3	50
CP (32)	0.0	0.0	0.0	0.0	1.8	1.9	0.0	0.0	1.0	0.0	0.0	0.0
ST (76/4)	0.6	2.0	0.0	0.8	0.9	18.9	6.4	0.0	11.6	0.0	0.0	0.0

BP units are in μg/mL.* Number of strains resistant to at least one agent.

Source: Asai T, Usui M, Sugiyama M, Izumi K, Ikeda T, Andoh M. Antimicrobial susceptibility of *Escherichia coli* isolates obtained from wild mammals between 2013 and 2017 in Japan. J Vet Med Sci. 82(3):345-349, 2020.

Table 71. Resistance rates (%) of *Escherichia coli* from wild animals

Agent (BP)	Deer (2016-2019)	Amami rabbit (2017-2020)	Common cormorant (2018-2019)	White-fronted goose (2019)
		Amami Oshima	Gunma, Gifu, Shiga, Oita	Miyajima swamp, Hokkaido
Number of strains	848	135	144	110
Number of resistant	9	0	8	1
Resistance rate (%)	1.1	0.0	5.6	0.9
ABPC (32)	0.1	0.0	3.5	0.9
CEZ (32)	0.1	0.0	0.0	0.9
CTX (4)	0.0	0.0	0.0	0.0
MEPM (2)	Not implemented	0.0	0.0	0.0
GM (16)	0.0	0.0	0.0	0.0
KM (64)	0.0	0.0	0.0	0.0
TC (16)	0.0	0.0	2.8	0.0
NA (16)	0.0	0.0	1.4	0.0
CPFX (2)	0.0	0.0	0.7	0.0
CL (4)	Not implemented	0.0	0.7	0.0
CP (32)	0.1	0.0	1.4	0.0
ST (76/4)	0.6	0.0	1.4	0.0

BP units are in μg/mL.* Number of strains resistant to at least one agent.

Source:

Deer: Tamamura-Andoh Y, Tanaka N, Sato K, Mizuno Y, Arai N, Watanabe-Yanai A, Akiba M, Kusumoto M. A survey of antimicrobial resistance in Escherichia coli J Vet Med Sci. 83(5):754-758, 2021.

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White-fronted goose: Fukuda A, Usui M, Ushiyama K, Shrestha D, Hashimoto N, Sakata MK, Minamoto T, Yoshida O, Murakami K, Tamura Y, Asai T. Prevalence of antimicrobial-resistant *Escherichia coli* in migratory Greater White-fronted Goose (*Anser albifrons*) and their habitat in Miyajimanuma, Japan. Wildl Dis. 57(4): 954-958, 2021.

Table 72. Resistance rates of *Escherichia coli* isolated from wild animals from 2018 to 2021 (%)

Agent (BP)	Deer	Masked palm civet	Wild boar	Nutria	Racoon dog	Fox	Weasel	Badger	Monkey	Small Japanese field mouse	Wild cat	Bear	Marten	Racoon
Number of strains	517	61	54	33	24	11	11	9	9	7	6	3	3	2
Number of resistant*	28	1	4	0	0	1	0	1	1	0	0	0	0	1
Resistance rate (%)	5.4	1.6	7.4	0.0	0.0	9.1	0.0	11.1	11.1	0.0	0.0	0.0	0.0	50.0
ABPC (32)	0.4	1.6	0.0	0.0	0.0	9.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
CEZ (32)	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
CTX (4)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
MEPM (2)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
GM (16)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
KM (64)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TC (16)	4.1	0.0	7.4	0.0	0.0	9.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NA (16)	0.0	0.0	0.0	0.0	0.0	9.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
CPFX (2)	0.0	0.0	0.0	0.0	0.0	9.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
CL (4)	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11.1	0.0	0.0	0.0	0.0	50.0
CP (32)	0.0	0.0	0.0	0.0	0.0	9.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
ST (76/4)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

BP units are in μg/mL.* Number of strains resistant to at least one agent.

Source: Asai T, Usui M, Sugiyama M, Andoh M. A survey of antimicrobial-resistant Escherichia coli prevalence in wild mammals in Japan using antimicrobial-containing media. J Vet Med Sci. 84(12):1645-1652, 2022.

Table 73. Survey of distribution of drug-resistant bacteria in wild animals using antimicrobial-containing media

Surveyed area	Surveyed year	Animal species	CTX-resistant *E. coli*	CPFX-resistant *E. coli*	Author
Gifu, Wakayama, Kagoshima	2018-2021	Deer	2/243 (0.8%)	2/243 (0.8%)	Asai et al., 2022
Gifu	2018-2021	Masked palm civet	0/22 (0%)	1/22 (4.5%)	
Gifu, Yamaguchi	2018-2021	Badger	1/6 (16.7)	0/6 (0%)	
Gifu	2018-2021	Fox	1/4 (25%)	2/4 (50%)	
Gifu	2018-2021	Racoon	1/2 (50%)	1/2 (50%)	
Kanagawa - Urban area	2016-2017	Racoon dog	20/80 (25%)	Not implemented	Shimizu et al., 2023
Nara - Urban area	2018	Deer	Not implemented	22/59（37.3%）	Ikushima et al., 2021
Nara - Urban area	2019-2020	Deer	35/144 (24.3%)	16/144 (11.1%)	
Naara – rural area	2018-2021	Deer	1/23 (4.3%)	1/23 (4.3%)	Ikushima et al., 2023
Nara - Mountain area	2019	Deer	0/30 (0%)	0/30 (0%)	

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(3) Food

The status of foodborne resistant bacteria is based on the results of a research project (2023 Health and Labour Sciences Research Grant General Report on the Research Project to Promote Food Safety: "Research to strengthen the surveillance system for food-borne drug-resistant bacteria based on One Health" Principal Investigator Motoyuki Sugai). After each local public health institute (CHIKEN, 22 CHIKEN participating voluntarily) purchased commercial meat from the relevant region, *Salmonella*, *Campylobacter*, *E. coli*, and other bacteria contaminating the meat were cultured and isolated using selective media according to the protocols established thus far. Antimicrobial susceptibility of the isolated strains were tested for 12 agents by the CLSI disk diffusion method. The emergence of agent-resistant strains of *Salmonella* is summarized in section (iv) ii, Non-typhoidal *Salmonella*, (local public health institutes) (see p. 32-38). In summary, for serotypes *S.* Infantis, *S.* Schwarzengrund, and *S.* Manhattan, food-derived isolates showed a high similarity to the drug-resistance rates and resistance patterns of human patient feces-derived isolates, suggesting a strong association between food-derived and human-derived resistant bacteria. *Salmonella* strains collected in 2023 included 186 food-derived isolates, 80% of which were from domestic chicken, with the proportion of strains resistant to one or more antibiotic agents (resistance rate) being 89.2%, higher than the 43.8% observed in human-derived strains. Among both human- and food-derived strains, the highest resistance rates were observed for TC and SM, while food-derived strains tended to show higher resistance rates for KM, SM, TC, ST, and NA. The resistance rates for cephalosporins (CTX, CAZ, CFX) in food-derived strains were lower in strains isolated in 2021–2022 but increased in 2023. In contrast, resistance rates to aminoglycosides (GM, AMK), quinolones (CPFX, NFLX), phosphomycin (FOM), and carbapenems (IPM, MEPM) were low or 0%. Among the 1,173 food-derived strains, *S.* Infantis, *S.* Schwarzengrund, and *S.* Manhattan accounted for about 80% of the total and were considered the major serotypes detected in domestic chicken. *S.* Infantis showed low resistance to NA, *S.* Schwarzengrund had low resistance to ABPC and cephalosporins, and *S.* Manhattan showed no resistance to KM. Additionally, *S.* Infantis and *S.* Schwarzengrund exhibited high resistance rates to SM and TC. In contrast, *S.* Enteritidis, isolated more frequently from chicken eggs than from chicken meat, had low resistance rates to SM and TC, with CPFX-resistant strains first detected among isolates in 2021. For *S.* Saintpaul and *S.* Thompson, which were less frequently isolated from food, the resistance rates to SM and TC were also low. Among the Salmonella strains isolated between 2015 and 2022, ESBL and AmpC genes were detected in 46 human-derived strains and 48 food-derived strains that were resistant to at least one cephalosporin (CTX, CAZ, CFX). Regarding the ESBL genes, the CTX-M-1 group and TEM type were detected in both human- and food-derived strains, while the CTX-M-9 group was detected only in human-derived strains. As for the AmpC gene, CIT was detected in both groups.

The emergence of agent-resistant strains of *Campylobacter*: A total of 51 strains of *C. jejuni*/*C. coli* were isolated, with 47% of the samples testing positive. Among these, 40 strains were *C. jejuni* and 10 strains were *C. coli* (1 strain was unidentified). The resistance rate to ABPC in *C. jejuni* was 20.0% (8/40). Seven strains (17.5%) of *C. jejuni* exhibited multidrug resistance (resistant to three or more drugs), all of which were resistant to NA and CPFX. In *C. coli*, 6 strains (60.0%) showed multidrug resistance, and all were resistant to NA and CPFX. No *C. jejuni* strains with EM resistance were detected, but 2 strains of *C. coli* were EM-resistant, and both were multidrug-resistant strains.

Emergence of agent-resistant *E. coli* from commercial chicken meat: Antimicrobial susceptibility testing was conducted using 403 strains isolated from 225 domestic chicken samples and 48 strains isolated from 35 imported chicken samples. The domestic strains showed higher resistance rates to seven antibiotics: KM, SM, TC, CP, NA, CPFX, and NFLX. In contrast, the imported strains showed higher resistance rates for six antibiotics: ABPC, CTX, CAZ, GM, ST combination, and FOM, revealing distinct resistance patterns between the two groups. Notably, the resistance rate to KM was 30.8% in domestic chicken strains, compared to 16.7% in imported chicken strains. However, the resistance rate to KM in imported chicken has shown an increasing trend, rising from 1.6% in 2021, suggesting that future trends should be closely monitored. For ABPC, the resistance rate was 36.2% in domestic chicken strains, compared to 52.1% in imported chicken strains. For CTX resistance, the rate was 1.5% in domestic chicken strains and 14.6% in imported chicken strains, showing a lower resistance tendency in domestic strains. The reasons for these differences in resistance are not clear. As in previous years, GM resistance was higher in imported chicken strains, with 20.8% resistance in imported strains and 3.2% in domestic strains in 2023. The CTX resistance rate in domestic chicken has fluctuated between 1.0% and 2.4% since 2019, after being 10.4% in 2012. In contrast, the resistance rate in imported chicken was 27.0% in 2015, but decreased to 2.8% in 2018, which remained low at 3.5% in 2020 and 6.6% in 2021. However, in 2023, the resistance rate increased to 14.6%. For imported chicken strains, the resistance rate fluctuated between 2.8% and 6.6% from 2018 onwards, rising to 12.2% in 2022 and 14.6% in 2023. The reason for the recent upward trend is unclear. The FOM resistance rate in chicken-derived strains was 12.5%, which was higher than previous years. The KM resistance rate in domestic strains has remained stable between 27.8% and 37.0% since 2018. In imported chicken, the resistance rate decreased from 27.0% in 2015 to 1.6% in 2021 but increased to 16.7% in 2023. Regarding plasmid-mediated colistin resistance, the plasmid-mediated colistin-resistance gene (mcr-1) was detected in 3 domestic strains (1.2%), which were isolated from chicken parts including tenderloin, skin, and thigh and breast meat.

Agent-resistant *E. coli* from feces of healthy subjects: In 2023, antimicrobial susceptibility testing was conducted on 304 strains isolated from the feces of healthy individuals, using 18 antibiotic agents. Of these, 134 strains (44.1%) exhibited resistance to at least one agent. When examining resistance by agent, the highest resistance rate was observed for ABPC at 29.3%, followed by NA at 22.4%, TC at 19.1%, and ST and SM, both at 14.5%. Resistance to CPFX and NFLX was 9.2% each, while resistance to cephalosporins was 5.6% for CTX, 1.0% for CAZ, with no strains exhibiting resistance to CFX. No strains showed resistance to AMK, IPM, or MEPM. The resistance rates of the 2023 isolates were similar to those of the 2022 isolates. A total of 17 strains (5.6%) exhibiting resistance to third-generation cephalosporins were subjected to AmpC/ESBL differentiation disc testing and genotyping. The results revealed that all 17 strains were ESBL producers. Among the ESBL-producing strains, the most common genotype was the CTX-M-9 group, with 8 strains, followed by the CTX-M-1 group with 7 strains, the CTX-M-8 group with 1 strain, and the SHV+TEM type with 1 strain. The presence of mcr-1 to mcr-5 was investigated in the 304 strains tested for antimicrobial susceptibility, and one strain was found to harbor the mcr-1 gene.

(4) Environment

In general, waste resulting from human activities is discharged into the environment (rivers or oceans) after being treated at sewage treatment plants or other household wastewater treatment facilities 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 into the environment (rivers and oceans) after waste resulting from human activities (rivers or oceans) is treated at sewage treatment plants or other household wastewater treatment facilities until it meets effluent standards, and considering how those antimicrobial-resistant bacteria (genes) could circulate into our daily lives and pose a risk to human health.

1) Results of the Ministry of Health, Labor and Welfare Scientific Research Grant Project

Survey Methods and Continuation of Fact-Finding Surveys in Japan

Currently, there are only a few quantitative reports on how many drug-resistant bacteria (AMR bacteria: ARB) and their derived drug-resistant genes (AMR genes: ARG) are released into the environment, and how much they continue to burden the environment. With only a few quantitative reports available at present concerning how many antimicrobial-resistant bacteria (AMR bacteria: ARB) and the antimicrobial-resistance genes (AMR genes: ARGs) that stem from them are being released into the environment and continuing to impose a burden on the environment, a systematic nationwide survey is regarded as important. Accordingly, Ministry of Health, Labour and Welfare research "Research for establishment of survey method of drug-resistant bacteria and antimicrobial agents in the environment. Principal Investigator: Hajime Kanamori H30-R02, R03-R05" has been formed for the purpose of conducting ongoing environmental AMR surveillance. Led by Hajime Kanamori, the research group (hereinafter referred to as “Kanamori’s group”) is conducting a study entitled “Research to Establish Methods of Surveying Antimicrobial-resistant Bacteria and Antimicrobials in the Environment” for three years from 2018 to 2020. In FY 2008 - FY 2020, this research group prepared a procedure manual contributing to environmental AMR monitoring and conducted research to establish a method for investigating agent-resistant bacteria and residual antimicrobial agents in environmental water. A system was established by this research to develop a nationwide environmental AMR monitoring survey of discharged treated water, and the actual environmental burden of local governments was elucidated at the genetic level. In addition, a domestic and international literature review was conducted to clarify the current status and issues related to agent resistance in the environment.

From 2018 to 2023, 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 discharged treated water samples from sewage treatment plants provided by 44 local governments (656 samples in total, collected in summer (August) and winter (February) from August 2018 to August 2023). As a result of the 6-year (11 times) continuous survey, since the winter of 2019, ARGs have shown a gradual declining trend, which is presumed to be influenced by the emergence of the COVID-19 pandemic. Although sulphate (sulfonamide) resistance genes had been showing an increasing trend until winter 2020, they showed a marked decrease in summer 2020 and remained low until winter 2023. Macrolide resistance genes once initially showed a decreasing trend in winter 2020, but it was subsequently confirmed that they increased and returned to levels observed prior to the emergence of the COVID-19 pandemic. As the research group’s metagenomic analysis technique conforms to metagenomic analysis techniques used globally and is important when comparing reports from different countries. The group plans to continue conducting nationwide surveillance twice a year (in summer and winter) with the cooperation of local governments and put in place Japanese environmental AMR (Resistome) infrastructure.

In addition to ARG in discharged treated water, it is vital to identify the presence of ARB that could potentially exist and proliferate in the environment. Kanamori’s group has reported that at a water reclamation center in Tokyo Bay, a KPC-2-producing *Klebsiella pneumoniae (Sequence type 11: ST11)* strain rarely found in clinical isolates, had been isolated from the environmental water, that ST11 was the same type as clinical isolates widely isolated in East Asia [1], that KPC-2 was found in *Aeromonas* spp. rarely isolated in wound infections,[2] and that *E. coli* with NDM- 5 carbapenemase, which has acquired broader-spectrum activity than NDM-1, had been isolated,[3] and information on the situation within Japan is gradually becoming increasingly clear. A report has also been published on a comprehensive AMR study carried out on hospital wastewater, inlet and treated 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 are isolated from non-ozone treated outlet water from sewage treatment plants and that hospital wastewater imposes an environmental AMR burden.[4] The reality is that, as in the case of the situation overseas, no small number of ARBs are isolated in environmental water in Japan.

In addition to metagenomic analysis, conventional culture methods were also important, and not only the detection of resistance genes, but also the analysis of the characteristics of live antimicrobial resistant bacteria in sewage was conducted. It is hoped that conducting both the metagenomic analysis and the culture method approaches will lead to a better understanding of the overall picture of drug resistance in environmental waters. As establishing surveillance techniques for monitoring environmental AMR and residual antimicrobials, and actually conducting fact-finding studies are important, a

procedure for metagenomic analysis of treated effluent from sewage treatment plants was developed as a method for investigating drug resistance in environmental water. In metagenomic analysis of effluent wastewater, an average of only 104 RPKM reads were obtained. However, by utilizing a hybrid capture-based metagenomic analysis technique (xHYB), the RPKM was concentrated to 601,576 reads, enabling the comprehensive detection of ARGs that could not be detected using conventional metagenomic methods. [13] In hospital wastewater from adult patients, the average RPKM value of ARGs detected by xHYB was significantly higher compared to mDNA-seq. [14]

In addition to a nationwide environmental water AMR survey, Kanamori's group also conducted a survey of the status of environmental AMR of local hospital effluent and the sewage from a local pig farm and a measurement of antimicrobial residue in local sewage treatment water in Japan. Risk assessment should be based on the findings from these studies and the results of the literature review on environmental AMR. To set out the evidence concerning the environmental AMR from overseas, the research group published a translation of Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges. 2018 [5].

Important issues for environmental AMR control include: 1) the environment can be contaminated with antimicrobial agents and resistant bacteria if wastes are not appropriately treated; 2) the impact of environmental contamination of antimicrobial agents and resistant bacteria in wastes on human health is not fully understood; 3) to understand the risk of resistant bacteria to human health, it is important to assess where and how many resistant bacteria are present in environmental water; and 4) to evaluate sampling and testing methods and standardize practices to measure resistant bacteria in environmental water.

A Japanese literature review reported that a considerable amount of resistant bacteria and resistant genes remain in effluent water after treatment and in the river water that receives it, placing a concern for the environmental contamination; resistant bacteria (such as KPC-2 and NDM-5-producing bacteria), which are rarely isolated clinically in Japan, have been detected in sewage, and suggesting sewage is useful for monitoring in the city. Although the existence of drug resistance in the environment has been proven in this way in Japan and overseas, the reality is that there is insufficient evidence on the risks to humans and animals due to the lack of established survey methods and assessment criteria for environmental AMR.

A literature review was conducted on sewage AMR in Japan.［6] AS a result, of 37 eligible papers from 1991-2021, 26 reported on AMR, 10 on antimicrobial agents and one on both AMR and antimicrobial agents. The presence of clinically important ARBs, ARGs and residual antimicrobials such as ESBL-producing bacteria, CRE, MDRP, MDRA, MRSA and VRE in Japanese sewage was observed. Hospital drainage may be a reservoir of clinically important resistant bacteria, but the direct risk to humans of ARBs in hospital drainage is not clear. In addition, antimicrobials commonly used in Japan may create an environment conducive to the growth of AMR in sewage and may further contribute to the dissemination of AMR through proliferation. While promotion of AMR control in humans, animals and the environment are necessary, knowledge on AMR in the environment is still limited compared to humans and animals. Progress in surveys and research on environmental AMR in Japan is anticipated.

Although efforts have been made to assess the risk of infection transmission and the health effects in cases of nosocomial infection based on the results of field epidemiology and molecular epidemiological analysis of isolates, as described above, research findings indicating that antimicrobial-resistant bacteria derived from the environment affect human and animal health are scarce. Overseas, as the contamination of vegetables believed to result from the use of river water for irrigation [7] and assessments of the risk of exposure to AMR through water-based recreation [8] are starting to be reported, albeit only little by little, a certain degree of a risk cycle is being calculated. 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. A multidisciplinary One Health approach at the human-animal-environment interface to infectious diseases is essential to assess the risk to humans and animals of agent resistance in the environment [9].

2) Results of the Environment Research and Technology Development Fund (FY2020-2023) [10-12]

It has been pointed out that the aquatic environment, where wastewater containing various antimicrobial agents and resistant bacteria ultimately flows into, may be a reservoir for the dissemination of resistant bacteria. To control the dissemination of resistant bacteria, it is important to clarify the mechanism of drug-resistant gene dissemination in the aquatic environment. Therefore, the "Elucidation of Transmission Potential and Transmission Mechanism of Drug Resistance Genes in the Environment" project funded by the Environment Research and Technology Development Fund (FY2020-2022), a survey of the distribution of resistant bacteria in major rivers in Japan and an evaluation experiment of the transmission potential of drug resistance genes using an *in vitro* transmission experiment were conducted. [10]

In the distribution survey of resistant bacteria, eight rivers in the Tohoku region (Aka, Mogami, Omono, Iwaki, Mabuchi, Kita, Natori, and Abukuma Rivers) were surveyed. In all rivers, the concentration of *E. coli* in river water was determined to be low in terms of *E. coli* contamination, meeting the environmental standard for Type A on the day of water sampling. The detected *E. coli* was isolated and identified, and their drug susceptibilities to 18 antimicrobial agents were evaluated. As a result, 26.8% of *E. coli* were detected to be resistant to one or more of the tested antimicrobial agents, and the largest number of 178 isolates (24.2%) were resistant to ampicillin. [11] Of the strains resistant to ABPC, 23 (3.5%) and 1 (0.2%) strains were detected to be resistant to cefotaxime and cefazolin, respectively. Of all *E. coli* isolates, 10% were multidrug-resistant (ampicillin, amoxicillin/clavulanic acid, tetracyclines, quinolones (ciprofloxacin, levofloxacin). ESBL-producing *E. coli*, which are positioned as having increased concerns by WHO, were also detected. Since a one-year river monitoring of the Akagawa and Mogami Rivers enabled the isolation of ESBL-producing *E. coli*, the ESBL-producing genes (bla) of the isolates were characterized. Of the 21 types of bla tested, 17 types were detected, with $bla_{\text{CTX-M-1-group}}$ being the most abundant. It is noteworthy that not only blaIMP, a domestic-type carbapenemase, but *bla*KPC, $bla_{\text{OXA-48}}$, bla_{VIM}, and bla_{NDM}, which are considered foreign types because there are few cases detected in Japan, were also detected. Comparing the number of *bla* detected at each location, the highest number of 15 types of *bla* was detected in the strains isolated directly under the sewage treatment plant. The results indicate that healthy people living in the city as well as in clinical care settings are also a source of resistant bacteria in rivers. In an experimental evaluation of the transmission potential of drug resistance genes using in vitro transmission experiments, in vitro transmission experiments were conducted using *enterococci* and *E. coli* as model bacteria to simulate the environment. As a result, only *vanA* was confirmed to be transmitted in *enterococci*, and the transmission potential was confirmed to be in the range of 10-3 to 10-7 depending on the combination of donor and recipient bacteria. In addition, no transmission was observed in the liquid phase of river water, and transmission was observed in activated sludge, an environment in which bacteria accumulate, although at a low probability (10-7). On the other hand, when *Enterobacteriales* harboring $bla_{\text{CTX-M}}$ were used, transmission was confirmed (10-4 to 10-8) under conditions simulating any of the environments. Furthermore, Gram-negative bacteria showed higher potential for a field (transmission field) to transmit drug resistance genes compared to Gram-positive bacteria. It was suggested that the dissemination of drug resistance genes in the environment is highly possible, and that intensive treatment is necessary, especially in areas where bacterial density is assumed to be high. It was highlighted that drug-resistant and ESBL-producing *E. coli* are already dispersed in the river water in Japan. On the other hand, the origin of these environmental AMRs and the extent of their impact on humans and animals are unknown. There is no doubt that drug-resistant bacteria are released into the environment from their human and animal origins; however, the active accumulation of information in the environmental field is needed to clarify the effects of these bacteria from the environment on humans and animals.

Starting from the 2023 fiscal year, research was conducted under the Environmental Research and Technology Development Fund project titled "Comprehensive Genomic Analysis of Antimicrobial-Resistant Bacteria in Environmental Water" (continuing until the 2025 fiscal year), focusing on the investigation of antimicrobial-resistant bacteria concentrations in rivers and lakes nationwide, as well as the genomic analysis of these resistant bacteria. [12]

In this study, the focus was on antimicrobial-resistant bacteria, specifically Extended-Spectrum Beta-Lactamase (ESBL)-producing *E. coli* and Carbapenem-Resistant *Enterobacterales* (CRE). In the first year, fiscal year 2023, water samples were collected from 17 locations across seven prefectures in the Kansai region, including rivers and lakes, for the cultivation and detection of ESBL-producing *E. coli* and CRE. Regarding CRE, due to the frequent detection of false-positive colonies, enumeration was not performed, and only the preservation of strains for genomic analysis was carried out. The results showed significant variation in the concentration of ESBL-producing *E. coli* across different locations. At sites considered to be heavily influenced by anthropogenic contamination, higher concentrations of ESBL-producing *E. coli* and a higher proportion of ESBL-producing *E. coli* relative to total *E. coli* were observed. Additionally, whole-genome sequencing was performed on 26 ESBL-producing *E. coli* strains and 25 CRE strains that were isolated and preserved during the cultivation and detection process. The analysis of the obtained genome sequences revealed that the ESBL-producing *E. coli* strains exhibited a high degree of similarity with clinical isolates in terms of phylogeny and the antimicrobial resistance genes they carried. On the

other hand, although the CRE strains were classified into general commonly found in clinical isolates, the carbapenemase genes (genes encoding carbapenem-degrading enzymes) detected in the CRE strains showed limited similarity to those found in clinical isolates.

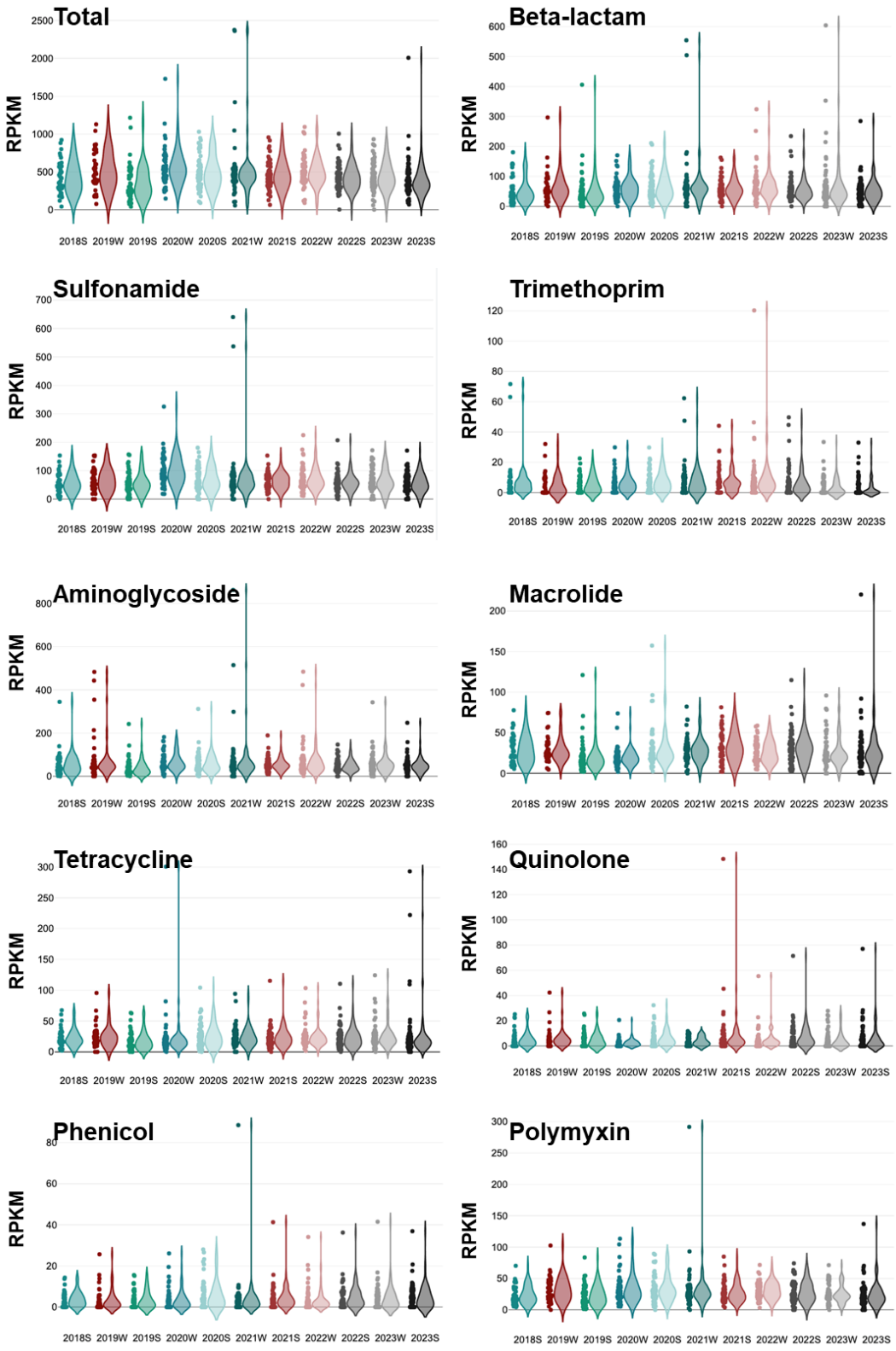

Figure 3. Metagenomic analysis (Metagenomic DNA-Seq) of wastewater discharged from Japanese sewage treatment plants (water reclamation centers)

The quantity of antimicrobial resistant genes (ARGs) in each category detected in treated effluent water provided by local governments were standardized using Reads Per Kilobase of gene per Million mapped reads (RPKM) for a total of 11 time periods from summer 2018 (18S) to summer 2023 (23S) in biannual surveys. Because of frequent updates of the ARGs database since 2018, metagenomic data from all samples were again used to calculate RPKMs for ARGs using ARGs_OAP v3.2.2. [13]

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(5) Genome comparison of Antimicrobial-resistant Bacteria: Exploring the relationships between humans, animals, food, and the environment

The Action Plan on Antimicrobial Resistance (AMR) (2016-2020) clearly stated the implementation of an integrated One Health trend survey on antimicrobial-resistant (AMR) bacteria isolated from humans, animals, food, and the environment. Since 2017, the Nippon AMR One Health Report has provided year-on-year data on the antimicrobial susceptibility of bacterial species of concern in relation to antimicrobial resistance in each of these sectors. The Nippon AMR One Health Report has played a critical role in enabling a comprehensive overview of data from various sectors in a one-stop format. The Action Plan on AMR (2016-2020) also outlined efforts to establish an integrated One Health trend surveillance system, which included analysis of antimicrobial resistance transfer factors present in humans, animals, food, and the environment, and research on the relationships between transmission processes. This initiative has been carried over into the new Action Plan (2023-2027). This paper presents the results of a study examining the relationships of AMR bacteria from various fields based on genomic comparisons of resistant strains.

1) Comparative genomics of antimicrobial-resistant bacteria derived from humans, food, and animals

In the Nippon AMR One Health Report, we have previously reported on the annual trends in antibiotic susceptibility data for bacterial species that are of concern due to antibiotic resistance. In particular, for non-typhoidal *Salmonella* spp., we have presented data for both human-derived and food-derived strains, highlighting similarities between the two. However, it is not possible to determine the extent of transmission of antibiotic-resistant bacteria between humans, food, and animals solely based on antibiotic susceptibility data. To address this knowledge gap, a research team funded by the Ministry of Health, Labour and Welfare's Health and Labour Sciences Research Grant (Research on Food Safety) has conducted genomic analysis of the strains shown in Table 74. Specifically, in addition to non-typhoidal *Salmonella* spp., *Campylobacter* spp. and *Enterococcus* spp. were also included. The study aims to investigate, through comparison of genome sequence data, how similar human-derived resistant strains are to food- and animal-derived strains at the genomic level, and whether instances can be found that suggest transmission of resistant bacteria between food, animals, and humans.

Table 74. Strains subjected to genomic analysis

Class	Derived from	Year of isolation	Number of strains (min-max per year)	Collecting Institution
Salmonella spp.	Food	2017-2022	563 (74-111)	Public Health Institutes
(non-typhoidal)	Humans	2017-2022	623 (90-126)	Public Health Institutes
	Animals	2019-2022	427 (96-129)	National Veterinary Assay Laboratory
Campylobacter spp.	Food	2024	57	National Institute of Health Sciences
	Humans	2018, 2021-2023	261 (45-106)	Tokyo Metropolitan Institute of Public Health
	Animals	2018-2021	364 (18-146)	National Veterinary Assay Laboratory
Enterococcus spp.	Food	2016-2019, 2021	38 (8-11)	Gunma University
	Humans	2020	34	National Institute of Infectious Diseases

non-typhoidal *Salmonella* spp.

Genomic analysis was conducted on 1,613 strains of non-typhoidal *Salmonella* spp. accepted by the National Institute of Infectious Diseases between 2021 and 2024. A phylogenetic tree was constructed based on the single nucleotide polymorphisms (SNPs) of the core genome (the nucleotide sequences formed by extracting and concatenating genes that are common to all analysed strains without using specific reference strain). The right side of the phylogenetic tree displays, information on each strain's serotype, origin (human, food, animal), and testing material by origin, as well as the types of ESBL or AmpC genes (usually located on plasmids) and their presence or absence, were displayed, along with the presence or absence of genes conferring resistance to phosphomycin, tetracycline, trimethoprim, kanamycin, and macrolides (Figure 4). The non-typhoidal *Salmonella* spp. strains used in this genomic analysis were isolated and preserved by regional public health institutes between 2017 and 2022, and underwent antibiotic susceptibility testing (see p.32, ii. non-typhoidal *Salmonella* spp.). Human-derived strains

were isolated from patient samples of infectious gastroenteritis or food poisoning, while food-derived strains were isolated from various foods, primarily domestic and imported chicken. These included strains collected through foodborne pathogen contamination surveys or local government collection inspections, as well as those isolated from food poisoning cases. These strains were randomly provided. The animal-derived strains were those isolated between 2019 and 2022, for which antimicrobial susceptibility testing was conducted under the JVARM program, and the strains were stored at National veterinary Assay Laboratory (see p.68, v. *Salmonella* spp.). The animal-derived strains were isolated from the cecal contents of chickens at 15 poultry slaughterhouses across the country. Many serotypes formed distinct clusters on the core genome phylogenetic tree, with each serotype clustering independently from others (Figure 4).

In the core genome phylogenetic tree, many strains harboring tetracycline, trimethoprim, or kanamycin resistance genes were found within the Infantis cluster located at the upper part of the tree and the Schwarzengrund cluster located at the lower part. Strains harboring ESBL or AmpC genes accounted for only 3% of the total and were scattered across multiple lineages (it should be noted that while ESBL or AmpC genes, typically located on plasmids, may be present, it was not possible to determine from this genomic analysis whether all of these genes are actually located on plasmids). Macrolide resistance genes were present in 1% of the strains and were detected across several lineages; of the 12 strains harboring the *mph(A)* gene, 8 strains (67%) were included in the Blockley cluster.

The complete dataset comprised 75 serotypes, with a balanced distribution of major serotypes observed in both food-derived and animal-derived strains (see Figure 5). Notably, the two most prevalent serotypes in both origins were Schwarzengrund (62% of food-derived strains and 72% of animal-derived strains) and Infantis (13% and 19%, respectively), accounting for over 75% of each origin group. However, divergence in serotype distribution was observed between these two origins and human-derived strains. In human-derived strains, Enteritidis (20% of human-derived strains, with the primary source being poultry eggs and related products, though eggs were not included in the food samples handled by the regional public health institutes mentioned above), 4:i:- (10%), and Thompson (8%) were most prevalent, but the overall distribution was highly diverse.

The distribution of detected resistance genes was compared among three groups: human-derived strains, food-derived strains, and animal-derived strains. For the kanamycin resistance gene, the proportion of *aph(3')-Ia* was over 98% in all three groups (see Figure 4). However, for the tetracycline resistance gene, the proportion of *tet(A)* was over 97% in food-derived and animal-derived strains, while in human-derived strains it was 61% with *tet(B)* detected at a rate of 28%. Similarly, for the trimethoprim resistance gene, the proportion of *dfrA14* was over 96% in food-derived and animal-derived strains, while in human-derived strains it was 58%, with *dfrA12* and *dfrA27* detected at rates of 18% and 11%, respectively. The data indicates that while the patterns of tetracycline and trimethoprim resistance gene possession were clearly similar between food- and animal-derived strains, they differed significantly among human-derived strains. This discrepancy can be attributed to the variation in serotype distribution observed among the different sources.

With regard to the fosfomycin resistance gene, it was detected at a low frequency in 43 out of 1,613 strains, and 39 strains out of 43 harbored *fosA*7 or *fosA*7.2. The distribution of the detected genes by source showed that the proportion of *fosA*7.2 was 100% (5/5 strains) in animal-derived strains, 65% (13/20 strains) in human-derived strains, in contrast, food-derived strains exhibited a fosA7.2 proportion of 17% (3/18 strains), highlighting a disparity between food- and animal-derived strains, with the former predominantly containing fosA7.2 Notably, 13 out of the 18 food-derived strains originated from imported chicken meat. Phylogenetic analysis revealed that *fosA7* was present in 83% (15/18) of food-derived strains, forming a closely adjacent cluster. Notably, 13 of these strains were derived from imported chicken meat, which may have contributed to the observed differences in the fosfomycin resistance gene patterns between food-derived and animal-derived strains.

Next, the potential for the transmission of strains with resistance genes from food to humans was investigated. Among the ESBL genes, $bla_{\text{CTX-M-15}}$ was the only gene found in both human-derived and food or animal-derived strains. Within a cluster formed by the Blockley serotype (three human strains and six food strains), the gene was present in three human-derived strains and two food-derived strains. The core genome phylogenetic tree of the Blockley strains is shown at the top of Figure 6. The five strains harboring $bla_{\text{CTX-M-15}}$ exhibited concordance in the presence of other resistance genes, and these human-derived and food-derived strains were isolated in 2017–2019 and 2018, respectively (within the two rectangular boxes in the Blockley phylogenetic tree in Figure 6). In the small number of Blockley strains that were subjected to genomic analysis, highly closely related (6-10 SNPs) pairs of human-derived and food-derived strains were revealed (A cluster in Figure 6), strongly suggesting that the human-derived strains harboring $bla_{\text{CTX-M-15}}$ may have been transmitted from food-derived strains. Although many of the human- and food-derived non-typhoidal *Salmonella* spp. strains isolated and stored by the regional public health laboratories in this study were not from the same foodborne outbreak case, there observed human-derived and food-derived strains with a similarity close to that used in the United Kingdom as the standard for the same foodborne outbreak strains of non-typhoidal *Salmonella* spp. (SNP count of 5 or fewer [1]).

Among the AmpC genes, $bla_{\text{CMY-2}}$ was the only one found in both human-derived and food or animal-derived strains. The human-derived and food-derived strains with identical resistance gene profiles were isolated 4 years

apart, suggesting that investigating the potential transmission of strains with resistance genes from food to humans would be inappropriate in this case.

A similar investigation was conducted regarding fosfomycin resistance genes, and it was found that human- and food-derived strains closely adjacent within Agona cluster in the tree had an identical resistance gene profile, including the *fosA7.2* gene possession. Thus, a core genome phylogenetic tree was constructed using Agona human-derived strains (13 strains) and food-derived strains (3 strains) (Figure 6, lower part). Genomic analysis of a small number of Agona strains revealed highly closely related (13-15 SNPs) pairs of human-derived and food-derived strains (B cluster in Figure 6), strongly suggesting that the human-derived strains harboring *fosA7.2* may have been transmitted from food-derived strains.

Next, core genome phylogenetic trees were constructed for each of the two major serotypes in food-derived strains, Schwarzengrund and Infantis. The results showed that human-derived strains were often found adjacent to either food-derived or animal-derived strains on the phylogenetic trees (Figures 7 and 8). To this end, the number of single nucleotide polymorphism (SNPs) was calculated for the following comparisons: between human-derived strains. It should be noted, however, that strains belonging to distinct phylogenetic lineages diverging significantly from the main lineages (as shown in Figures 7 and 8) were excluded from this analysis).The distribution of SNP counts between human-derived strains, human-derived versus food-derived strains, and human-derived versus animal-derived strains largely overlapped (Figures 9 and 10). In the case of Schwarzengrund (Figure 9), there was no significant difference in the frequency distribution of SNPs (with a p-value of 0.92 for the comparison between the differences among human-derived strains and the differences between human-derived and food-derived strains, and a p-value of 0.096 for the comparison between the differences among human-derived strains and the differences between human-derived and animal-derived strains, as indicated by the Wilcoxon rank-sum test). In the case of Infantis (Figure 10), the median number of SNPs (131), between human-derived and food-derived strains as well as between human-derived and animal-derived strains, was smaller than the median number of SNPs among human-derived strains (142). The p-values for these comparisons were 0.019 for the comparison between the differences among human-derived strains and the differences between human-derived and food-derived strains and 0.0066 for the comparison between the differences among human-derived strains and the differences between human-derived and animal-derived strains, indicating that the differences in core genomes between human-derived strains and food- or animal-derived strains were comparable to or smaller than those observed among human-derived strains. The human-derived *S.* Schwarzengrund and *S.* Infantis strains isolated from patients with infectious enteritis or food poisoning in this study were generally considered to have likely been transmitted to humans through animals or food. Notably, closely related pairs of human-derived and food-derived strains with an SNP count of 15 or under were detected, with 57 pairs in Schwarzengrund and 1 pair in Infantis. However, these strains did not harbor the ESBL, AmpC, or fosfomycin resistance genes.

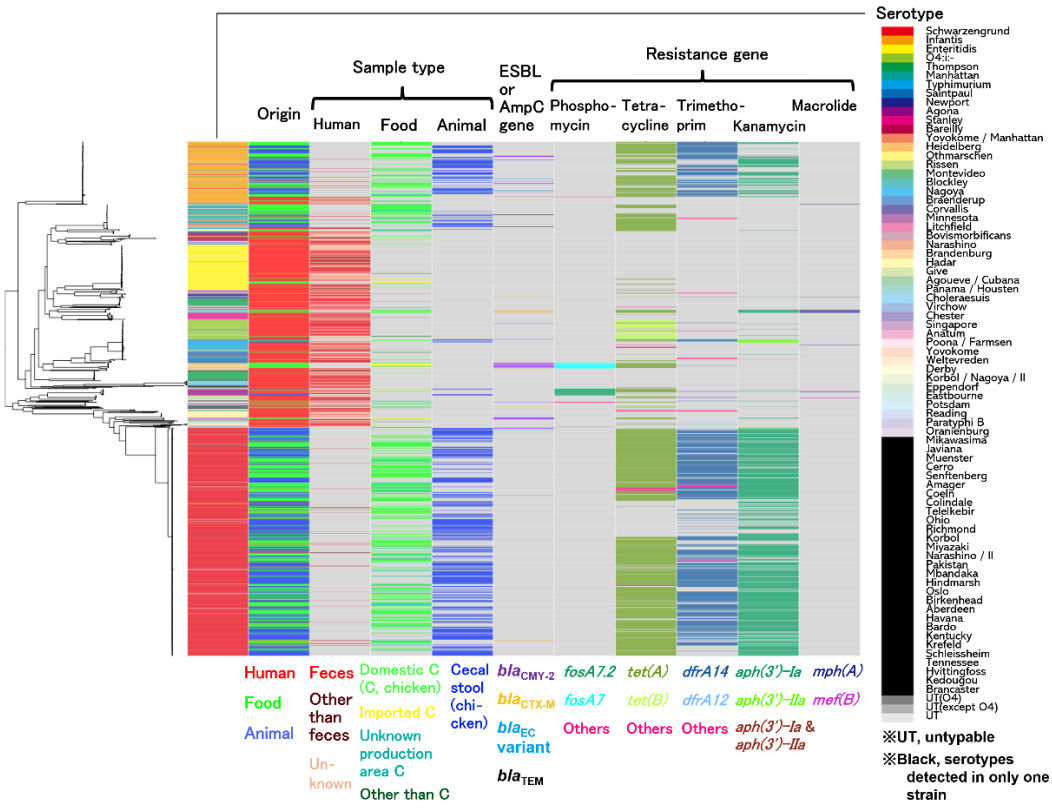


Figure 4: Core genome phylogenetic tree of 1613 non-typhoidal *Salmonella* spp. strains, along with the serotype, origin (human, food, animal), sample type by origin, and the presence or absence of key resistance genes, including ESBL or AmpC genes (typically located on plasmids), phosphomycin resistance genes, tetracycline resistance genes, trimethoprim resistance genes, kanamycin resistance genes, and macrolide resistance genes.

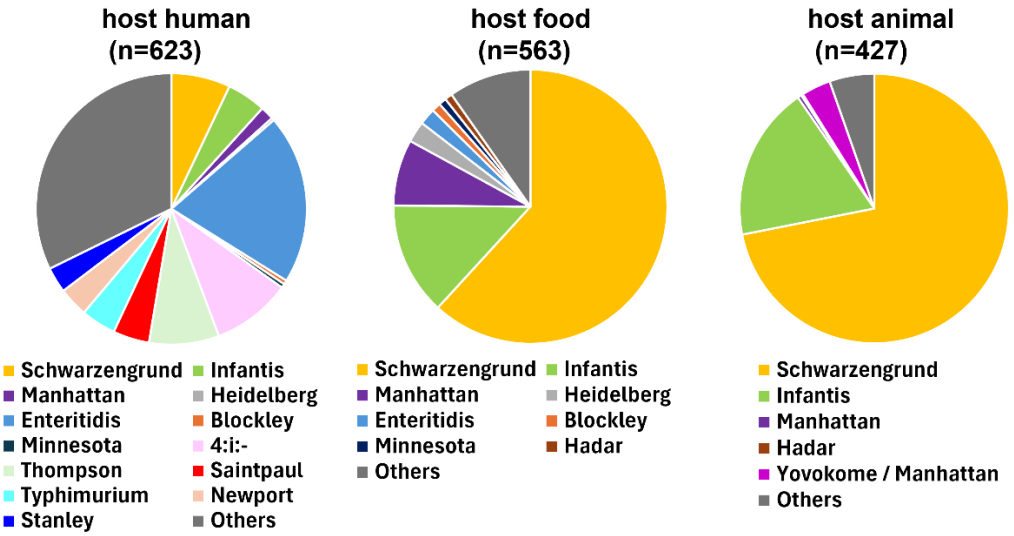


Figure 5: Serotype distribution (percentage) of human-derived strains (left), food-derived strains (middle), and animal-derived strains (right) used in the genomic analysis of non-typhoidal *Salmonella* spp.

Note: Food-derived strains are colored according to the top 8 most frequent serotypes, while human- and animal-derived strains are colored for these serotypes as well as those with a frequency exceeding 3%. All other serotypes are shown in dark gray.

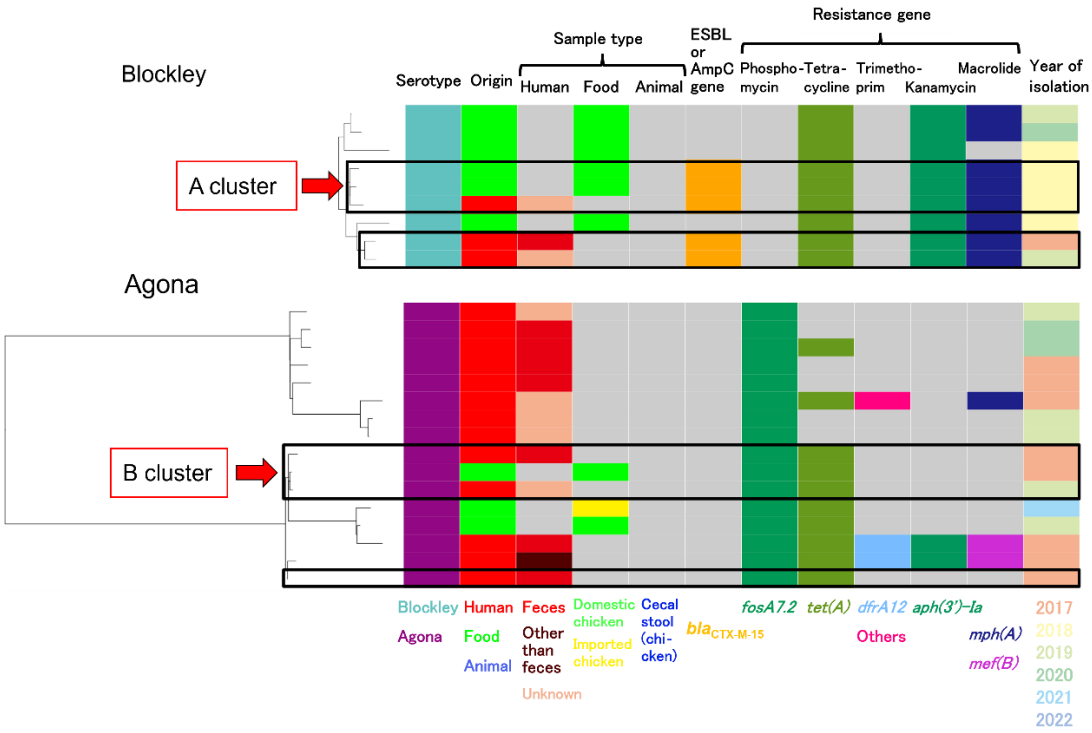


Figure 6: Core genome phylogenetic tree of Blockley strain (upper) and core genome phylogenetic tree of human-derived and food-derived strains of serotype Agona (lower)

The two boxes in the Blockley phylogenetic tree indicate strains that carry the *bla*$_{\text{CTX-M-15}}$ gene and share the same resistance gene profile. The two boxes in the Agona phylogenetic tree indicate closely related human- and food-derived strains that carry the *fosA7.2* gene and have the same resistance gene profile.

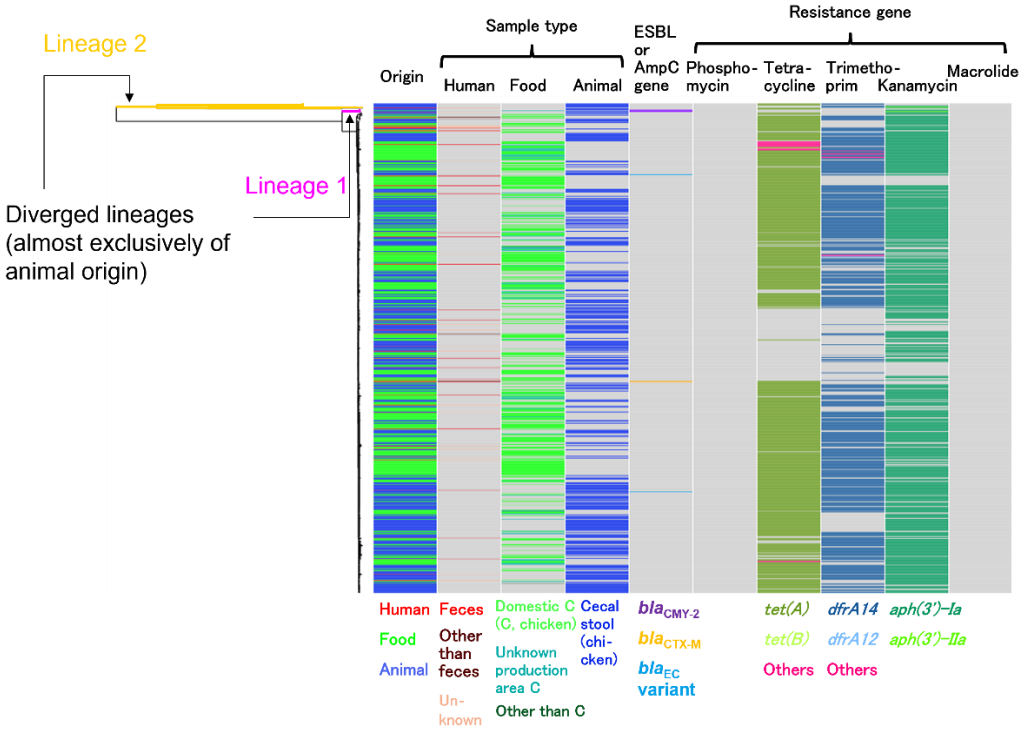


Figure 7: Core genome phylogenetic tree of *Salmonella* Schwarzengrund strains

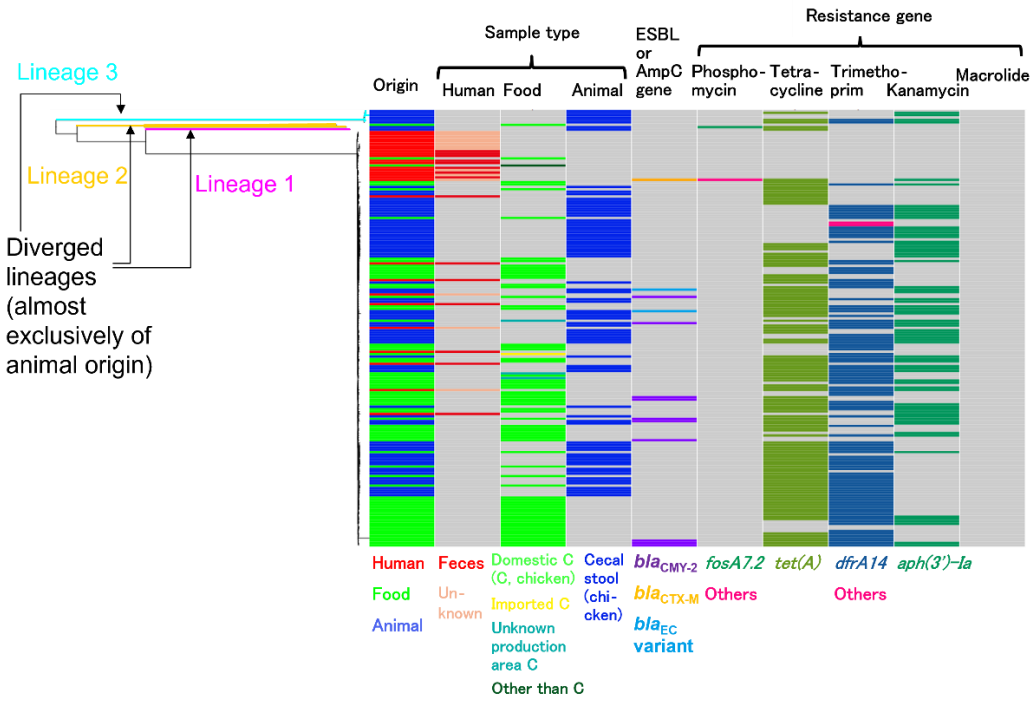


Figure 8: Core genome phylogenetic tree of *Salmonella* Infantis strains

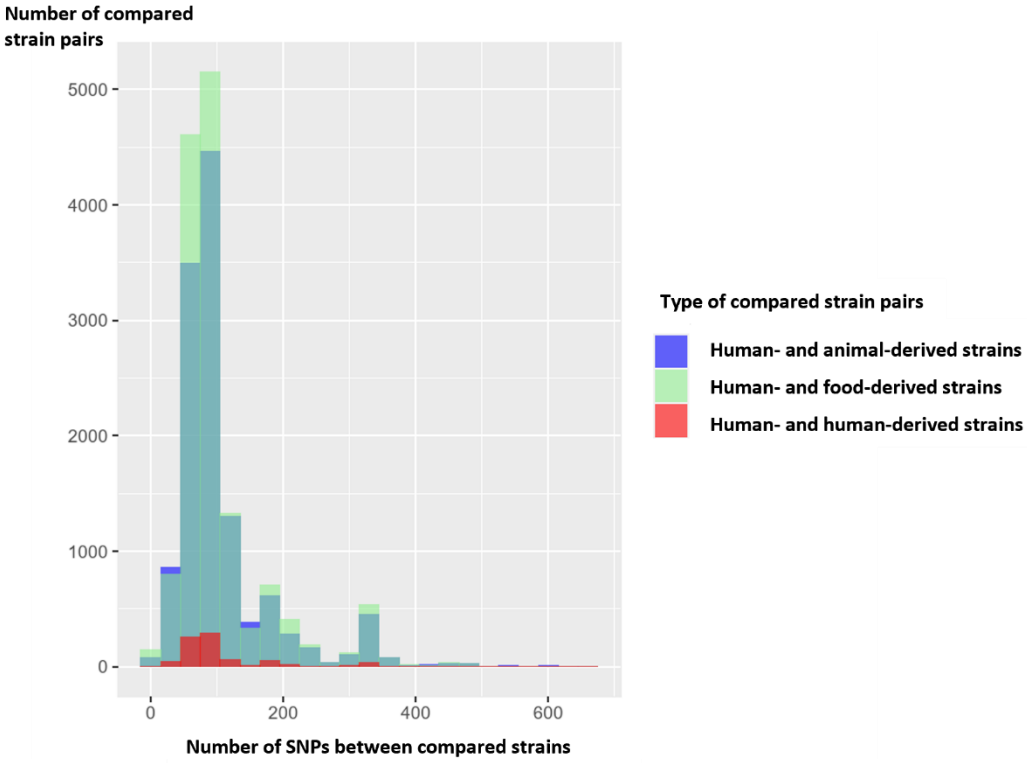


Figure 9: Distribution of SNP counts among human-derived strains, between human-derived and food-derived strains, and between human-derived and animal-derived strains of *Salmonella* Schwarzengrund

The light blue represents the overlap between blue (human-derived and animal-derived strains) and green (human-derived and food-derived strains).

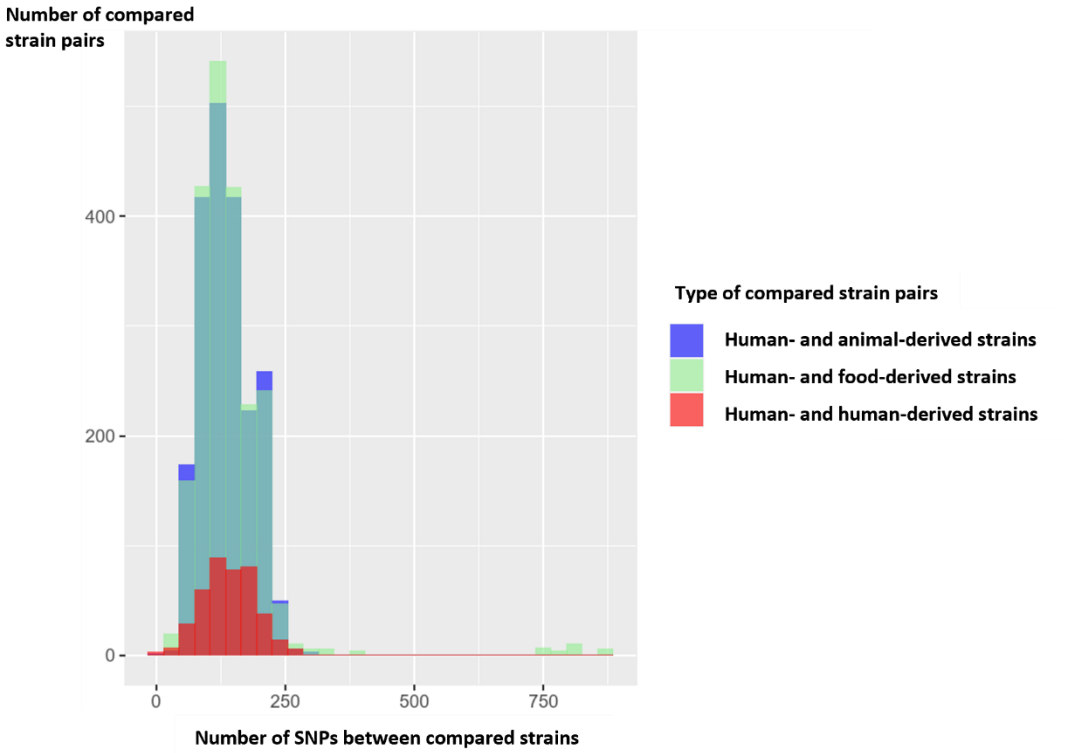


Figure 10: Distribution of SNP counts among human-derived strains, between human-derived and food-derived strains, and between human-derived and animal-derived strains of *Salmonella* Infantis

The light blue represents the overlap between blue (human-derived and animal-derived strains) and green (human-derived and food-derived strains).

***Campylobacter* spp.**

From the genomic data of 682 *Campylobacter* spp. strains accepted for genome analysis by the National Institute of Infectious Diseases between 2021 and 2024 (57 strains from food sources, specifically chicken meat distributed in the Tokyo metropolitan area; 364 strains from animal sources, including rectal feces from cattle and swine at slaughterhouses and cecal feces from chickens at poultry slaughterhouses; and 261 human-derived strains), core genome phylogenetic trees were constructed for *Campylobacter jejuni* (635 strains) and *Campylobacter coli* (47 strains) (Figures 11 and 12). The trees indicate the Clonal Complex (CC), source of origin, and the presence or absence of resistance genes or mutations contributing to resistance against tetracycline, fluoroquinolones, macrolides, and aminoglycosides. The most prevalent CC in *C. jejuni* was the ST-21 complex (232/635 = 37%), while in *C. coli*, the most frequent was the ST-828 complex (32/47 = 68%). Among the resistance genes, the most prevalent tetracycline resistance genes were *tet(O)* and *tet(O/M/O)*. In *C. jejuni*, the proportions of strains harboring *tet(O)* among those with tetracycline resistance genes were 52% for human-derived strains, 45% for food-derived strains, and 44% for animal-derived strains, with no significant differences between the groups. The factors contributing to macrolide resistance detected were amino acid substitutions in the 50S ribosomal protein L22 and base substitutions in the 23S rRNA gene, while *erm(B)* was not detected. The proportion of strains harboring amino acid substitutions in the 50S ribosomal protein L22 or base substitutions in the 23S rRNA gene was 43% in *C. coli* and 15% in *C. jejuni*. With regard to the source of isolation of the bacteria, *C. jejuni* was most frequently derived from sources other than swine (humans, chickens, cattle) (Figures 11, 13), whereas *C. coli* was predominantly derived from swine (Figures 12, 14). When comparing the breakdown of CCs (or STs) between different sources for *C. jejuni* and *C. coli*, no clear similarities in the CC breakdown between sources were observed for either species (Figures 13, 14). Furthermore, *C. coli* exhibited a higher proportion of strains harboring genes contributing to tetracycline resistance, mutations contributing to macrolide resistance, and genes contributing to aminoglycoside resistance compared to *C. jejuni* (Figure 15). When defining multidrug resistance as the presence of three or more genes or mutations contributing to resistance against tetracycline, fluoroquinolones, macrolides, or aminoglycosides, the proportion was 45% for *C. coli* and 5% for *C. jejuni*. No strains harboring ESBL genes were found in either *C. jejuni* or *C. coli*. Furthermore, Figure 16 illustrates combinations of human-derived and food-derived strains that are adjacent to each other in the *C. jejuni* phylogenetic tree. These combinations are characterized by short branch lengths between them (indicated by fewer SNPs in the comparison of core genome sequences) and an isolation year of human-derived strains relatively close to that of food-derived strains (2022 and 2023, compared to 2024 for food-derived strains) are shown in Figure 16. The combinations of these strains

belonged to either the ST-21 complex, ST-48 complex, or ST-22 (among these, ST-22 is known for its higher risk of causing Guillain-Barré syndrome). For each pair of human-derived and food-derived strains, SNPs on the core genome were detected, with at least 23 SNPs identified. The human-derived and food-derived strains analyzed in this study were not isolated from the same foodborne outbreak involving humans and the implicated food. In this analysis, pairs of strains that were closely related to the level detected in Salmonella were not found in *C. jejuni*. In contrast, in *C. coli*, no combinations with short branch lengths between human-derived and food-derived strains, similar to those found in *C. jejuni*, were observed. In *C. jejuni* used for this analysis, the number of food-derived strains was approximately one-fifth that of human-derived strains. To further investigate the potential for *C. jejuni* transmission from food to humans, expanding the dataset of food-derived strains is recommended.

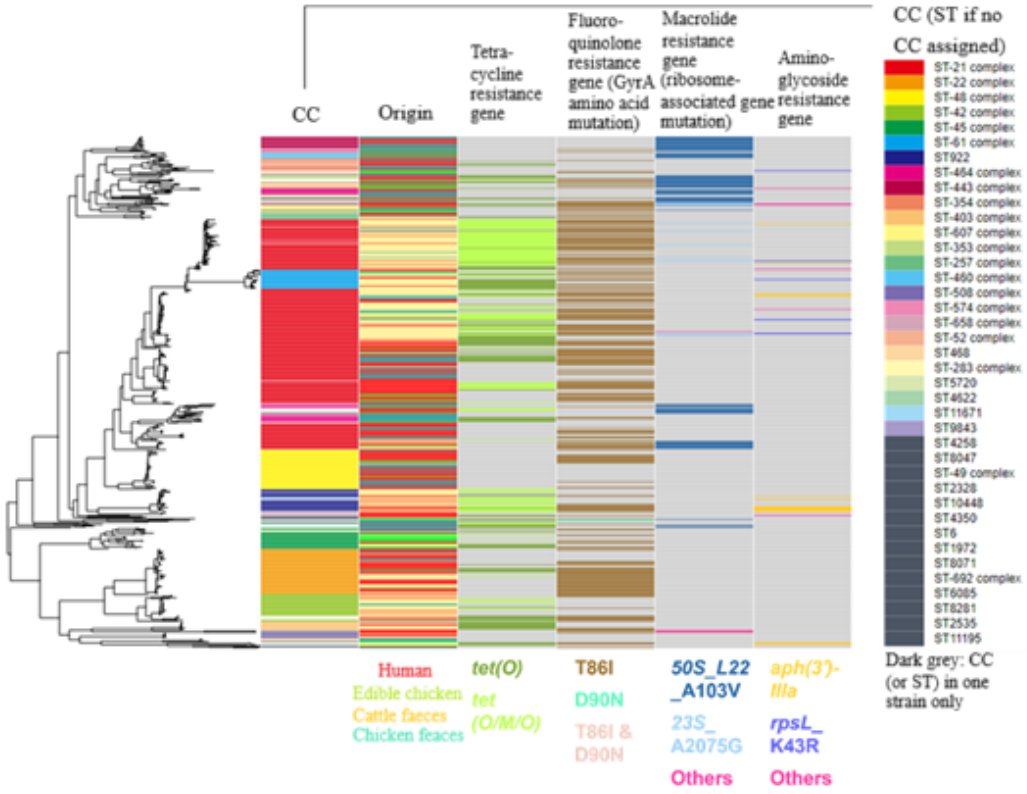


Figure 11 The phylogenetic tree constructed from the genomic data of 249 human-derived *C. jejuni* strains, 48 food (chicken)-derived strains, and 338 animal-derived strains, each strain's CC and origin, and the presence or absence of *tet* genes contributing to tetracycline resistance, amino acid substitutions in GyrA (mutation located in the quinolone resistance-determining region of the DNA gyrase A gene) contributing to fluoroquinolone resistance, amino acid substitutions in the 50S ribosomal protein L22 and base substitutions in the 23S rRNA gene contributing to macrolide resistance, and genes contributing to aminoglycoside resistance (primarily *aph(3')-IIIa* and amino acid substitutions in the ribosomal protein S12, encoded by the *rpsL* gene)

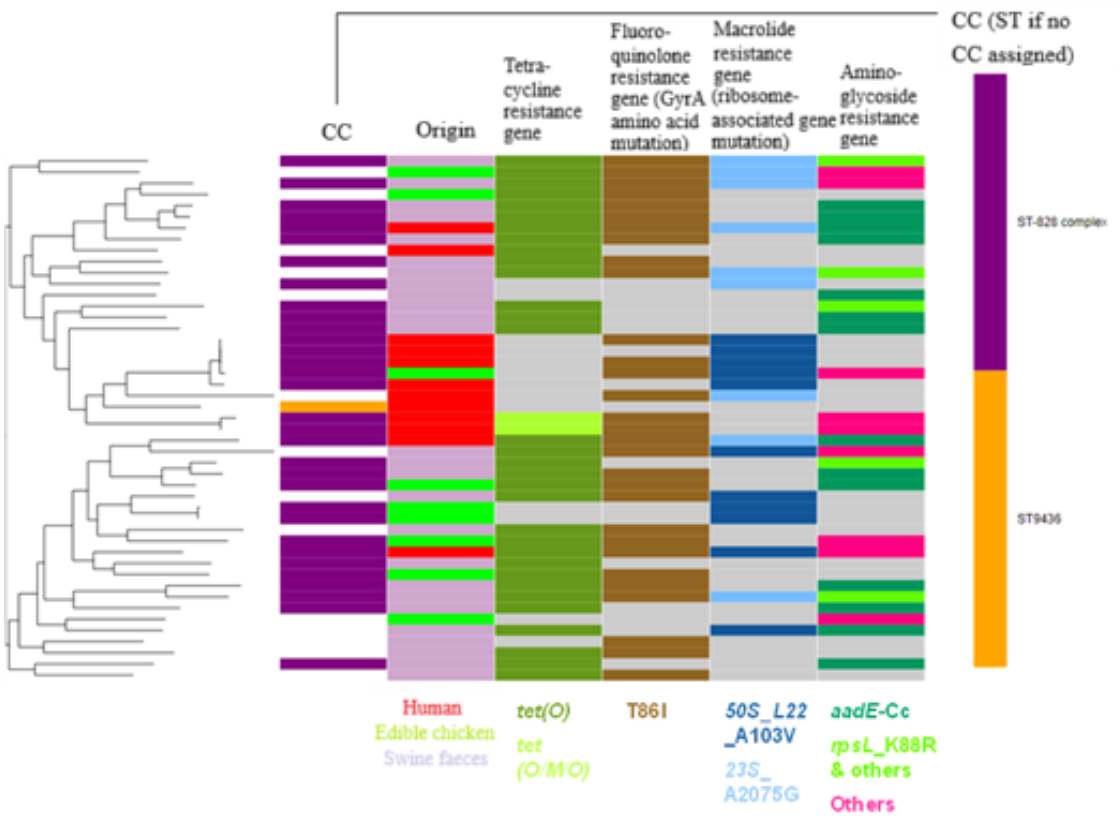


Figure 12 The phylogenetic tree constructed from the genomic data of 12 human-derived *C. coli* strains, 9 food (chicken)-derived strains, and 26 animal-derived strains, each strain's CC and origin, and the presence or absence of *tet* genes contributing to tetracycline resistance, amino acid substitutions at T86I in GyrA (mutation located in the quinolone resistance-determining region of the DNA gyrase A gene) contributing to fluoroquinolone resistance, amino acid substitutions in the 50S ribosomal protein L22 and base substitutions in the 23S rRNA gene contributing to macrolide resistance, and genes contributing to aminoglycoside resistance (primarily *aadECc* and amino acid substitutions in the ribosomal protein S12)

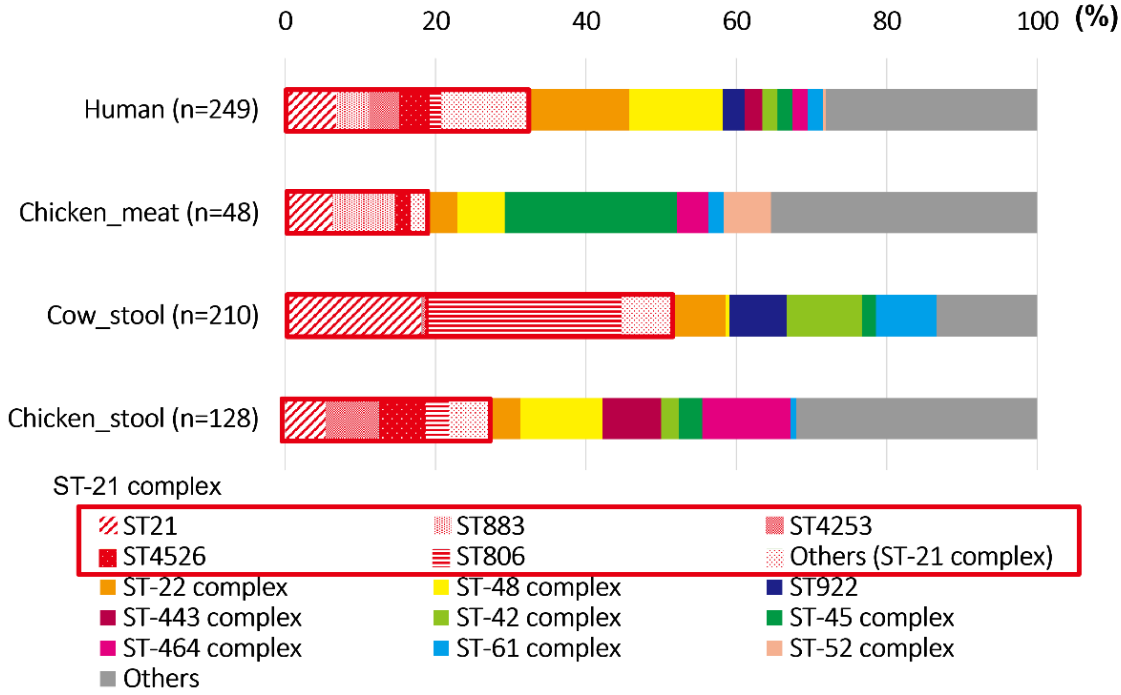


Figure 13 The breakdown of CC (or ST) by the source of *C. jejuni* (human, poultry meat, cattle rectal feces, and chicken cecal feces)

Note: All groups representing more than 5% of each source were highlighted, while the remaining strains, including those without assigned types, were colored gray. "Others (ST-21 complex)" refers to STs that account for less than 5%.

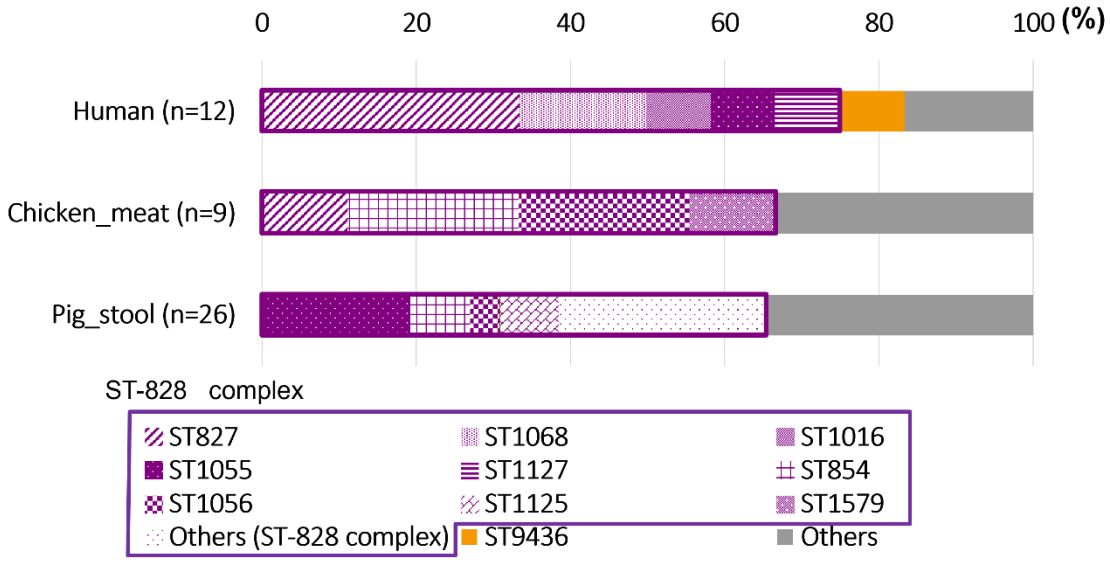
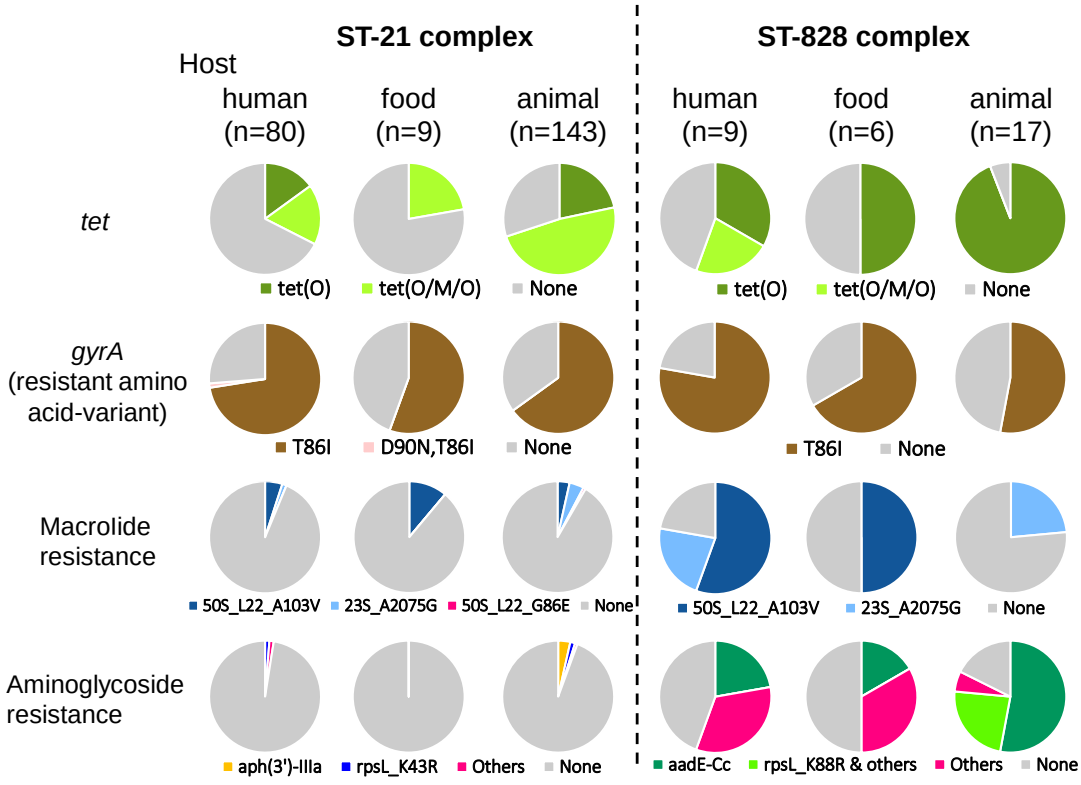


Figure 14 The breakdown of CC (or ST) by the source of *C. coli* (human, poultry meat, and swine rectal feces)

Note: "Others" (gray) refers to strains with no assigned ST, and "Others (ST-828 complex)" refers to STs that account for less than 5%.



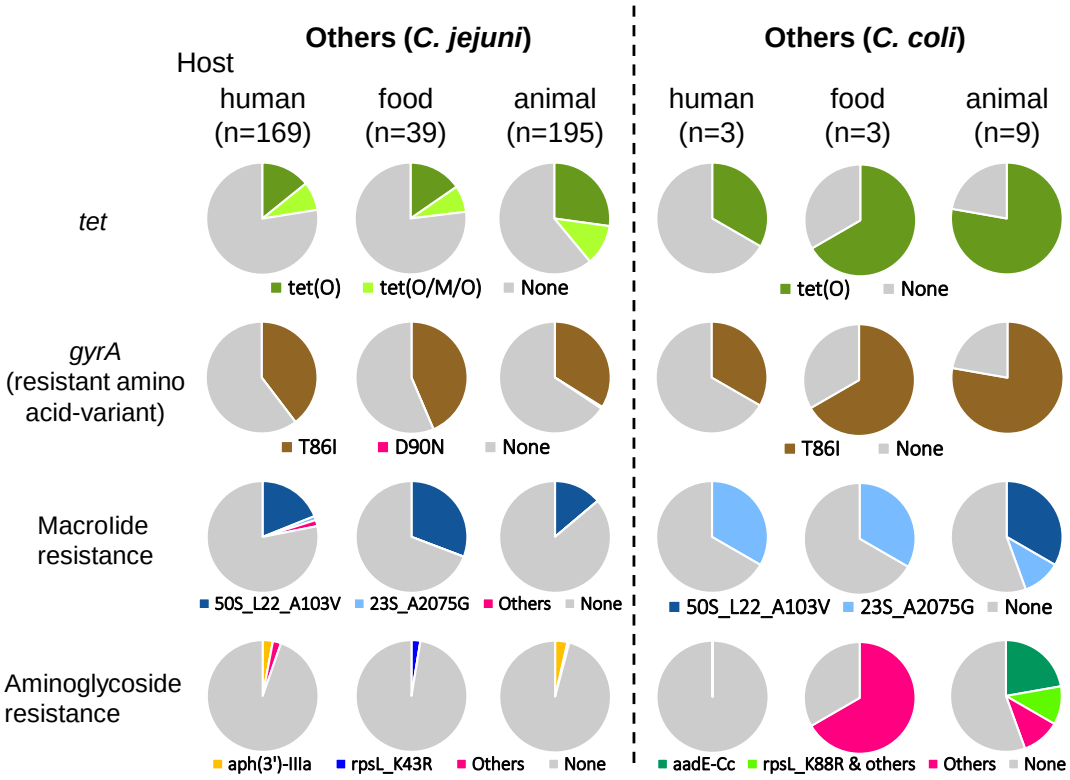


Figure 15 Proportions of major resistance genes in three different sources (human, food [chicken], and animals [rectal feces from cattle and swine at slaughterhouses, cecal feces from poultry slaughterhouses]) in two major CCs and other strains (strains outside the *C. jejuni* ST-21 complex and *C. coli* ST-828 complex). (Top: Two major CCs, Bottom: Other strains)

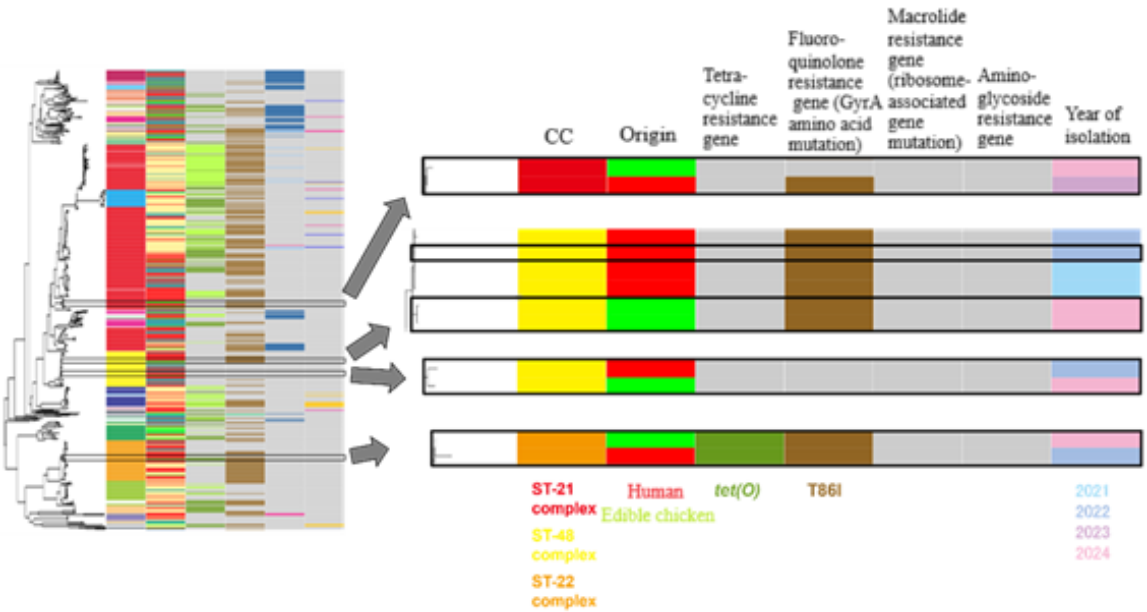


Figure 16 The expanded view (right) of the core genome phylogenetic tree (left) shown in Figure 11, highlighting the adjacent and closely related regions between food-derived strains (isolates from 2024) and human-derived strains (isolates from 2022 or 2023) within the ST-21 complex, ST-48 complex, and ST-22 complex

The rectangular frame in the expanded view indicates information on closely related food-derived strains and human-derived strains.

***Enterococcus* spp.**

The core genome phylogenetic tree constructed from the genome data of 38 *Enterococcus* spp. strains isolated from food (chicken meat samples from the meat hygiene inspection stations and the quarantine stations) between 2016 and 2021.The figure 17 shows the core genome phylogenetic tree for these samples. The data also includes 34 vancomycin-resistant *Enterococcus* (VRE) strains collected from hospitals across Japan in 2019 and 2020 by the Antimicrobial Resistance Research Center of National Institute of Infectious Diseases in 2019 and 2020, is shown in Figure 17. The species composition included one human-derived strain of *Enterococcus gallinarum*, 42 strains of *Enterococcus faecium*, and 29 strains of *Enterococcus faecalis*. Both *E. faecium* and *E. faecalis* were isolated from both food and human sources (Figures 17 and 18). In *E. faecium*, all human-derived VRE strains were classified into CC17, while none of the food-derived strains belonged to CC17, indicating a phylogenetic separation between human-derived VRE and food-derived strains. Similarly, in *E. faecalis*, human-derived VRE strains were classified into either ST6 or ST179, while none of the food-derived strains belonged to ST6 or ST179, indicating that human-derived and food-derived strains of *Enterococcus* spp. are phylogenetically distinct.

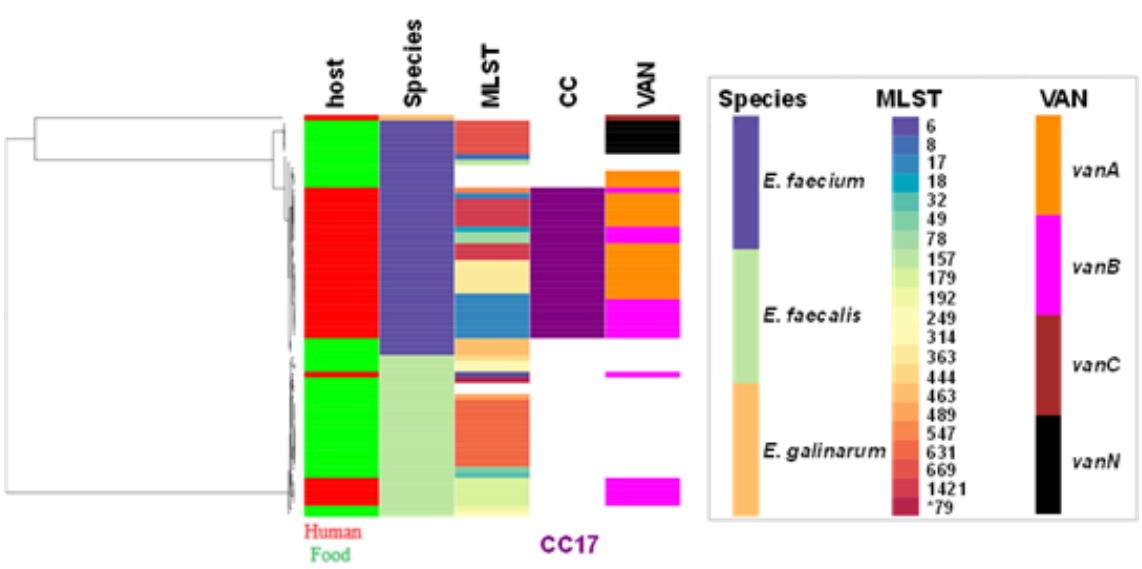


Figure 17 The phylogenetic tree constructed from the genome data of 38 food-derived and 34 human-derived *Enterococcus* spp. strains, along with information on the origin of each strain (human or food), species, ST, CC, and the types of van genes present

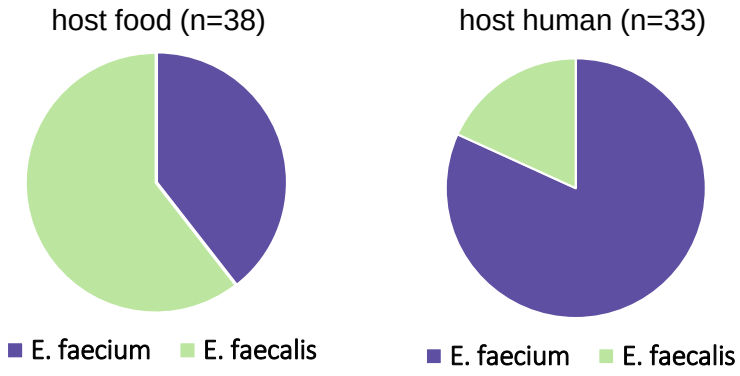


Figure 18 The proportion of the two *Enterococcus* species in food-derived and human-derived strains

2) The Antimicrobial Resistance (AMR) One Health Surveillance in coordination with the WHO surveillance (Tricycle Project)

This section presents an overview of the Tricycle Surveillance (Japanese name: SANRINSHA (tricycle) Project) using ESBL-producing *Escherichia coli* (ESBL-Ec), along with the results obtained thus far in Japan.

1. Background

At the G7 Elmau Summit in June 2015, antimicrobial resistance (AMR) was addressed as one of the key issues, and a policy was presented to develop and promote an integrated approach (One Health approach) involving humans, animals, food, and the environment. In 2017, the WHO Food Safety and Zoonoses Department, along with its advisory body AGISAR (the Advisory Group on Integrated Surveillance on Antimicrobial Resistance), proposed the Tricycle Surveillance using ESBL-producing Escherichia coli (ESBL-Ec) (https://www.who.int/publications/i/item/9789240021402), allowing participation by member countries. This initiative focuses on ESBL-Ec as a key indicator, and like the three wheels of a tricycle, it follows a common protocol across countries to calculate the proportion of ESBL-Ec among *Escherichia coli* from three sectors: human-derived, food-derived, and environment-derived. In addition to this, molecular characterization of the isolated strains and epidemiological analyses are conducted. By leveraging collaboration with GLASS, comparisons between regions and links with antimicrobial consumption are also explored. In Japan, surveys on antimicrobial-resistant bacteria in humans, food, and the environment have been conducted sporadically or as isolated studies across various fields and regions.

For example, it has been reported that 26% of *E. coli* cases resulting in community-acquired infections in humans carry ESBL [2]. The carriage rate of ESBL-producing Enterobacteriaceae in infants is 19.3%, with all but one case involved *E. coli* [3]. In the food sector, *K. pneumoniae* carrying bla_{NDM-1}, bla_{VIM-1}, and *mcr-9* was isolated from Japanese chicken meat obtained from grocery stores [4]. Furthermore, studies have identified minor carbapenemases such as bla_{GES-5}, bla_{FRI}, and bla_{IMI} from *Enterobacter* spp. and other bacteria in river and lake samples in Japan, suggesting that the environment may function as a potential reservoir for these resistance genes [5]. Investigating the interrelationship between these sectors is expected to be essential in future research. In Japan, nationwide surveillance over the long term based on a unified protocol, such as the WHO Tricycle Project, has not been conducted to date, and no data has been available to provide an overview of the current situation. In light of the need for continuous surveillance of antimicrobial-resistant bacteria in humans, food, and the environment in Japan, a research group was established for the study titled "Research on Antimicrobial-Resistant Bacteria One Health Trend Survey, Coordinated with WHO Surveillance" (Principal Investigator: Motoyuki Sugai, from April 1, 2020, to March 31, 2023) [6] as part of the Japan Agency for Medical Research and Development's (AMED) initiative for Research Program on Emerging and Re-emerging Infectious Diseases.

2. Objectives

The objective of this research group is to establish a system to accurately implement a protocol in accordance with the Tricycle Project. The aim is to establish a surveillance system capable of national-level comparisons by analyzing collected *E. coli* and ESBL-Ec strains, determining the antimicrobial resistance rates of *E. coli* in humans, food, and the environment, identifying trends in resistance development within each sector, and examining the transmission of resistance genes between sectors.

3. Samples and Methods

The isolation of *E. coli* and ESBL-Ec was conducted as follows:

(1) Human-derived samples

a) Prevalence of ESBL-Ec in patients (Blood culture origin, single institution)

- The rate of ESBL-Ec/Ec using E. coli counts from blood cultures obtained from a university hospital in A Prefecture was calculated.

b) Prevalence of ESBL-Ec in patients (Blood culture origin, nationwide)

- The rate of CTX resistant Ec/Ec using E. coli counts from blood cultures obtained from JANIS (hospitalization).

c) Prevalence of ESBL-Ec in healthy individuals (Rectal swabs from pregnant women)

- The rate of ESBL-Ec-positive pregnant women/total pregnant women was calculated using rectal swabs collected from healthy pregnant women in their third trimester (35–37 weeks) who visited outpatient clinics and university hospitals for prenatal checkups. ESBL-producing *E. coli* (ESBL-Ec) was identified from isolates grown on CTX-containing MacConkey agar.

d) Prevalence of ESBL-Ec in healthy individuals (Fecal samples from food service workers)

- The rate of ESBL-Ec/Ec was calculated using E. coli isolated from fecal samples of food service

workers, and samples themselves.

(2) Samples from chicken cecal feces at poultry processing plants (as an index for food-derived)

- The rate of ESBL-Ec/Ec was calculated for *E. coli* collected by the Ministry of Agriculture, Forestry and Fisheries' National Veterinary Assay Laboratory for the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) The isolates were derived from broiler chicken cecal feces collected at poultry processing plants.

(3) Environmental-derived samples

- The presence of *E. coli* and ESBLwas confirmed from isolates obtained on TBX agar, which is designed for *E. coli* isolation. The rate of ESBL-Ec/Ec was calculated using sewage inflow water from wastewater treatment plants and river water, in specific regions (including Hokkaido, Saitama, Nagano, Hiroshima).

4. Results and discussion

The proportion of ESBL-Ec was determined for each of the human, environmental and food sectors by implementing and analyzing the collection of bacterial strains in humans, the environment, and food in Japan (Figure 19).

With regard to the proportion of ESBL-Ec among *E. coli* isolates in the human sector, a study conducted from 2019 to 2021 on blood culture-derived E. coli at a university hospital in A Prefecture revealed that ESBL-Ec accounted for 29.7% of E. coli isolates. Meanwhile , the nationwide statistics for blood culture-derived *E. coli* from hospitalized patients as reported by JANIS, indicated that the proportion of CTX-resistant strains from 2019 to 2020 was 24.0%. It should be noted that, as JANIS does not collect bacterial strains but instead gathers phenotypic data based on antimicrobial susceptibility test results, CTX-resistant strains were considered to be ESBL-producing strains. Consequently, the ESBL E. coli prevalence among patients with underlying conditions was found to be 20–30%. In contrast, for healthy individuals, the proportion of ESBL-Ec among E. coli isolated from rectal swabs of pregnant women in a specific region from 2022 to 2023 was 12.0%, and from fecal samples of food service workers from 2019 to 2020, it was 4.0%. Both of these values were lower than the ESBL prevalence in E. coli isolates from patient samples. It has been reported that the proportion of ESBL-Ec in human feces is higher in hospital environments than in the community, with antimicrobial use potentially contributing to this difference [7, 8]. Additionally, a literature review summarizing the situation until 2015 [9] reported that the global prevalence of ESBL-producing *E. coli* was 14%, with regional variations: 46% in Asia, 15% in Africa, 3% in Central Europe, 4% in Northern Europe, 6% in Southern Europe, and 2% in North and South America. Furthermore, the ESBL production rate among *E. coli* in pregnant women was reported as 2.9% in Norway [10], 22.3% in Benin [11], and the prevalence of ESBL-producing Gram-negative bacilli was 19.1% in Lebanon [12] and 18.5% in Madagascar [13]. Moreover, a meta-analysis reported that 21.1% of hospitalized patients and 17.6% of healthy individuals globally harbor ESBL-Ec in their intestines, and that the global prevalence of ESBL-Ec in healthcare settings has increased threefold, from 7% in 2001–2005 to 25.7% in 2016–2020 [14].

Additionally, the proportion of ESBL-producing *E. coli* (ESBL-Ec) isolated from the cecal feces of chickens collected at poultry processing plants, which serve as indicators for food (2019–2021 strains collected by JVARM), was 1.78% in this study (with 3.05% of the strains exhibiting resistance to CTX). In Japan, third-generation cephalosporins are used as a second-line drugs for cattle and swine but sales are low (1.07 t, 0.17% in 2021) [15] Cephalosporins are not approved for use in chickens. Prior to 2012, some off-label use in chickens was conducted, but this practice has since been discontinued. Furthermore, in the case of swine, where the sales volume of third-generation cephalosporins is highest, the resistance rate of *E. coli* from healthy swine to cefotaxime, a third-generation cephalosporin, is low at 2.1%.

With regard to environmental-derived samples, a survey conducted from 2020 to 2021 revealed that the proportion of ESBL-Ec was 1.96% in upstream river water, 0.39% in downstream river water, 4.77% in sewage inflow water, and 0.72% in wastewater from poultry and other animal slaughterhouses. While there have been numerous individual reports of antimicrobial-resistant bacteria being isolated from river water, there are fewer studies reporting the proportion of ESBL-Ec among the total *E. coli* isolates. For instance, a study from Ghana reported that 98% of *E. coli* from river water were ESBL-Ec [16], a study from Indonesia reported that 4.2–30.2% of *E. coli* from environmental water were ESBL-Ec [17], and a study from the United States reported that the ESBL prevalence among *E. coli* in all environmental samples was 8.5% [18].

The ESBL-Ec strains obtained in this study were analyzed using NGS, and the distribution of the identified Sequence Types (STs) is shown in a Venn diagram (Figure 20). According to the results, strains from the cecal feces of chickens collected at poultry processing plants shared few common STs with human- and environmental-derived strains. In contrast, human- and environmental-derived strains shared many common STs, accounting for 28.2% (27 strains) of the total. Furthermore, the common STs identified across the three sectors were ST93, ST117, ST155, and ST162. With regard to the patterns of ST and CTX-M genes, human-derived and environmental-derived (sewage) strains shared common ST and CTX-M variants, while strains derived from the cecal feces of chickens at

poultry processing plants did not exhibit common strains with those. The relationship between these strains and plasmids, as well as the mechanisms of antimicrobial resistance gene transmission, are planned for further analysis.

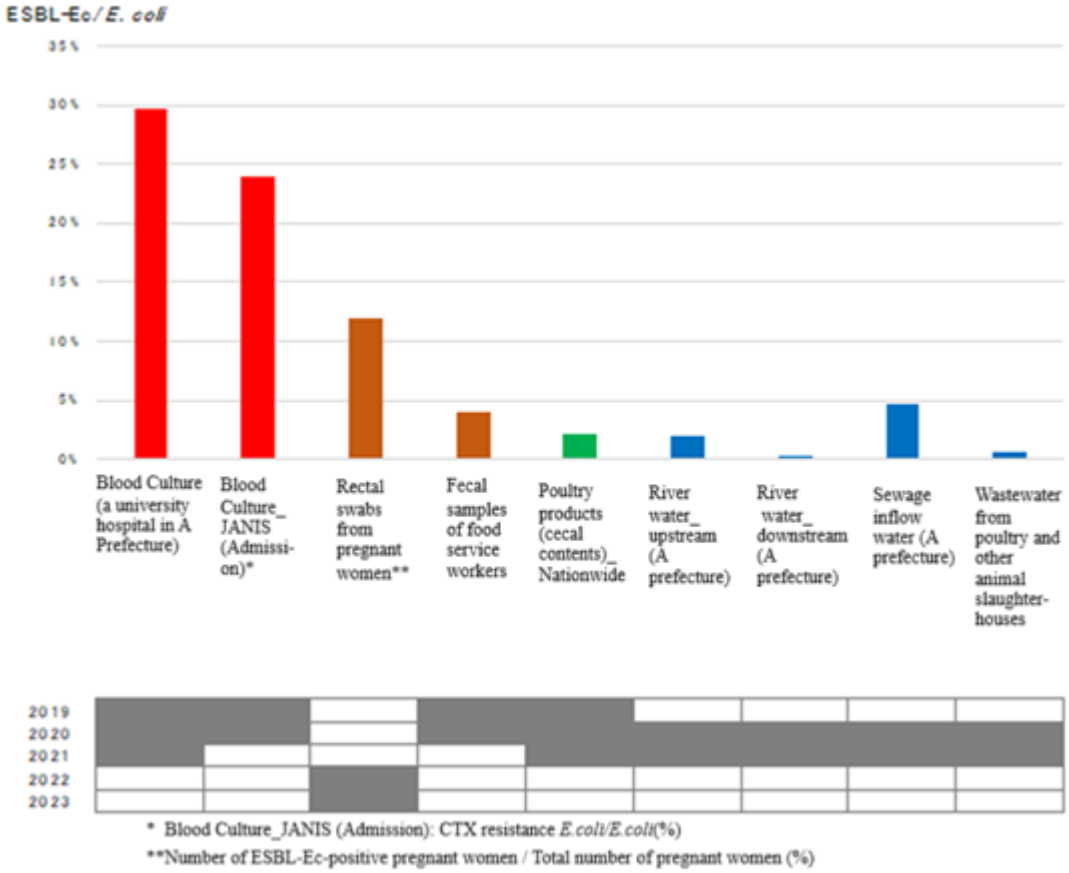


Figure 19 The proportion of ESBL-Ec among the total *E. coli* isolates

The proportion of ESBL-producing *E. coli* among the total *E. coli* isolates is shown [5]. The years of analysis are indicated below the bar graph for each sample. For the population groups under analysis, please refer to the cited literature.

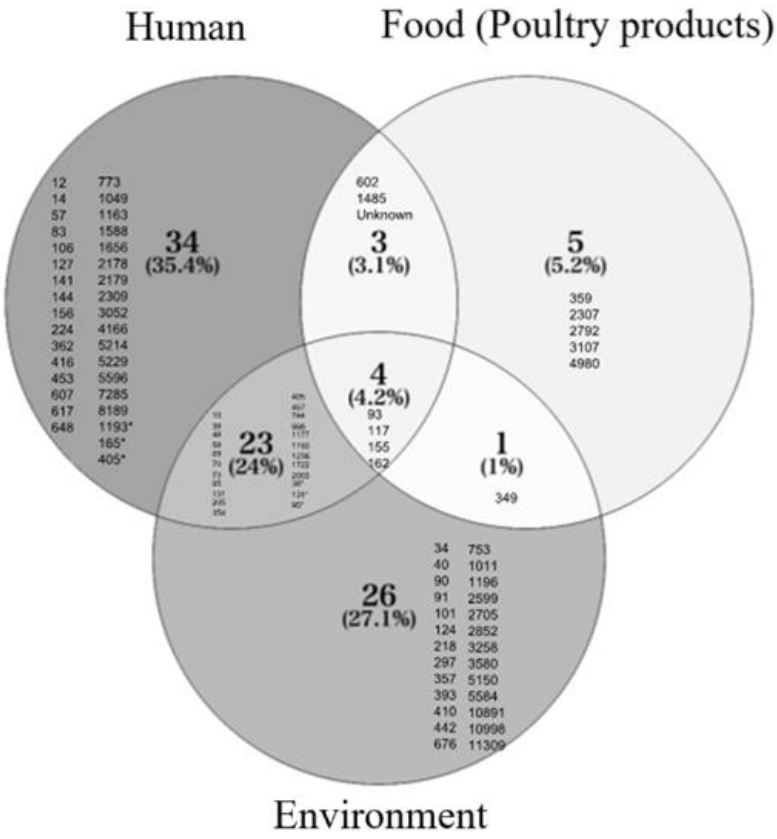


Figure 20 Venn diagram illustrating the types of STs of ESBL-Ec isolated from humans, food, and the environment

The large numbers within the circles represent the number and proportion of ST types (please note that the number of strains is not reflected). The smaller numbers indicate the STs. An asterisk (*) next to the STs in the figure denotes subtypes that differ by only one housekeeping gene.

3) A Study on the Quantitative Evaluation of Vegetable Contamination through Aquatic and Soil Environments Infected by Livestock-Derived Antimicrobial-Resistant Bacteria and Its Transmission to Humans (Results from the Food Safety Impact Assessment Technology Research (FY2020–FY2021)) [19]

An examination was conducted with the aim of evaluating the risk of contamination of vegetables by livestock-derived antimicrobial-resistant bacteria through aquatic and soil environments and their potential transmission to humans.

Using university-affiliated farms and others as a model, the extent of transmission of livestock-derived antimicrobial-resistant bacteria to crops was investigated. The study identified, strains closely related to antimicrobial-resistant bacteria found in livestock waste in the soil and crops on the farm, while the transmission of livestock-derived antimicrobial-resistant bacteria to vegetables through soil cannot be ruled out, it was confirmed that the transmission from livestock waste to crops was extremely limited.

In addition, a comparative analysis was conducted on the genomes of ampicillin-resistant bacteria (primarily *E. coli*) isolated from livestock (rectal feces, farm soil, etc.), aquatic environments (wastewater before and after treatment), vegetables, and human clinical cases from fiscal year 2020 to 2021. The genomic analysis revealed that the phylogenetic classification of resistant bacteria from livestock, aquatic environments, vegetables, and human clinical sources was diverse, and no clear relationships were found between the isolates from these different sources. On the other hand, among 332 strains harboring the bla_{TEM} gene isolated from livestock, aquatic environments, vegetables, and humans, NGS analysis revealed that 47 strains possessed structures including *IS26* in the bla_{TEM} gene and its surrounding regions. Sequence comparison of 19 of these strains were identified to have similar gene sequences. While the epidemiological relationships and transmission routes of these strains remain unclear, it is suggested that resistance genes and their surrounding structures may be transmitted and disseminated across different sources, potentially via plasmids. However, as the genomic comparison focuses on identical structures, there is a possibility that the frequency of dissemination or transmission may have been overestimated.

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7. Current Volume of Use of Antimicrobials in Japan

(1) Antimicrobials for humans

1) Usage of antimicrobials in Japan

Source: Japan Surveillance of Antimicrobial Consumption (JSAC)

Antimicrobial use based on sales volume in Japan from 2014 to 2023 is shown in Table 75 (oral agents), Table 76 (injectable agents), and Table 77 (total of oral and injectable antimicrobial agents). Overall use of antimicrobials in Japan in 2021 amounted to 9.77 DID. A comparison with DID in major countries in 2020 shows that this was lower than France (21.5 DID), Italy (17.5 DID), and Sweden (10.1 DID), but higher than the Netherlands (8.5 DID) and Austria (8.8 DID) [1]. Looking at changes over time, no significant changes in antimicrobial use were observed from 2013 to 2016, but the decline began in 2017, with the decrease becoming smaller. During such a trend, there was an epidemic of COVID-19 infections, and overall antimicrobial use in 2020 declined more sharply compared to the previous years. The years 2021 and 2022 exhibited a flat trend, with a 3.9% decrease in 2022 compared to 2020. However, in 2023, the overall figure was 11.96 DID, representing a 17.4% increase compared to 2020.

The use of oral agents in 2023 (Table 75) as a percentage of total antimicrobial use is 10.96 DID (91.6%), of which oral third generation cephalosporins (1.94 DID) which are targeted to be reduced by 40% in the Nippon AMR Action Plan, oral fluoroquinolones (2.07 DID), which are targeted for a 30% reduction, and oral macrolides (3.45 DID), which are targeted for a 25% reduction, together accounted for 68.1% of all oral antimicrobial agents. While this trend has not changed since 2013, when comparing each use to 2020, use of oral cephalosporins, oral fluoroquinolones, and oral macrolides in 2023 increased by 14.7%, 25%, 17.7%, respectively. The use of parenteral carbapenems decreased by 6.7% between 2020 and 2023 (Table 76). It was thought that 2019 may have seen a decrease in first-generation cephalosporins and an increase in narrow-range penicillins, penicillin with be-lactamase inhibitors, second- and third generation cephalosporins, and carbapenems, especially due to cephazolin supply shortage issues. [2] Overall antimicrobial use decreased scince 2020, which may be due not only to the promotion of appropriate antimicrobial use, but also to the impact of COVID-19 (e.g., fewer patients seen with infections other than new coronavirus infections). A similar trend was seen to continue until 2022 also due to the continuing pandemic.

Table 78 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. This classification was amended in 2019 to add the new category of "discouraged antibiotics," consisting of antimicrobials whose clinical use the WHO does not recommend (for example, cefoperazone-sulbactam). The WHO has set a target of at least 60% of antimicrobial consumption being from medicines classified as the Access Group. While consumption of antimicrobials classified as the Access Group as a proportion of total use tends to be lower in Japan than other countries,[3] the figure has risen gradually over the years since 2014 from 11.8% to 22.94% in 2023, with the percentage of antimicrobials classified as the Watch Group falling from 86.7% to 75.98%, which can mean that Japan is on its way towards the actions recommended in the Action Plan (2023-2027).

However, various factors, such as the problem of antimicrobial supply shortages and the impact of new coronavirus infections and lifting of restrictions on activities, are also of concern and require continued close monitoring.

A survey of oral and parenteral antimicrobial use in terms of potency by weight from a One Health perspective (Table 79) also confirmed an increase in 2023 in overall use, which had been showing a decrease. The decrease in the use of oral third generation cephalosporins, fluoroquinolones, and macrolides accounted for half of the total, and it is necessary to clarify the factors from the viewpoint of appropriate use, considering the impact of COVID-19 infection, the subsequent lifting of restrictions on activities, the emergence of various infectious diseases, and limitations in the supply of antibiotics. Since there may be a future impact of the incentives for appropriate use of antibiotics, continuous monitoring of future trends in antimicrobial use is deemed essential

The establishment of a surveillance system, which was one of the goals of the Action Plan for AMR control, made it possible to assess the use of antimicrobial agents in Japan over time. In addition to the various influencing factors mentioned above, the impact of the increasing elderly population should also be considered, necessitating closer attention. In 2020, however, oral agents declined further, and parenteral antimicrobial agents also began to decline. One reason for the decrease may be the various effects associated with the new coronavirus infections, and although there has not been another increase at this time, it is necessary to understand future trends. Furthermore,

the purpose of antimicrobial use needs to be clarified and its appropriateness evaluated by continuing surveillance of antimicrobial use, based not only on sales volume data but also on the National Database for Prescription and National Health Checkups (NDB).

Table 75. Trends in oral antimicrobial use in Japan based on the volume of sales

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Tetracyclines	0.75	0.77	0.80	0.81	0.88	0.96	1.10	1.18	1.18	1.28
Amphenicols	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	＜0.01	＜0.01
Penicillins with extended spectrum	0.61	0.68	0.66	0.65	0.69	0.77	0.61	0.59	0.60	0.83
Beta Lactamase-sensitive penicillins	0.01	0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	＜0.01	＜0.01
Combinations of penicillins, including beta lactamase inhibitors	0.16	0.17	0.18	0.19	0.20	0.23	0.18	0.19	0.19	0.23
1st generation cephalosporins	0.07	0.07	0.07	0.07	0.08	0.09	0.09	0.10	0.11	0.13
2nd generation cephalosporins	0.30	0.29	0.29	0.28	0.28	0.30	0.29	0.31	0.32	0.37
3rd generation cephalosporins	3.41	3.46	3.32	3.08	2.83	2.63	1.85	1.70	1.63	1.94
Carbapenems	0.02	0.02	0.02	0.01	0.01	0.01	0.01	0.01	＜0.01	0.01
Other cephalosporins and penems	0.14	0.13	0.12	0.12	0.11	0.10	0.09	0.09	0.08	0.09
Combinations of sulfonamides and trimethoprim, including derivatives	0.27	0.29	0.31	0.33	0.36	0.38	0.41	0.44	0.46	0.48
Macrolides	4.50	4.59	4.56	4.18	3.96	3.84	2.93	2.72	2.66	3.45
Lincosamides	0.01	0.02	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Fluoroquinolones	2.83	2.71	2.75	2.57	2.42	2.32	1.66	1.48	1.52	2.07
Other quinolones	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	＜0.01	＜0.01
Other antibacterials	0.10	0.10	0.10	0.09	0.08	0.08	0.06	0.06	0.06	0.06
Total	13.18	13.30	13.19	12.38	11.92	11.74	9.31	8.88	8.84	10.96

* As a unit, DIDs (DDDs/1,000 inhabitants/day) is used.

* Figures for DDD (defined daily dose) are those for January 1, 2024.

Table 76. Trends in parenteral antimicrobial use in Japan based on the volume of sales

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Tetracyclines	0.02	0.02	0.02	0.02	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	＜0.01	＜0.01	＜0.01	＜0.01
Penicillins with extended spectrum	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Beta-lactamase sensitive penicillins	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	0.01	＜0.01	＜0.01	＜0.01	＜0.01
Combinations of penicillins, incl. beta-lactamase inhibitors	0.15	0.16	0.18	0.19	0.21	0.22	0.18	0.20	0.23	0.26
First generation cephalosporins	0.13	0.14	0.14	0.15	0.15	0.12	0.13	0.14	0.15	0.15
Second generation cephalosporins	0.11	0.10	0.10	0.10	0.09	0.10	0.08	0.08	0.09	0.09
Third generation cephalosporins	0.19	0.21	0.22	0.23	0.24	0.27	0.22	0.21	0.22	0.24
Fourth generation cephalosporins	0.03	0.03	0.03	0.03	0.03	0.02	0.02	0.02	0.02	0.03
Monobactams	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01
Carbapenems	0.08	0.08	0.08	0.08	0.08	0.08	0.07	0.07	0.07	0.06
Other cephalosporins and penems	-	-	-	-	-	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01
Combinations of sulfonamides and trimethoprim, incl. derivatives	＜0.01	＜0.01	＜0.01	＜0.01	＜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	＜0.01	＜0.01	＜0.01	＜0.01
Lincosamides	0.02	0.02	0.02	0.02	0.02	0.02	0.01	0.01	0.01	0.01
Streptogramins	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	-	-	-	-
Streptomycins	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01
Other aminoglycosides	0.05	0.05	0.04	0.04	0.03	0.03	0.03	0.02	0.02	0.02
Fluoroquinolones	0.03	0.03	0.04	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Glycopeptide antibacterials	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.04
Polymyxins	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01
Imidazole derivatives	＜0.01	＜0.01	＜0.01	＜0.01	＜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	0.01	0.01	0.01	0.01
Total	0.90	0.94	0.96	0.98	0.99	1.01	0.87	0.89	0.94	1.00

* As a unit, DID (DDDs/1,000 inhabitants/day) is used.

* Figures for DDD (defined daily dose) are those for January 1, 2024.

Table 77. Trends in oral and parenteral antimicrobial use in Japan based on the volume of sales

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Tetracyclines	0.77	0.79	0.82	0.83	0.90	0.98	1.12	1.19	1.19	1.30
Amphenicols	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01
Penicillins with extended spectrum	0.64	0.70	0.68	0.67	0.71	0.79	0.63	0.61	0.62	0.85
Beta-lactamase sensitive penicillins	0.01	0.01	0.01	0.01	0.01	0.01	0.01	＜0.01	＜0.01	0.01
Combinations of penicillins, incl. beta-lactamase inhibitors	0.31	0.34	0.36	0.38	0.41	0.45	0.36	0.38	0.42	0.48
First generation cephalosporins	0.20	0.20	0.21	0.22	0.23	0.21	0.22	0.24	0.26	0.29
Second generation cephalosporins	0.40	0.39	0.39	0.37	0.38	0.41	0.38	0.39	0.41	0.45
Third generation cephalosporins	3.60	3.67	3.54	3.31	3.07	2.90	2.07	1.91	1.85	2.18
Fourth generation cephalosporins	0.03	0.03	0.03	0.03	0.03	0.02	0.02	0.02	0.02	0.03
Monobactams	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01
Carbapenems	0.10	0.10	0.10	0.09	0.09	0.09	0.07	0.08	0.07	0.07
Other cephalosporins and penems	0.14	0.13	0.12	0.12	0.11	0.10	0.09	0.09	0.08	0.09
Combinations of sulfonamides and trimethoprim, incl. derivatives	0.27	0.29	0.32	0.34	0.36	0.39	0.41	0.44	0.46	0.48
Macrolides	4.51	4.59	4.56	4.18	3.96	3.84	2.93	2.73	2.66	3.45
Lincosamides	0.04	0.04	0.04	0.03	0.03	0.04	0.03	0.03	0.03	0.04
Streptogramins	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	-	-	-	-
streptomycins	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01
Other aminoglycosides	0.05	0.05	0.04	0.04	0.03	0.03	0.03	0.02	0.02	0.02
Fluoroquinolones	2.86	2.74	2.78	2.60	2.45	2.35	1.69	1.51	1.55	2.10
Other quinolones	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.10
Glycopeptide antibacterials	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.04
Polymyxins	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01
Imidazole derivatives	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01	＜0.01
Other antibacterials	0.12	0.12	0.12	0.10	0.10	0.10	0.08	0.07	0.07	0.08
Total	14.08	14.23	14.15	13.36	12.91	12.75	10.18	9.77	9.78	11.96

* As a unit, DID (DDDs/1,000 inhabitants/day) is used.

* Figures for DDD (defined daily dose) are those for January 1,2024.

Table 78. Trends in antimicrobial use in Japan by AWaRe classification

AWaRe Classification	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Access (%)	1.67	1.79	1.84	1.90	2.06	2.25	2.17	2.29	2.39	2.80
	(11.79)	(12.49)	(12.92)	(14.16)	(15.90)	(17.57)	(20.91)	(22.85)	(23.79)	(22.94)
Watch (%)	12.26	12.31	12.18	11.33	10.72	10.38	8.07	7.58	7.52	9.29
	(86.73)	(86.07)	(85.70)	(84.47)	(82.76)	(81.11)	(77.67)	(75.77)	(74.90)	(75.98)
Reserve (%)	0.18	0.18	0.17	0.16	0.15	0.15	0.13	0.12	0.12	0.12
	(1.31)	(1.27)	(1.22)	(1.20)	(1.18)	(1.16)	(1.25)	(1.22)	(1.15)	(0.99)
Non-recommended (%)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.01
	(0.16)	(0.15)	(0.15)	(0.16)	(0.16)	(0.16)	(0.17)	(0.16)	(0.16)	(0.09)
Unclassified (%)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	(0.01)	(0.01)	(0.01)	(0.01)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)
Total	14.14	14.30	14.21	13.41	12.96	12.79	10.39	10.01	10.03	12.23

* As a unit, DID (DDDs/1,000 inhabitants/day) is used.

* Figures for DDD (defined daily dose) are those for January 1, 2023. AWaRe classification 2021 edition was used.

* The above is consistent with the medications included in the GLASS Report, based on the WHO's AWaRe classification, resulting in slight modifications to the previous values.

Table 79. Antimicrobial consumption by weight based on sales volume in Japan, converted to potency (t)

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Tetracyclines	6.9	7.1	7.2	7.0	7.3	7.7	8.4	8.7	8.5	9.0
Amphenicols	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Penicillins with extended spectrum	53.6	57.6	56.3	54.5	57.3	62.6	49.3	47.9	48.5	64.3
Beta Lactamase-sensitive penicillins	1.8	1.7	1.5	1.4	1.3	1.8	1.3	1.1	1.1	1.3
Combinations of penicillins, including beta lactamase inhibitors	95.7	106.1	114.9	124.4	132.2	146.0	118.0	129.2	146.4	163.3
1st generation cephalosporins	24.9	25.2	26.3	27.2	28.4	24.9	26.5	28.9	30.2	33.1
2nd generation cephalosporins	27.4	27.0	26.7	25.9	26.0	28.6	25.5	26.5	27.7	29.5
3rd generation cephalosporins	95.1	97.8	95.9	91.2	86.6	85.3	64.0	59.8	58.8	65.1
4th generation cephalosporins	6.1	6.0	5.7	5.5	4.8	4.5	4.3	4.2	4.4	4.7
Monobactams	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Carbapenems	9.9	10.1	10.2	10.1	9.8	10.0	8.8	9.1	9.1	8.2
Other cephalosporins and penems	4.7	4.6	4.3	4.0	3.8	3.6	3.3	3.0	2.9	3.2
Combinations of sulfonamides and trimethoprim including derivatives	49.9	53.7	58.6	62.1	65.7	71.0	75.7	81.3	84.6	87.5
Macrolides	101.4	103.4	102.9	94.5	89.7	87.2	67.8	63.4	61.9	79.0
Lincosamides	2.7	2.6	2.5	2.4	2.4	2.7	2.1	2.1	2.2	2.4
Streptogramins	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	ー	ー	-	<0.1
Streptomycin	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Other aminoglycosides	0.9	0.9	0.8	0.8	0.7	0.7	0.5	0.5	0.5	0.5
Fluoroquinolones	60.2	56.6	57.4	53.2	50.1	47.7	33.0	29.2	29.1	36.9
Other quinolones	0.4	0.3	0.3	0.2	0.1	0.1	0.1	<0.1	<0.1	0.0
Glycopeptides	2.1	2.3	2.4	2.5	2.4	2.6	2.7	2.4	2.6	2.8
Polymyxins	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
Imidazole derivatives (parenteral)	<0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.3
Other antibacterials	16.5	16.6	16.7	14.3	13.8	13.1	10.3	9.3	8.9	9.8
Total	560.6	580.1	591.4	581.6	582.9	600.2	501.9	507.0	527.8	601.1

Table 80. Trends in the use of total oral and parenteral antimicrobial agents in Japan based on NDB

	2013	2014	2015	2016	2017	2018	2019	2020	2021
Tetracyclines	0.75	0.74	0.75	0.78	0.79	0.85	0.93	1.06	1.13
Amphenicols	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Penicillins with extended spectrum	0.53	0.56	0.64	0.64	0.63	0.67	0.76	0.61	0.61
Beta-lactamase sensitive penicillins	0.01	0.01	0.01	0.01	< 0.01	< 0.01	0.01	0.01	< 0.01
Combinations of penicillins, incl. beta-lactamase inhibitors	0.25	0.27	0.29	0.31	0.33	0.35	0.38	0.31	0.33
First-generation cephalosporins	0.14	0.15	0.16	0.16	0.17	0.18	0.17	0.19	0.22
Second-generation cephalosporins	0.34	0.35	0.36	0.35	0.34	0.34	0.37	0.35	0.36
Third generation cephalosporins	3.47	3.54	3.69	3.57	3.34	3.11	2.94	2.10	1.91
Fourth generation cephalosporins	0.03	0.03	0.03	0.03	0.02	0.02	0.02	0.02	0.02
Monobactams	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Carbapenems	0.08	0.08	0.08	0.08	0.08	0.07	0.07	0.06	0.06
Other cephalosporins and penems	0.12	0.12	0.12	0.11	0.11	0.10	0.10	0.09	0.08
Combinations of sulfonamides and trimethoprim, incl. derivatives	0.23	0.25	0.27	0.29	0.31	0.33	0.36	0.38	0.42
Macrolides	4.97	4.93	5.07	5.03	4.64	4.44	4.37	3.30	3.04
Lincosamides	0.04	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Streptogramins	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	-
streptomycins	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Other aminoglycosides	0.05	0.05	0.05	0.04	0.04	0.03	0.03	0.02	0.02
Fluoroquinolones	2.78	2.74	2.93	2.93	2.74	2.61	2.51	1.78	1.63
Other quinolones	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Glycopeptide antibacterials	0.02	0.02	0.02	0.02	0.02	0.02	0.03	0.03	0.03
Polymyxins	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Imidazole derivatives	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01
Other antibacterial agents	0.11	0.11	0.11	0.11	0.09	0.09	0.09	0.07	0.06
Total	13.93	13.99	14.63	14.51	13.70	13.28	13.15	10.41	9.96

* As a unit, DID (DDDs/1,000 inhabitants/day) is used.

* Figures for DDD (defined daily dose) are those for January 1, 2024.

2) Usage of parenteral antimicrobials in hospitals

Source: J-SIPHE

J-SIPHE, operated by AMRCRC, uses an integrated inpatient EF file* to survey antimicrobial use in participating facilities and publishes the annual reports.[5] In 2023, overall, in-hospital use of intravenous antimicrobial agents followed a similar trend to the previous year. Penicillins (AUD 3.95, DOT 6.02) were the most commonly used, followed by 3rd generation cephalosporins (AUD 2.99, DOT 3.86), 1st generation cephalosporins (AUD 2.10, DOT 2.88), cephamycins (AUD 0.91, DOT 1.69), and carbapenems (AUD 0.71, DOT 1.42). It is necessary to continuously monitor the trend in the future.

*E file: An information file for details about medical services; *F file: A claims file for medical service fees for inpatients that integrates procedural detail information

Table 81. Use of parenteral antimicrobials at medical institutions (AUD, DOT)

	2019		2020		2021		2022		2023	
	AUD (IQR)	DOT (IQR)	AUD (IQR)	DOT (IQR)	AUD (IQR)	DOT (IQR)	AUD (IQR)	DOT (IQR)	AUD (IQR)	DOT (IQR)
Penicillin	3.92 (2.71-5.10)	5.96 (4.15-7.82)	3.48 (2.15-4.82)	5.19 (3.53-7.01)	3.92 (2.32-5.32)	5.77 (3.70-7.35)	3.86 (1.85-5.75)	5.64 (3.20-7.99)	3.95 (1.87 -6.38)	6.02 (3.19 -8.88)
1st generation cephalosporins	1.71 (0.83-2.86)	2.23 (1.21-3.94)	2.28 (1.15-3.27)	3.11 (1.58-4.36)	2.52 (1.22-3.62)	3.40 (1.72-4.73)	2.21 (0.79-3.62)	3.02 (1.08-4.75)	2.10 (0.74 -3.70)	2.88 (1.03 -4.85)
2nd generation cephalosporins	0.18 (0.09-0.41)	0.37 (0.19-0.83)	0.15 (0.06-0.35)	0.29 (0.13-0.69)	0.14 (0.06-0.29)	0.27 (0.12-0.60)	0.15 (0.07-0.32)	0.31 (0.14-0.66)	0.14 (0.06 -0.31)	0.30 (0.13 -0.62)
3rd generation cephalosporins	3.33 (2.18-4.74)	4.58 (3.05-6.30)	3.00 (1.95-4.32)	4.04 (2.87-5.60)	2.91 (1.90-4.32)	4.02 (2.68-5.42)	2.84 (1.74-4.17)	3.91 (2.52-5.36)	2.99 (1.69 -4.35)	3.86 (2.35 -5.40)
4th generation cephalosporins	0.34 (0.14-0.70)	0.53 (0.25-1.01)	0.31 (0.14-0.76)	0.49 (0.26-1.05)	0.32 (0.16-0.74)	0.55 (0.28-1.02)	0.27 (0.14-0.62)	0.46 (0.25-0.97)	0.27 (0.14 -0.62)	0.48 (0.26 -0.97)
Oxacefemmes	0.30 (0.11-0.70)	0.31 (0.12-0.76)	0.25 (0.11-0.61)	0.27 (0.11-0.64)	0.20 (0.09-0.54)	0.20 (0.10-0.55)	0.22 (0.10-0.46)	0.22 (0.10-0.48)	0.22 (0.10 -0.49)	0.23 (0.10 -0.52)
Cephamycins	0.89 (0.52-1.41)	1.70 (0.99-2.62)	0.91 (0.47-1.42)	1.67 (0.93-2.62)	1.01 (0.53-1.52)	1.87 (1.04-2.76)	0.94 (0.43-1.55)	1.76 (0.84-2.78)	0.91 (0.36 -1.58)	1.69 (0.74 -2.84)
Cephalosporins with beta-lactamase inhibitors	0.06 (0.03-0.10)	0.07 (0.03-0.11)	0.09 (0.06-0.14)	0.09 (0.06-0.13)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.10 (0.06-0.18)	0.10 (0.06-0.14)	0.12 (0.07 -0.23)	0.10 (0.06 -0.18)
Carbapenems	1.23 (0.63-1.79)	2.05 (1.15-3.00)	1.09 (0.55-1.87)	1.95 (1.04-2.90)	1.12 (0.56-1.91)	2.04 (1.09-3.05)	0.88 (0.43-1.71)	1.71 (0.89-2.83)	0.71 (0.32 -1.43)	1.42 (0.70 -2.50)
Monobactams	0.04 (0.02-0.09)	0.07 (0.03-0.11)	0.04 (0.02-0.09)	0.07 (0.04-0.10)	0.05 (0.03-0.07)	0.07 (0.05-0.11)	0.06 (0.03-0.11)	0.07 (0.05-0.14)	0.06 (0.03 -0.09)	0.07 (0.05 -0.13)
Glycopeptides	0.56 (0.27-0.94)	0.81 (0.46-1.32)	0.48 (0.25-0.92)	0.77 (0.40-1.30)	0.50 (0.26-0.95)	0.77 (0.43-1.32)	0.42 (0.22-0.79)	0.70 (0.38-1.20)	0.40 (0.21 -0.77)	0.66 (0.39 -1.19)
Oxazolidinones	0.11 (0.07-0.16)	0.11 (0.07-0.17)	0.11 (0.07-0.18)	0.12 (0.08-0.20)	0.12 (0.07-0.19)	0.13 (0.08-0.21)	0.12 (0.07-0.20)	0.13 (0.08-0.22)	0.13 (0.07 -0.21)	0.14 (0.08 -0.23)
Arbekacine	0.07 (0.04-0.13)	0.07 (0.04-0.12)	0.08 (0.04-0.14)	0.08 (0.04-0.15)	0.08 (0.04-0.16)	0.08 (0.04-0.16)	-	-	-	-
Lipopeptides	0.25 (0.14-0.38)	0.17 (0.11-0.28)	0.24 (0.14-0.39)	0.16 (0.11-0.26)	0.26 (0.15-0.44)	0.18 (0.11-0.30)	0.26 (0.15-0.43)	0.18 (0.11-0.29)	0.25 (0.15 -0.40)	0.17 (0.11 -0.28)
Quinolones	0.39 (0.21-0.61)	0.41 (0.23-0.64)	0.37 (0.22-0.59)	0.40 (0.25-0.63)	0.35 (0.22-0.59)	0.38 (0.24-0.63)	0.35 (0.21-0.59)	0.38 (0.23-0.62)	0.37 (0.22 -0.60)	0.39 (0.24 -0.64)
Aminoglycosides	0.10 (0.06-0.18)	0.23 (0.14-0.45)	0.10 (0.05-0.17)	0.24 (0.14-0.43)	0.10 (0.05-0.20)	0.25 (0.15-0.49)	0.11 (0.06-0.21)	0.27 (0.15-0.49)	0.11 (0.06 -0.21)	0.27 (0.14 -0.48)
Streptomycins							0.05 (0.03-0.09)	0.06 (0.03-0.10)	0.05 (0.03 -0.12)	0.06 (0.03 -0.12)
Tetracyclines	0.14 (0.09-0.26)	0.17 (0.10-0.29)	0.15 (0.09-0.27)	0.17 (0.10-0.33)	0.15 (0.09-0.30)	0.17 (0.10-0.32)	0.18 (0.11-0.34)	0.21 (0.12-0.39)	0.19 (0.11 -0.35)	0.22 (0.12 -0.40)
Lincosamides	0.22 (0.13-0.39)	0.32 (0.19-0.55)	0.20 (0.13-0.33)	0.28 (0.18-0.46)	0.19 (0.12-0.32)	0.27 (0.18-0.43)	0.20 (0.12-0.32)	0.28 (0.18-0.43)	0.20 (0.12 -0.32)	0.28 (0.17 -0.44)
Macrolides	0.07 (0.04-0.10)	0.07 (0.04-0.10)	0.07 (0.05-0.11)	0.07 (0.05-0.12)	0.07 (0.04-0.11)	0.07 (0.05-0.11)	0.08 (0.05-0.13)	0.08 (0.05-0.13)	0.08 (0.05 -0.14)	0.08 (0.05 -0.14)
ST	0.07 (0.03-0.11)	0.06 (0.03-0.09)	0.07 (0.03-0.14)	0.06 (0.03-0.11)	0.08 (0.04-0.14)	0.07 (0.04-0.11)	0.08 (0.05-0.15)	0.07 (0.04-0.12)	0.08 (0.04 -0.14)	0.07 (0.05 -0.11)
Imidazole derivatives	0.10 (0.07-0.17)	0.11 (0.07-0.18)	0.11 (0.06-0.17)	0.12 (0.07-0.19)	0.12 (0.08-0.18)	0.14 (0.09-0.21)	0.14 (0.09-0.22)	0.15 (0.10-0.24)	0.15 (0.09 -0.24)	0.16 (0.10 -0.25)

AUD: Antimicrobial Use Density, DOT: Days of Therapy, tabulated by DDDs/100 patient-days

DOT: Days of Therapy, tabulated by DOTs/100 patient-days

*Note: Cephalosporin/a beta-lactamase inhibitor combination is not used in 2021 due to supply disruptions.

*Note: Benzylpenicillin benzathine is counted as penicillin agent starting in September 2022.

* Note: Imipenem/cilastatin/relebactam were counted as carbapenems from September 2022.
* Tabulation definitions have changed since 2022.
- Arbekacin and spectinomycin are counted as aminoglycosides.
- Streptomycin is counted as streptomycin instead of aminoglycoside.
- Change of class names: Ceftarosan/tazobactam is changed to cephalosporin with beta-lactamase inhibitor, daptomycin to lipopeptide, lincomycin to lincosamide, sulfamethoxazole/trimethoprim to ST.
* Tabulation definitions have changed since 2023.
- Metronidazole is counted as imidazole.

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(2) Veterinary agents

Source: Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

Based on the same volumes of sales of antibiotics and synthesized antimicrobials, as reported under Article 72-2 of the Veterinary Agent Control Regulations, the amounts of veterinary antimicrobials were calculated in terms of active ingredients (metric tons (t)). In the period from 2013 to 2022 the volume of sales of veterinary antimicrobials ranged between 748.44 to 858.09 t. The total volume of sales in 2022 decreased by approx. 24 t since 2021. Antimicrobials reduced their sales including macrolides (approx. 23 t) and tetracyclines (approx. 5 t), with the decrease in macrolides primarily due to a reduction of 12 tons in livestock animals and 11 tons in aquatic animals. Tetracyclines represented the largest share of antimicrobial sales volume over the period monitored, accounting for between 36.1% and 43.7%, which, however, have fallen below 40% in recent years.

On the other hand, third generation cephalosporins and fluoroquinolones, which are important antimicrobials for human medicine, accounted for approx. 0.2% and 1.0% of overall volume of sales, respectively.

Table 82. Amounts of veterinary antimicrobials in terms of active ingredients by class (t)

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Penicillins	78.17	77.96	83.73	90.01	88.08	88.99	92.41	96.97	89.02	91.15
Cephalosporins(total)	5.58	5.50	5.89	6.45	6.65	7.06	8.02	7.72	8.03	7.37
1st generation cephalosporins	(4.71)	(4.58)	(4.98)	(5.41)	(5.50)	(5.67)	(6.62)	(6.40)	(6.61)	(5.96)
2nd generation cephalosporins	(0.19)	(0.20)	(0.12)	(0.16)	(0.18)	(0.22)	(0.14)	(0.15)	(0.13)	(0.13)
3rd generation cephalosporins	(0.68)	(0.71)	(0.79)	(0.88)	(0.96)	(1.18)	(1.26)	(1.16)	(1.28)	(1.27)
Aminoglycosides	39.52	40.64	35.47	47.86	44.76	35.61	35.17	36.89	29.84	31.31
Macrolides	77.70	70.43	98.41	134.12	140.83	154.72	180.71	173.72	157.72	134.69
Lincosamides	38.99	43.26	28.66	21.87	25.26	22.76	21.29	21.45	22.45	23.70
Tetracyclines	340.52	324.85	333.86	331.55	347.05	311.18	313.03	304.38	305.75	300.41
Peptides	11.78	9.98	14.54	14.02	19.99	12.34	19.56	19.06	18.40	18.55
Other antibioitics	25.98	28.85	32.39	31.96	36.19	37.50	35.96	36.34	37.45	35.92
Sulfonamides	103.90	97.57	96.67	95.85	99.06	88.77	84.69	98.53	81.96	84.37
Quinolones	1.01	1.91	1.71	1.74	1.84	1.48	2.57	2.34	1.72	2.29
Fluoroquinolones	5.53	5.63	7.35	6.08	6.83	6.65	7.53	7.06	8.39	7.54
Amphenicols	21.53	26.15	29.73	26.49	27.11	24.82	27.38	25.55	27.02	28.28
Furan and derivatives	14.46	1.76	1.24	1.57	1.36	1.34	1.35	1.23	1.55	1.45
Other synthetic antibacterials	15.02	13.97	13.35	12.12	13.09	11.98	11.71	11.68	11.57	9.88
Total	779.70	748.44	782.98	821.70	858.09	805.19	841.37	842.92	800.87	776.90

* 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, swine accounted for the largest amount, followed by seawater fish. Since 2018, sales have decreased in swine, with the decrease in livestock possibly due to increased awareness of the need for prudent use and improved rearing hygiene management due to outbreaks of classical swine fever and highly pathogenic avian influenza.

In order to conduct comparisons of usage by animal species, the number of heads and weight per head of the animal should be taken into account. 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. The WOAH has recently set out a method for calculating biomass weight as part of its data collection of veterinary antimicrobial usage data and published data on use per biomass weight (sales volume) by region, but this is a summary of all livestock and is not comparable by species. Therefore, the risk management working group within Ministry of Agriculture, Forestry and Fisheries is currently considering specific calculation methods, taking cues from the WOAH methodology.

Table 83. Estimated amounts of veterinary antimicrobials in terms of active ingredients by animal species (t)

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Beef cattle	23.02	20.35	23.77	25.00	25.92	33.17	33.40	58.33	59.27	58.00
Dairy cow	31.73	30.45	32.48	35.10	34.55	41.01	36.79	48.71	47.97	45.34
Horse	2.18	2.01	2.10	2.31	2.17	3.90	3.49	3.84	1.84	1.87
Swine	502.64	490.42	503.13	513.86	541.61	471.36	450.24	421.27	410.52	391.57
Broiler	65.90	70.14	62.36	63.81	61.74	62.79	69.81	77.53	69.14	61.53
Layer	23.29	23.67	19.36	19.78	15.32	15.86	17.56	17.13	9.32	9.68
Fish (saltwater)	112.36	93.41	123.02	143.03	159.07	164.00	217.66	204.15	190.56	197.26
Fish (freshwater)	6.84	5.61	7.28	10.10	9.07	2.91	2.74	2.27	2.03	2.15
Ornamental fish	0.72	1.07	1.60	1.95	1.74	1.63	1.64	1.56	2.14	2.09
Dog/Cat	8.49	8.10	7.78	6.67	6.90	8.56	8.03	8.11	8.08	7.40
Other	2.54	3.22	0.09	0.10	0.00	0.00	0.00	0.00	0.00	0.00
Total	779.70	748.44	782.96	821.70	858.09	805.19	841.37	842.92	800.87	776.9

1) Food-producing animals

The estimated volumes of veterinary antimicrobials sold for food-producing animals (cattle, swine, horses, chickens, and others) in terms of active ingredients are listed in Table83. In the period from 2013 to 2022, the estimated volume of sales ranged between 567.99 t and 681.31 t, with sales in 2022 being the lowest volume since 2013. The most common antimicrobials were tetracyclines (236.49 t to 286.74 t), which accounted for 38.3% to 44.0% of the antimicrobials for livestock animals, but in 2021 they were at their lowest volume (220.70 t) since 2013. This is largely due to the decreased use in swine. In contrast, third generation cephalosporins and fluoroquinolones, which are critically important antimicrobials for human medicine, each accounted for approximately from 0.1% to 0.2% and 1% of the antimicrobial agents for livestock animals, respectively.

Table 84. The estimated volumes of sales of veterinary antimicrobials for food-producing animals (cattle, swine, horses, chickens, and others) in terms of active ingredients (t)

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Penicillins	59.50	61.96	67.25	73.82	71.75	74.48	73.76	76.22	72.44	72.88
Cephalosporins (total)	3.12	3.06	3.22	3.34	3.44	3.91	4.11	3.79	4.05	3.99
1st generation cephalosporins	(2.45)	(2.34)	(2.52)	(2.52)	(2.51)	(2.73)	(2.93)	(2.68)	(2.85)	(2.77)
2nd generation cephalosporins	(0.19)	(0.20)	(0.12)	(0.16)	(0.18)	(0.22)	(0.14)	(0.15)	(0.13)	(0.13)
3rd generation cephalosporins	(0.49)	(0.51)	(0.58)	(0.65)	(0.74)	(0.96)	(1.04)	(0.95)	(1.07)	(1.08)
Aminoglycosides	37.40	38.66	34.07	47.46	44.37	34.69	34.77	36.52	29.75	31.22
Macrolides	56.00	53.30	60.36	72.68	71.96	72.09	73.29	72.71	73.03	61.00
Lincosamides	35.88	36.61	23.65	15.62	19.39	16.72	16.26	17.48	19.11	19.60
Tetracyclines	286.74	275.83	276.24	280.66	286.01	257.36	242.93	240.12	236.49	220.70
Peptides	11.77	9.97	14.54	14.01	19.98	12.34	19.56	19.05	18.39	18.54
Other antibiotics	25.71	28.43	32.23	31.55	35.72	36.87	35.64	35.54	37.30	35.61
Sulfonamides	95.62	88.43	84.40	78.57	84.10	78.59	68.64	84.38	64.16	62.53
Quinolones	0.22	0.20	0.20	0.16	0.31	0.01	0.11	0.18	0.16	0.26
Fluoroquinolones	4.64	4.73	6.41	5.19	5.93	5.80	6.66	6.18	7.54	6.70
Amphenicols	19.66	25.14	27.39	24.82	25.34	23.28	23.89	23.11	24.23	25.27
Furan and derivatives	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Other synthetic antibacterials	14.98	13.92	13.32	12.07	13.02	11.96	11.68	11.53	11.41	9.70
Total	651.24	640.25	643.28	659.95	681.31	628.09	611.29	626.83	598.07	567.99

* 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 84. In the period from 2013 to 2022, the estimated volume of sales ranged between 100.09 t (2014) to 222.05 t (2019), accounting for between 13.4% (2014) and 26.4% (2019) of the total volume of veterinary antimicrobial sales. The most commonly sold antimicrobial agent was tetracyclines until 2015; however, from 2016 to 2021, macrolides (such as erythromycin) took the lead. In 2022, tetracyclines regained their position as the most widely sold. The approximately 82 t increase in the volume of sales between 2013 and 2022 was due to a rise in sales of a macrolide (erythromycin), which was presumably attributed to the occurrence and treatment of infections caused by Group A Streptococcus (α-hemolytic) types II, which were first identified around 2013, and type III, which began to be identified around 2021. On the other hand, the decrease in the sales volume of macrolides (erythromycin) is thought to be due to the fact that it was widely known that Florfenicol and Lincomycin had been approved in addition to erythromycin and oxytetracycline. Following a renewed awareness campaign in 2022 regarding the appropriate use of multiple approved drugs, it is speculated that the exclusive use of macrolides was discontinued. Notably, the sales volume of macrolides (erythromycin) in 2022 was 73.68 tons, a decrease of 11.01 tons from the previous year's 84.69 tons.

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

Table 85. The estimated volumes of sales of veterinary antimicrobials for aquatic animals (seawater fish, freshwater fish, and ornamental fish) in terms of active ingredients (t)

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Penicillins	16.31	13.87	14.38	14.62	14.66	12.85	17.01	19.21	14.29	16.16
Cephalosporins (total)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1st generation cephalosporins	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2nd generation cephalosporins	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3rd generation cephalosporins	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Aminoglycosides	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Macrolides	21.70	17.13	38.05	61.44	68.87	82.61	107.40	101.01	84.69	73.68
Lincosamides	3.02	6.56	4.90	6.12	5.73	5.91	4.88	3.82	3.19	3.94
Tetracyclines	53.78	49.01	57.62	50.89	61.05	52.55	69.57	63.84	68.84	79.28
Peptides	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Other antibioitics	0.27	0.42	0.16	0.42	0.47	0.63	0.32	0.80	0.16	0.31
Sulfonamides	7.68	8.59	11.71	16.74	14.39	9.64	15.56	13.36	17.53	21.49
Quinolones	0.79	1.71	1.51	1.58	1.53	1.47	2.45	2.15	1.56	2.03
Fluoroquinolones	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Amphenicols	1.87	1.01	2.33	1.67	1.77	1.53	3.48	2.43	2.78	2.99
Furan and derivatives	14.46	1.76	1.24	1.57	1.36	1.34	1.35	1.23	1.55	1.45
Other synthetic antibacterials	0.02	0.04	0.02	0.04	0.06	0.02	0.02	0.12	0.13	0.16
Total	119.91	100.09	131.91	155.08	169.88	168.54	222.05	207.98	194.72	201.50

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 86. In the period from 2013 to 2022, the estimated volume of sales ranged between 6.67 to 8.56 t, with 7.40 t in 2022, marking a decline from 2021. Sales volume 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 Agents & 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. The results of its surveillance revealed that the volume of human antimicrobials sold for use in companion animals is slightly less than the volume of veterinary antimicrobials sold for that purpose. Including those for human antimicrobials, the most commonly sold antimicrobials were first-generation cephalosporins and penicillins.

Table 86. The estimated volumes of sales of veterinary and human antimicrobials for companion animals (dogs and cats) in terms of active ingredients (t) (1/2)

	2013	2014	2015	2016		2017		2018	
	Veterinary	Veterinary	Veterinary	Veterinary	Human	Veterinary	Human	Veterinary	Human
Penicillins	2.36	2.13	2.08	1.57	1.93	1.68	1.75	1.66	2.14
Cephalosporins(total)	2.45	2.44	2.67	3.12	3.23	3.21	2.39	3.16	1.98
1st generation cephalosporins	(2.26)	(2.23)	(2.46)	(2.89)	(3.08)	(2.99)	(2.27)	(2.93)	(1.86)
2nd generation cephalosporins	(0.00)	(0.00)	(0.00)	(0.00)	(0.04)	(0.00)	(0.03)	(0.00)	(0.03)
3rd generation cephalosporins	(0.20)	(0.20)	(0.21)	(0.23)	(0.11)	(0.22)	(0.09)	(0.22)	(0.09)
Aminoglycosides	2.07	1.97	1.40	0.41	0.02	0.39	0.01	0.91	0.01
Macrolides	0.00	0.00	0.00	0.00	0.17	0.00	0.16	0.02	0.17
Lincosamides	0.09	0.09	0.11	0.13	0.10	0.13	0.10	0.14	0.10
Tetracyclines	0.00	0.00	0.00	0.00	0.28	0.00	0.31	1.27	0.33
Peptides	0.01	0.01	0.01	0.01	0.00	0.01	0.00	0.01	0.00
Other antibiotics**	0.00	0.00	0.00	0.00	0.22	0.00	0.21	0.00	0.22
Sulfonamides	0.60	0.55	0.56	0.53	0.19	0.57	0.19	0.53	0.22
Quinolones	0.00	0.00	0.00	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	0.11	0.84	0.12
Amphenicols	0.00	0.00	0.00	0.00	0.12	0.01	0.10	0.01	0.11
Furan and derivatives	0.00	0.00	0.00	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	0.10	0.01	0.10
Total	8.49	8.10	7.78	6.67	6.48	6.90	5.43	8.56	5.51

Table 86. The estimated volumes of sales of veterinary and human antimicrobials for companion animals (dogs and cats) in terms of active ingredients (t) (2/2)

	2019		2020		2021		2022	
	Veterinary	Human	Veterinary	Human	Veterinary	Human	Veterinary	Human
Penicillins	1.64	1.98	1.54	1.56	1.64	1.98	1.54	2.14
Cephalosporins(total)	3.91	2.04	3.93	1.62	3.91	2.04	3.93	1.98
1st generation cephalosporins	(3.69)	(1.90)	(3.72)	(1.49)	(3.69)	(1.90)	(3.72)	(1.86)
2nd generation cephalosporins	(0.00)	(0.03)	(0.00)	(0.03)	(0.00)	(0.03)	(0.00)	(0.03)
3rd generation cephalosporins	(0.22)	(0.11)	(0.21)	(0.10)	(0.22)	(0.11)	(0.21)	(0.09)
Aminoglycosides	0.40	0.02	0.37	0.02	0.40	0.02	0.37	0.01
Macrolides	0.02	0.18	0.00	0.18	0.02	0.18	0.00	0.17
Lincosamides	0.15	0.09	0.15	0.08	0.15	0.09	0.15	0.10
Tetracyclines	0.53	0.35	0.42	0.34	0.53	0.35	0.42	0.33
Peptides	0.01	0.00	0.01	0.00	0.01	0.00	0.01	0.00
Other antibiotics**	0.00	0.22	0.00	0.23	0.00	0.22	0.00	0.22
Sulfonamides	0.50	0.25	0.78	0.25	0.50	0.25	0.78	0.22
Quinolones	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Fluoroquinolones	0.87	0.16	0.88	0.11	0.87	0.16	0.88	0.12
Amphenicols	0.01	0.12	0.01	0.11	0.01	0.12	0.01	0.11
Furan and derivatives	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Other synthetic antibacterials***.	0.00	0.13	0.02	0.11	0.00	0.13	0.02	0.10
Total	8.03	5.53	8.11	4.60	8.03	5.53	8.11	5.51

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

** Includes fosfomycin and rifamycin, etc. (vancomycin for human was 0.0006 t in 2016, 0.0005 t in 2017, 0.0006 t in 2018, 0.0006 t in 2019, 0.0006 t in 2020, 0.0004 t in 2021, 0.0005 t in 2022)

*** Includes trimethoprim, penems, carbapenems, etc. (carbapenems for human was 0.0066 t in 2016, 0.0057 t in 2017, 0.0062 t in 2018, 0.0083 t in 2020, 0.0070 t in 2021, 0.0060 t in 2022)

References

1. Gochez D., Raicek M., Ferreira J. P., Jeannin M., Moulin G., Erlacher-Vindel E. OIE annual report on antimicrobial agents intended for use in animals: methods used. Frontiers in Vet. Sci. 2019. 6. doi: 10.3389/fvets.2019.00317

(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 86. While the volume of such additives distributed showed a slight decrease in the period 2021 to 2022, ranging between 211.1 t and 203.3 t, with a major decrease of approximately 5.7 t in polypeptides. The designation of the polypeptide colistin as a feed additive was revoked in July 2018, followed by the macrolide tylosin in May 2019 and two tetracyclines in December 2019. Distribution of these antimicrobials ceased from the time their designation was revoked.

Table 87. Volume of distribution of antibiotic feed additives in terms of effective value (t)

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Aminoglycosides	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Polypeptides	35.0	28.3	29.6	32.1	15.2	9.4	6.4	7.1	10.4	4.7
Tetracyclines	1.6	2.2	2.6	2.0	0.0	0.0	0.0	0.0	0.0	0.0
Macrolides	5.6	5.3	5.5	1.4	3.5	0.0	0.0	0.0	0.0	0.0
Polysaccharides	0.2	0.0	0.1	0.1	0.1	0.0	2.3	3.4	1.4	1.3
Polyethers	136.0	142.5	141.7	159.9	165.5	161.0	174.1	192.5	169.7	166.8
Other antimicrobials	20.8	18.3	12.5	14.6	19.8	26.2	17.6	11.9	12.5	13.4
Synthetic antimicrobials	35.9	29.3	24.4	18.1	17.1	20.1	25.1	20.0	17.1	17.1
Total	235.1	225.9	216.4	228.2	221.2	216.7	225.5	234.9	211.1	203.3

(4) Agrochemicals

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

The volume of shipment in Japan of antimicrobials that are used as agrochemicals is shown in the table, in terms of active ingredients (unit: tons). In the period from 2013 to 2022, the volume of shipments of antimicrobials used as agrochemicals remained at around the 150 t mark, ranging from 133.24 to 181.43 t.

Table 88. The volume of shipment in Japan of antimicrobials that are used as agrochemicals, in terms of active ingredients (t)

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Streptomycin	45.19	45.30	44.41	49.80	56.04	36.19	35.90	37.52	36.78	37.51
Oxytetracycline	19.49	22.23	23.25	19.46	17.81	0.13	0.16	0.35	0.91	0.87
Kasugamycin	23.43	23.92	23.69	23.68	23.90	21.22	19.79	18.41	18.35	18.88
Validamycin	23.11	25.50	24.97	24.80	24.71	23.35	23.85	24.78	23.67	23.64
Oxolinic acid	40.08	40.79	41.16	42.17	44.38	44.53	43.29	41.33	41.85	40.81
Polyoxins	16.24	15.49	15.25	15.80	14.59	13.65	13.23	13.52	11.67	13.20
Total	167.54	173.24	172.73	175.71	181.43	139.07	136.22	135.90	133.24	134.91

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

Table 89 shows the total use (or sales) of antimicrobials in humans, food producing animals, aquatic animals, companion animals, antimicrobial feed additives, and agrochemicals. Antimicrobial selective pressure in Japan from a One Health perspective has decreased by approximately 4% compared to 2013. The highest frequency was observed among tetracyclines at 18-21%, followed by penicillins at 13-17%, and macrolides at 11-15%. Use of 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 89. Current volume of antimicrobial use (or sales) in Japan (t)

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
Penicillins	222.0	229.0	249.0	262.8	268.3	279.9	302.8	265.5	267.3	287.1
Cephalosporins	168.3	163.7	166.5	165.6	160.5	156.6	154.9	131.3	130.4	131.4
Monobactams	0.1	0.1	0.1	0.1	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	10.0	8.8	9.1	9.1
Aminoglycosides	109.1	110.8	104.5	122.2	125.5	93.7	91.5	93.4	85.5	88.2
Macrolides	191.3	177.2	207.3	238.4	238.8	244.4	267.9	241.5	221.1	196.6
Lincosamides	41.8	45.9	31.3	24.4	27.7	25.2	24.0	23.6	24.6	25.9
Tetracyclines	368.7	356.3	366.8	360.1	371.9	318.6	320.9	313.2	315.4	309.8
Peptides and glycopeptides	49.0	40.5	46.5	48.5	37.6	24.1	28.5	28.8	31.1	25.9
Sulfonamides*.	149.7	147.5	150.4	154.4	161.1	154.5	155.7	174.2	163.2	169.0
Fluoroquinolones	66.8	65.8	63.9	63.5	60.1	56.7	55.2	40.0	37.6	36.7
Other quinolones	41.6	43.1	43.2	44.2	46.5	46.1	45.9	43.7	43.6	43.1
Amphenicols, thiamphenicols and derivatives	21.7	26.3	29.8	26.6	27.2	24.9	27.5	25.6	27.1	28.3
Furan and derivatives	14.5	1.8	1.2	1.6	1.4	1.3	1.4	1.2	1.5	1.5
Polysaccharides	0.2	0.0	0.1	0.1	0.1	0.0	2.3	3.4	1.4	1.3
Polyethers	136.0	142.5	141.7	159.9	165.5	161.0	174.1	192.5	169.7	166.8
Polyoxins	16.2	15.5	15.3	15.8	14.6	13.7	13.2	13.5	11.7	13.2
Others*.	138.5	132.5	124.6	118.5	125.5	133.3	127.5	115.2	111.9	109.2
Total	1745.2	1708.3	1752.2	1816.9	1842.3	1743.8	1803.3	1715.4	1652.2	1643.0

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

Table 90. Changes in the volume of antimicrobial use (or sales) in Japan by year (unit: metric tons) (cont.) (1/4)

	2013						2014						2015					
	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	143.8	59.5	16.3	2.4	0.0	0.0	151.1	62.0	13.9	2.1	0.0	0.0	165.3	67.3	14.4	2.1	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
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
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
Aminoglycosides	1.0	37.4	0.0	2.1	0.0	68.6	0.9	38.7	0.0	2.0	0.0	69.2	0.9	34.1	0.0	1.4	0.0	68.1
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	38.0	0.0	5.5	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	23.6	4.9	0.1	0.0	0.0
Tetracyclines	7.1	286.7	53.8	0.0	1.6	19.5	6.9	275.8	49.0	0.0	2.2	22.2	7.1	276.2	57.6	0.0	2.6	23.2
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
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
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
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
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
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
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
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
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
Others*	17.6	40.7	0.3	0.0	56.7	23.1	16.6	42.4	0.5	0.0	47.6	25.5	16.9	45.5	0.2	0.0	37.0	25.0
Total	563.0	651.2	119.9	8.5	235.1	167.5	560.6	640.2	100.1	8.1	226.0	173.2	580.1	643.3	131.9	7.8	216.4	172.7
Total for year						1745.2						1708.3						1752.2

Table 90. Changes in the volume of antimicrobial use (or sales) in Japan by year (unit: metric tons) (cont.) (2/4)

	2016						2017						2018					
	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	172.8	73.8	14.6	1.6	0.0	0.0	180.2	71.7	14.7	1.7	0.0	0.0	190.9	74.5	12.9	1.7	0.0	0.0
Cephalosporins	159.1	3.3	0.0	3.1	0.0	0.0	153.8	3.4	0.0	3.2	0.0	0.0	149.5	3.9	0.0	3.2	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
Carbapenems	10.2	0.0	0.0	0.0	0.0	0.0	10.1	0.0	0.0	0.0	0.0	0.0	9.8	0.0	0.0	0.0	0.0	0.0
Aminoglycosides	0.8	47.5	0.0	0.4	0.0	73.5	0.8	44.4	0.0	0.4	0.0	79.9	0.7	34.7	0.0	0.9	0.0	57.4
Macrolides	102.9	72.7	61.4	0.0	1.4	0.0	94.5	72.0	68.9	0.0	3.5	0.0	89.7	72.1	82.6	0.0	0.0	0.0
Lincosamides	2.5	15.6	6.1	0.1	0.0	0.0	2.4	19.4	5.7	0.1	0.0	0.0	2.4	16.7	5.9	0.1	0.0	0.0
Tetracyclines	7.2	280.7	50.9	0.0	2.0	19.5	7.0	286.0	61.0	0.0	0.0	17.8	7.3	257.4	52.5	1.3	0.0	0.1
Peptides and glycopeptides	2.4	14.0	0.0	0.0	32.1	0.0	2.5	20.0	0.0	0.0	15.2	0.0	2.4	12.3	0.0	0.0	9.4	0.0
Sulfonamides	58.6	78.6	16.7	0.5	0.0	0.0	62.1	84.1	14.4	0.6	0.0	0.0	65.7	78.6	9.6	0.5	0.0	0.0
Fluoroquinolones	57.4	5.2	0.0	0.9	0.0	0.0	53.2	5.9	0.0	0.9	0.0	0.0	50.1	5.8	0.0	0.8	0.0	0.0
Other quinolones	0.3	0.2	1.6	0.0	0.0	42.2	0.2	0.3	1.5	0.0	0.0	44.4	0.1	0.0	1.5	0.0	0.0	44.5
Amphenicols, thiamphenicols and derivatives	0.1	24.8	1.7	0.0	0.0	0.0	0.1	25.3	1.8	0.0	0.0	0.0	0.1	23.3	1.5	0.0	0.0	0.0
Furan and derivatives	0.0	0.0	1.6	0.0	0.0	0.0	0.0	0.0	1.4	0.0	0.0	0.0	0.0	0.0	1.3	0.0	0.0	0.0
Polysaccharides	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	0.0	0.0
Polyethers	0.0	0.0	0.0	0.0	159.9	0.0	0.0	0.0	0.0	0.0	165.5	0.0	0.0	0.0	0.0	0.0	161.0	0.0
Polyoxins	0.0	0.0	0.0	0.0	0.0	15.8	0.0	0.0	0.0	0.0	0.0	14.6	0.0	0.0	0.0	0.0	0.0	13.7
Others*	17.0	43.6	0.5	0.0	32.6	24.8	14.6	48.7	0.5	0.0	37.0	24.7	14.1	48.8	0.6	0.0	46.3	23.4
Total	591.4	659.9	155.1	6.7	228.1	175.7	581.6	681.3	169.9	6.9	221.2	181.4	582.9	628.1	168.5	8.6	216.7	139.1
Total for year						1816.9						1842.3						1743.8

Table 90 Changes in the volume of antimicrobial use in Japan by year (unit: metric tons) (cont.) (3/4)

	2019						2020						2021					
	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	210.4	73.8	17.0	1.6	0.0	0.0	168.6	76.2	19.2	1.5	0.0	0.0	178.3	72.4	14.3	2.3	0.0	0.0
Cephalosporins	146.9	4.1	0.0	3.9	0.0	0.0	123.5	3.8	0.0	3.9	0.0	0.0	122.3	4.1	0.0	4.0	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
Carbapenems	10.0	0.0	0.0	0.0	0.0	0.0	8.8	0.0	0.0	0.0	0.0	0.0	9.1	0.0	0.0	0.0	0.0	0.0
Aminoglycosides	0.7	34.8	0.0	0.4	0.0	55.7	0.5	36.5	0.0	0.4	0.0	55.9	0.5	29.8	0.0	0.1	0.0	55.1
Macrolides	87.2	73.3	107.4	0.0	0.0	0.0	67.8	72.7	101.0	0.0	0.0	0.0	63.4	73.0	84.7	0.0	0.0	0.0
Lincosamides	2.7	16.3	4.9	0.1	0.0	0.0	2.1	17.5	3.8	0.2	0.0	0.0	2.1	19.1	3.2	0.2	0.0	0.0
Tetracyclines	7.7	242.9	69.6	0.5	0.0	0.2	8.4	240.1	63.8	0.4	0.0	0.3	8.7	236.5	68.8	0.4	0.0	0.9
Peptides and glycopeptides	2.6	19.6	0.0	0.0	6.4	0.0	2.7	19.0	0.0	0.0	7.1	0.0	2.4	18.4	0.0	0.0	10.4	0.0
Sulfonamides	71.0	68.6	15.6	0.5	0.0	0.0	75.7	84.4	13.4	0.8	0.0	0.0	81.2	64.2	17.5	0.3	0.0	0.0
Fluoroquinolones	47.7	6.7	0.0	0.9	0.0	0.0	33.0	6.2	0.0	0.9	0.0	0.0	29.2	7.5	0.0	0.8	0.0	0.0
Other quinolones	0.1	0.1	2.5	0.0	0.0	43.3	0.1	0.2	2.2	0.0	0.0	41.3	0.0	0.2	1.6	0.0	0.0	41.8
Amphenicols, thiamphenicols and derivatives	0.1	23.9	3.5	0.0	0.0	0.0	0.1	23.1	2.4	0.0	0.0	0.0	0.1	24.2	2.8	0.0	0.0	0.0
Furan and derivatives	0.0	0.0	1.4	0.0	0.0	0.0	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	1.5	0.0	0.0	0.0
Polysaccharides	0.0	0.0	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	3.4	0.0	0.0	0.0	0.0	0.0	1.4	0.0
Polyethers	0.0	0.0	0.0	0.0	174.1	0.0	0.0	0.0	0.0	0.0	192.5	0.0	0.0	0.0	0.0	0.0	169.7	0.0
Polyoxins	0.0	0.0	0.0	0.0	0.0	13.2	0.0	0.0	0.0	0.0	0.0	13.5	0.0	0.0	0.0	0.0	0.0	11.7
Others*	13.3	47.3	0.3	0.0	42.7	23.8	10.5	47.1	0.9	0.0	31.9	24.8	9.6	48.7	0.3	0.0	29.6	23.7
Total	600.2	611.3	222.0	8.0	225.5	136.2	501.9	626.8	208.0	8.1	234.7	135.9	507.0	598.1	194.7	8.1	211.1	133.3
Total for year	1803.3						1715.4						1652.2					

Table 90. Changes in the volume of antimicrobial use in Japan by year (unit: metric tons) (cont.) (4/4)

	2022					
	Humans	Food-producing animals	Aquatic animals	Companion animals	Antimicrobial feed additives	Agrochemicals
Penicillins	196.0	72.9	16.2	2.1	0.0	0.0
Cephalosporins	124.0	4.0	0.0	3.4	0.0	0.0
Monobactams	0.1	0.0	0.0	0.0	0.0	0.0
Carbapenems	9.1	0.0	0.0	0.0	0.0	0.0
Aminoglycosides	0.5	31.2	0.0	0.1	0.0	56.4
Macrolides	61.9	61.0	73.7	0.0	0.0	0.0
Lincosamides	2.2	19.6	3.9	0.2	0.0	0.0
Tetracyclines	8.5	220.7	79.3	0.4	0.0	0.9
Peptides and glycopeptides	2.6	18.5	0.0	0.0	4.7	0.0
Sulfonamides	84.6	62.5	21.5	0.4	0.0	0.0
Fluoroquinolones	29.1	6.7	0.0	0.8	0.0	0.0
Other quinolones	0.0	0.3	2.0	0.0	0.0	40.8
Amphenicols, thiamphenicols and derivatives	0.1	25.3	3.0	0.0	0.0	0.0
Furan and derivatives	0.0	0.0	1.5	0.0	0.0	0.0
Polysaccharides	0.0	0.0	0.0	0.0	1.3	0.0
Polyethers	0.0	0.0	0.0	0.0	166.8	0.0
Polyoxins	0.0	0.0	0.0	0.0	0.0	13.2
Others*	9.2	45.3	0.5	0.0	30.5	23.6
Total	527.8	568.0	201.5	7.4	203.4	134.9
Total for year						1643.0

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

(6) Research into antimicrobial stewardship

The following provides a summary of past reports on key studies related to the appropriate use of antimicrobial agents in Japan and those published since this report last year (from the latter half of 2023). It covers only studies using medical insurance claims data for outpatient consultations across the whole of Japan and excludes studies limited to a specific region and studies that analyzed only the amount of antimicrobials used.

The medical insurance claims data used includes the NDB[2,3] developed by the Ministry of Health, Labour and Welfare, the National Health Insurance database,[4] and commercial databases created by combining medical insurance claims data from multiple health insurance societies (JMDC Inc.'s JMDC Claims Database[1, 5-7], IQVIA Inc.'s IQVIA Claims8, and MDV's MDV analyzer[11]). Unless otherwise indicated, figures in square brackets ([]) in the text show the 95% confidence interval.

1. Past reports on antimicrobial stewardship

Studies have been reported on the appropriate use of antimicrobial agents for acute respiratory tract infections and acute diarrhea, which are addressed in the Manual of Antimicrobial Stewardship[1-7]. It was suggested that although antimicrobial use has been gradually decreasing, there is still room for intervention to support appropriate use, as there are still many prescribed for acute respiratory tract infections and acute diarrhea. In this context, in 2018, the appropriate use of pediatric antimicrobial agents was introduced as a premium national health insurance (NHI) item for children under 3 years of age, and the eligible age was further raised to under 6 years of age in the 2020 revision. Muraki et al. examined the effect of this premium item in 2018 for children under 15 years of age using the IQVIA's database, revealing that the percentage of antimicrobial prescriptions was lower at facilities that had claimed this premium item compared to those that had not.[8] In addition to these results, the eligible age range for the item is being expanded, and expansion of the study period and age, and more detailed investigation of the effect on appropriate use of antimicrobials with and without age-specific introduction are also to be considered for the promotion of appropriate use of antimicrobial agents in the future. As for children, a new study investigating the effects of Action Plans targeting pediatric clinics has been reported and is described in the next section.[9] With regard to acute diarrhea, Okubo et al. previously showed antimicrobial use from April 2012 to December 2015 for children (<18 years old) using the JMDC's database7. Insurance claims on 4,493 outpatients with acute diarrhea were studied, of which 29.6% of the patients were prescribed some type of antimicrobial agent, with fosfomycin being the most common antimicrobial agent (20.3%). For adults, Ohno et al. used the JMDC database to investigate antimicrobial use for acute diarrhoea among 0–65-year-olds from January 2013 to December 2018.10 Over the 6-year study period, 94.6% of all subjects had non-bacterial diarrhoea, but the antimicrobial prescription rate (number of prescriptions/visits) was 46.5% in adult males and 40.8% in adult females. The antimicrobial prescription rate for children (0-17 years) was 30.5% for boys and 30.4% for girls, which was not significantly different from a previous survey by Okubo et al [7]. Sugiyama et al. also investigated the status of oral antimicrobial prescriptions for acute diarrhoea using a practice database-based analysis tool (MDV analyzer: Medical Data Vision Inc., Tokyo, Japan) [11]. The investigation was conducted between January 2013 and December 2019 with hospitals participating in the Diagnosis Procedure Combination / Per-Diem Payment System and registered on the MDV analyzer nationwide, which showed that the number of patients prescribed has decreased over time, similarly to the results of Ohno et al.'s study.

On the other hand, Tsuzuki et al. pointed out that despite a continuous decrease in antibiotic usage from 2015 to 2021, there was no significant reduction in the disease burden of bacteremia caused by resistant bacteria during the same period. Several hypotheses can be proposed to explain this phenomenon; however, it suggests that merely reducing antibiotic usage may be insufficient as an effective strategy for antimicrobial resistance (AMR) control [12].

Additionally, various factors influencing the appropriate use of antibiotics, such as the introduction of incentives for appropriate use of antibiotics, the introduction of Pharmacist for Primary Antimicrobial Chemotherapy certified by the Japanese Society of Chemotherapy, and supply issues, including those related to amoxicillin, must be taken into account. This underscores the need for further investigation in the future.

[Study on the impact of the introduction of the premium for appropriate use of pediatric antimicrobials].

Using the JMDC database, Jindai investigated the impact of the premium, introduced in April 2018, that offers incentives for not prescribing antimicrobials for respiratory tract infections and diarrhoea (0-2 years) and the healthcare provider education (6 years and older) based on the information from April 2013 to February 2020. The effect was assessed using interrupted time series analysis.[13] The results showed that antimicrobial prescribing decreased significantly after the introduction of the premium in the 0-2 age group (-47.5 prescriptions [77.3 to -17.6] per 1,000 monthly clinic visits). Education for healthcare providers reduced antimicrobial prescribing for all ages. These showed an immediate effect after introduction, but no long-term effect.

Okubo et al. used NDB to similarly assess the effect of the premium using finite differential methods and found a reduction in antimicrobial prescribing (DID estimate, -228.6 DOT per 1,000 cases [-272.4 to -184.9]) [14]. There was also no increase in out-of-hour consultations with treatment of respiratory symptoms (DID estimate, -

256.9 DOT [-379.3 to -134.5] per 1,000 cases) or antihistamines (DID estimate, -198.5 DOT [-282.1 to -114.9] per 1,000 cases) [DID estimate, -4.43 per 1,000 cases [-12.8 to -3.97]. There was also no increase in hospital admissions [DID estimate, -0.08 per 1,000 cases [-0.48 to 0.31]. The study showed that it led to a reduction in unnecessary antimicrobial prescribing without any negative impact on healthcare.

[Research on prescribing status]

Using JMDC, Sato et al. analysed the prescribing of prophylactic antimicrobials after tooth extractions for people aged 18 years and older between September 2015 and August 2018 to investigate the impact of the AMR Action Plan [15]. The results showed that of the 662,435 eligible patients, those who were prescribed prophylactic antimicrobials accounted for 83% of the overall patients and 82% of those defined as being at low risk of post-operative infection. Although this proportion did not change within the study period, the breakdown by class showed a decrease in the prescriptions for third generation cephalosporins from 58% to 34% (hospitals) and from 57% to 56% (clinics).

There was an increase in amoxicillin from 16% to 37% (hospitals) and from 6% to 10% (clinics).

Araki et al. also used JMDC to survey 18,659 working-age population members who had undergone medical examinations for at least five years and had been diagnosed with the common cold at least twice between January 2005 and February 2016 [16]. The results showed 49.2% (9,180 patients) were prescribed antimicrobials, and it was revealed that its factors included lack of chronic disease, male patients, and clinics or hospitals with less than 20 beds. In addition, 40-45% were prescribed cephalosporins. In interpretation, it should be noted that the study subjects were from the working age population.

The situation of inappropriate prescribing was revealed, with cephalosporins being the most commonly used, indicating the need to promote ASP.

Ide et al. used JMDC to study the prescribing of oral macrolide antimicrobials from 2013 to 2018. Macrolides accounted for 30% of oral antimicrobial prescriptions, of which clarithromycin accounted for 60%. Most prescriptions were for the common cold, with some prescriptions for chronic conditions such as allergic diseases and skin conditions. The study suggests a need to review the use of macrolides for the common cold and to properly evaluate their long-term use for skin and allergic diseases.[17]

2. New research reports on the antimicrobial stewardship

Kitano et al. conducted a study using the NDB to investigate the factors contributing to regional variations in antibiotic usage [18]. They performed a multivariate analysis considering factors such as the number of clinics treating respiratory infections, pediatric population, number of clinics, facility size, and the number of infectious disease specialists by prefecture. The results revealed that the number of visits for respiratory infections, with an "adjusted RR1.21," had a significant impact. This highlighted the need for further efforts to reduce unnecessary antibiotic prescriptions for respiratory infections.

Ito et al. conducted a study using IQVIA Claims to examine concomitant diseases, antibiotic prescriptions, and infection test statuses recorded for pediatric patients diagnosed with respiratory infections in otolaryngology outpatient settings [19]. The results revealed that only 6.5% of the cases were diagnosed with respiratory infections alone, with concurrent diagnoses of allergic rhinitis, acute bronchitis, acute sinusitis, and earwax impaction being common. Additionally, third-generation cephalosporins, macrolides, and broad-spectrum penicillins were frequently prescribed, while the testing rate was low, ranging from 2.9% to 21.7%. Careful patient selection is important when evaluating acute upper respiratory infections using claims data. The study suggested the need for improving the availability of diagnostic testing in outpatient settings, given the low implementation rates of necessary tests for diagnosis.

Muramatsu et al. conducted a study using the JMDC database to investigate the prescribing patterns and effectiveness of oral antibiotics in the treatment of pediatric urinary tract infections (UTI) [20]. The study focused on UTI patients under the age of six who were prescribed oral antibiotics between 2016 and 2020. The results showed that 67.0% of the patients were prescribed third-generation cephalosporins, 8.4% were prescribed amoxicillin, 1.5% were prescribed trimethoprim/sulfamethoxazole (TMP-SMX), and 1.2% were prescribed amoxicillin/clavulanate. Treatment failure occurred in 2.9% of cases, with a higher failure rate observed in patients treated with amoxicillin compared to cefcapene pivoxil [OR 2.18 (95% CI: 1.04-4.58)]. Sato et al. conducted a study using the JMDC database to investigate the prescribing patterns of prophylactic antibiotics and the incidence of postoperative infections during the extraction of impacted mandibular third molars in dentistry [21]. The study focused on amoxicillin, the first-choice antibiotic, and third-generation cephalosporins, which are widely used in Japan. The results showed that amoxicillin was prescribed to 36.2% of patients, while third-generation cephalosporins were prescribed to 67.8%. After adjusting for background factors, the incidence of surgical site infections was 3.5% in the amoxicillin group and 3.7% in the third-generation cephalosporin group (p=0.003). These findings highlight the need for promoting the appropriate use of antibiotics in the field of dentistry also.

3. New data collection and analysis methods for appropriate use of antimicrobial agents

A system is being developed to tabulate the percentage of antimicrobial use for respiratory tract infections using NDB information. We are examining the ratio of antimicrobial prescriptions for specific illnesses and injuries. Monitoring by region, age group, and type of antimicrobial agent is planned, and system development is currently underway.

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(7) Research on the prudent use of antimicrobial agents for veterinary use

A new Action Plan has been published, setting targets for the reduction of antimicrobial agents in the animal (livestock) sector. While building up information on diseases for which veterinary antimicrobial agents are used, it is necessary to develop prevention and treatment guidelines for major diseases. In addition, since pet animals share living space with their family members in the home, it has been pointed out that antimicrobial-resistant bacteria may be cross-transmitted within the home, so it is extremely important to understand the actual status of antimicrobial agent use. The following is a survey on the prudent use of antimicrobial agents for veterinary antimicrobial settings although the study area is limited.

1. Utilization of digital medical record data of Agricultural Mutual Ais Associations

Terashi et al. used digital medical record data maintained by NOSAI Gifu to tabulate the therapeutic purposes and net end equivalents of antimicrobial agents used to treat cattle.[1] Antimicrobial agents were used predominantly (85%) for gastrointestinal (50.4%) and respiratory (34.4%) diseases, with sulfoamides (49.2%) for coccidiosis and phenicol agents (21.7%), mainly florfenicol, for respiratory disease, being the main components. National data from the Ministry of Agriculture, Forestry, and Fisheries (MAFF) indicate that tetracycline antibiotics are also commonly used in cattle, suggesting that there are regional differences in antimicrobial use.

2. Use of second-line drugs in companion animals

Murakami et al. in cooperation with the Gifu Veterinary Medical Association surveyed 35 pet hospitals where cases receiving fluoroquinolone (FQ), third generation cephalosporins, carbapenems, and/or vancomycin products were investigated.[2] They were used in 1,209 cases during the study period, including 734 cases of FQ, 467 cases of third generation cephalosporins, and 8 cases of carbapenems, and no vancomycin products were used; for both FQ and third generation cephalosporins, the percentage of injectable formulations used was significantly higher in cats than in dogs. These two agents tended to be used more frequently for skin/ear diseases regardless of animal species, but their use for other diseases differed between dogs and cats.

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(8) Environment

Pharmaceutical products including antimicrobials, agents, 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 CPFX 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, CPFX and clarithromycin were contained in sewage at the respective concentrations of 51 to 442 ng/L and 886 to 1,866 ng/L.

1. Survey on the Presence of Antibiotics in the Environment [5, 6, 7, 8, 9]

The Ministry of the Environment conducts an ongoing survey on the residual status of chemicals in the general environment, known as the Environmental Survey and Monitoring of Chemicals, to continuously track the presence of various chemicals, including antibiotics, in the environment.

As a result, antibiotics have been detected in river water and other environmental samples, with the following maximum concentrations: erythromycin at 30 ng/L, clarithromycin at 490 ng/L, roxithromycin at 47 ng/L, clindamycin at 11 ng/L, lincomycin at 17 ng/L, sulfamethoxazole at 190 ng/L, sulfadiazine at 29 ng/L, sulfanilamide at 210 ng/L, sulfapyridine at 290 ng/L, sulfisomidine at 13 ng/L, ormetoprim at 11 ng/L, diaveridine at 10 ng/L, trimethoprim at 61 ng/L, azithromycin at 130 ng/L, amoxicillin at 2.3 ng/L, tiamulin at 3.1 ng/L, levofloxacin at 540 ng/L, the clarithromycin metabolite 14-(R)-hydroxyclarithromycin at 230 ng/L, ampicillin at 1.4 ng/L, and streptomycin at 2.3 ng/L.

2. Initial Environmental Risk Assessment of Antibiotics [10, 11, 12, 13]

The Ministry of the Environment compiles reports of initial environmental risk assessments to screen substances that are considered to pose relatively high environmental risks among a wide range of chemicals. These assessments include evaluations of risks to human health (health risk) and risks to ecosystems (ecological risk).

In the initial environmental risk assessment of antibiotics, all substances were evaluated for their ecological risks. Roxithromycin and sulfamethoxazole were identified as candidates for detailed evaluation, while lincomycin, sulfadiazine, and erythromycin were noted as requiring further information gathering. Trimethoprim, however, was determined not to require additional information collection at this time.

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8. Public Awareness regarding Antimicrobial Resistance in Japan

(1) Surveys of the general public

1) Surveys of attitudes among the public

Public awareness surveys concerning antimicrobial resistance funded by a Ministry of Health, Labour and Welfare research grant were conducted in March 2017, February 2018, September 2019, September 2020, and October 2022, and the sixth survey in October 2023. [1, 2, 3, 4] In these studies, consumers (excluding medical professionals) who had registered with INTAGE Research Inc. to participate in various market research surveys completed an online questionnaire. The survey was initiated with a target number of 3,000 respondents, and the 2017 survey had 3,390 valid responses, the 2018 survey 3,192, the 2019 survey 3,218, the 2020 survey 3,200, the 2022 survey 3,193, and the 2023 survey 3,202. Women comprised 48.8% of respondents in 2017, 49.7% in 2018, 52.2% in 2019, 50.4% in 2020, 50.4% in 2022, and 49.9% in 2023. Until 2019, more than 40% of all respondents experienced taking antibiotics because of cold, which decreased to 19.6% in 2022 and to 22.9% in 2023. 20.2% of respondents reported taking oral antibiotics for new coronavirus infection, and 43.1% when combined with a cold. Compared to before 2019, the percentage of respondents taking antimicrobials against a cold had decreased. However, approximately 40% of respondents indicating that "antibiotics are effective against colds and influenza". Approximately 20% indicated that they have "discontinued taking antibiotics or adjusted the dosage based on their own judgment"; and approximately 10% indicated that they "keep the remaining antibiotics at home". Among the respondents who "keep remaining antibiotics at home", 79.5% have "used them based on their own judgment". The results of this survey were similar to the trends of responses in the previous four surveys, so ongoing efforts to raise public awareness using a variety of measures, including behavioural economics methodology, are required in order to change attitudes among the public.

Table 91. Reasons for taking oral antibiotics (multiple responses)

	2017 (%) (n=1,566)	2018 (%) (n=1,737)	2019 (%) (n=1,330)	2020 (%) (n=1,078)	2022 (%) (n=1,051)	2023 (%) (n=1,100)
Cold	45.5	44.7	41.2	29.8	19.6	22.9
Others/unknown	24.3	21.2	23.2	30.4	32.5	29.4
Influenza	11.6	12.4	12.0	5.8	2.6	3.7
Fever	10.7	11.3	8.5	7.8	9.9	9.4
Nasopharyngitis	9.5	10.8	10.5	9.9	8.3	9.1
Cough	9.0	10.8	6.9	4.5	5.0	8.6
Sore throat	7.7	7.8	8.2	7.1	8.1	7.5
Skin or wound infection	6.5	7.0	9.0	14.5	11.8	10.8
Bronchitis	5.4	6.6	5.1	5.9	5.8	5.4
Headache	4.3	5.0	4.1	5.0	7.0	4.5
Diarrhea	3.1	3.2	2.6	3.1	2.3	2.5
Urinary tract infection	2.3	2.5	2.7	4.7	3.5	3.0
Pneumonia	1.4	1.7	1.3	1.2	1.2	1.7
Novel coronavirus infection	-	-	-	-	15.5	20.2

Table 92. Do you think each of the following statements is correct or incorrect? (%)

		2017 (n=3,390)	2018 (n=3,192)	2019 (n=3,218)	2020 (n=3,200)	2022 (n=3,193)	2023 (n=3,202)
Antibiotics beat viruses	Correct	46.8	46.6	52.4	42.6	46.3	45.3
	Incorrect	21.9	20.3	17.7	23.5	19.5	20.5
	Do not know	31.3	33.0	29.9	33.9	34.2	34.3
Antibiotics have effect on cold and influenza	Correct	40.6	43.8	43.9	40.4	43.1	44.5
	Incorrect	24.6	22.1	22.7	23.1	20.7	20.6
	Do not know	34.8	34.1	33.4	36.4	36.2	34.8
Unnecessary use of antibiotics may result in the loss of their effect	Correct	67.5	68.8	66.4	64.9	60.8	61.4
	Incorrect	3.1	3.7	3.4	3.3	4.3	5.2
	Do not know	29.4	27.5	30.2	31.8	34.9	33.4
Adverse effects are involved in the use of antibiotics	Correct	38.8	41.5	45.7	45.6	42.6	58.2
	Incorrect	12.7	13.4	10.5	9.9	11.2	16.3
	Do not know	48.6	45.0	43.8	44.5	46.2	25.5

Table 93. Do any of the statements below apply to you? (%)

		2017 (n=3,390)	2018 (n=3,192)	2019 (n=3,218)	2020 (n=3,200)	2022 (n=3,193)	2023 (n=3,202)
I have discontinued taking antibiotics, or adjusted a dose or frequency based on my own judgment	Yes	23.6	24.0	24.6	23.3	22.2	19.7
	No	76.4	76.0	75.4	76.7	77.8	80.3
I keep antibiotics in my house	Yes	11.7	11.9	9.8	9.3	10.2	9.6
	No	88.3	88.1	90.2	90.7	89.8	90.4

Table 94. Do any of the statements below apply to you? (%)

		2017 (n=396*)	2018 (n=426*)	2019 (n=3,218)	2020 (n=298)	2022 (n=326)	2023 (n=307)
I have used antibiotics that I kept at home for myself	Yes	75.8	77.5	75.6	76.2	81.3	75.9
	No	24.2	22.5	24.4	23.8	18.7	24.1
I have given antibiotics that I kept at home to my family or friend	Yes	26.5	27.2	28.5	25.5	35.6	24.4
	No	73.5	72.8	71.5	74.5	64.4	75.6

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

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(2) Surveys of healthcare providers

1) Awareness survey of clinic physicians

The Joint Survey Committee on Appropriate Use of Antimicrobial Agents in Outpatients of the Japanese Society of Chemotherapy and the Japanese Association of Infectious Diseases conducted the second survey of awareness among physicians working in clinics in February 2018, from September to October 2020, and from December 2022 to February 2023. The survey questionnaire was distributed to 3,000 randomly selected clinics nationwide, and the forms were filled and returned. Compared to the survey in 2020, awareness of the Action Plan decreased, with responses indicating "able to explain to others" or "understanding" declining from 31.6% to 25.2% (Table 95). Regarding the proportion of antibiotic prescriptions for the common cold, the number of respondents selecting the lowest prescription rate, "0-20%," increased from 71.1% to 82.4%, indicating a decrease in the prescription rate for the common cold (Table 96). Responding to requests for antimicrobial prescriptions, 39.2% of the respondents said they would "explain and not prescribe," while 6.8% and 51.3% said they would "prescribe as requested" and "prescribe if not satisfied after explanation," respectively, hardly different from the results of the previous survey (Table 97). It is possible that intention to be actively involved in patient education and communication is not necessarily high. As in the previous survey, the percentage of prescribing antimicrobial agents for acute bronchitis was also high (Table 98). The development of simpler pathogen diagnostic tests may be effective in promoting the appropriate use of antimicrobial agents. The majority of respondents cited the campaign to the public as necessary to achieve the Action Plan, which was unchanged from the previous survey.

Table 95 Awareness of Action Plan (%)

	2018 (n=267)	2020 (n=627)	2022 (n=389)
Able to explain it to people	1.9	3.5	2.3
Understand	21.0	27.8	22.9
Only know the name	32.2	33.1	37.3
Do not know anything	44.9	34.8	37.5

Table 96 Percentage of antimicrobials prescribed when diagnosing with a common cold (%)

	2018 (n=242)	2020 (n=543)	2022 (n=323)
0-20%	62.0	71.1	82.4
21-40%	17.8	16.6	10.2
41-60%	7.4	6.8	5.0
61-80%	8.3	3.5	1.5
81% or more	4.5	2.0	0.9

Table 97 Response when patients or family members diagnosed with a common cold request for antimicrobial agent (%)

	2018 (n=252)	2020 (n=609)	2022 (n=380)
Prescribe it if they are not convinced by explanation	50.4	49.1	51.3
Explain and not prescribe	32.9	35.5	39.2
Prescribe as requested	12.7	10.8	6.8
Other	3.7	4.6	2.6

Table 98 Frequency of antimicrobial prescription when diagnosing an acute bronchitis (in the past year) (%)

	2018 (n=232)	2020 (n=522)	2022 (n=308)
0-20%	31.0	35.4	46.1
21-40%	23.7	24.9	24.7
41-60%	14.2	15.7	13.6
61-80%	9.5	9.0	6.8
81% or more	21.6	14.9	8.8

2) Research on infectious diseases and antimicrobials in pharmacy education

Pharmacists are important members of the healthcare team responsible for in-hospital and community ICT and ASP activities, and the need for education on AMR and clinical infectious diseases among pharmacists is increasing. However, the current state of education on clinical infectious diseases in the faculty of pharmacy of Japanese universities was not clear, so a nationwide survey of pharmacy schools in Japan was conducted from February to March 2022. Questionnaires were sent to pharmacy schools across Japan and 44 out of 74 universities responded.
The median number of teaching staff members in charge of infectious disease education was 7 [4-12], of which practitioners were 3 [1-6].

62.8% of the universities had teaching staff members with clinical experience in infectious diseases. Regarding the contents of education, the most frequently reported as “inadequate” or “not implemented” were: the concept of prophylactic antimicrobials in the perioperative period (74.5% inadequate or not implemented in total), how to explain to patients when antimicrobial is not necessary (76.8% total), patient education on prudent antimicrobial (79% in total), team approach to infectious disease care and infection control (53.5% in tot), and education on antimicrobial research and development (76.8%in total). Insufficient time for lectures and lack of specialists were the top issues in clinical infectious disease education. The survey also revealed that educational status and resources for clinical infectious diseases and AMR varied widely. It was suggested that resources, including the overall curriculum and the number of teachers, need to be examined and improved.

3) Survey of Stakeholders in the Animal Field

The Ministry of Agriculture, Forestry and Fisheries conducted a survey in the 2023 fiscal year to assess awareness of antimicrobial resistance among producers, veterinary clinicians specializing in livestock, veterinary clinicians specializing in small animals, and pet owners.

The survey was conducted via an online questionnaire.

It should be noted that the following results represent the responses from producers and pet owners by species who have responded.

1) Awareness Survey of Producers and Pet Owners

The number of respondents was 238 producers and 1,112 pet owners. Among the producers, 141 (59.2%) raised cattle, 55 (23.1%) raised swine, and 41 (17.2%) raised chickens. Among the pet owners, 402 (36.2%) owned dogs, and 748 (67.3%) owned cats.

Awareness of Japan's Antimicrobial Resistance (AMR) Action Plan was reported by approximately 25% of producers and less than 10% of pet owners (Table 99). In terms of awareness of specific AMR measures, nearly 80% of producers recognized that "antimicrobial-resistant bacteria make it difficult to treat bacterial infections in humans and livestock/pets," while less than 50% of pet owners were aware of this (Table 100). Approximately 85% of producers and about 70% of pet owners were aware that "inappropriate use of antibiotics leads to an increase in antimicrobial-resistant bacteria" (Table 101).

Additionally, 60% of producers were aware of "the types of antimicrobial feed additives mixed into feed," and 90% recognized that "improving farming conditions and using vaccines can help prevent disease outbreaks," with 80% reporting they had implemented such measures.

When compared to the results of the awareness surveys conducted by the Japan Livestock Industry Association in fiscal years 2017 and 2018 among livestock keepers and veterinary clinicians specializing in industrial animals, awareness levels across various items remained relatively stable.

However, it was revealed that awareness of AMR measures among pet owners, who were newly surveyed, was generally lower compared to livestock producers.

Table 99. Awareness of Japan's Antimicrobial Resistance Action Plan (%)

	Producers (n=238)	Veterinary clinicians specializing in livestock (n=315)	Veterinary clinicians specializing in small animals (n=279)	Pet owners (n=1112)
Aware	26.1	73.3	66.6	6.8
Not aware	73.9	26.7	33.3	93.2

Table 100. Awareness of the Impact of Antimicrobial Resistant Bacteria on the Treatment of Bacterial Infections in Humans and Livestock/Pets (%)

	Producers (n=238)	Pet owners (n=1112)
Aware	78.2	46.7
Not aware	21.8	53.3

Table 101. Awareness of the Link Between Inappropriate Use of Antibiotics and the Increase in Antimicrobial-Resistant Bacteria (%)

	Producers (n=238)	Pet owners (n=1112)
Aware	85.3	69.2
Not aware	14.7	30.8

2) Awareness Survey of Veterinary Clinicians Specializing in Industrial and Small Animals

A total of 594 responses were received, with 315 (53.0%) from veterinary clinicians specializing in industrial animals and 279 (47.0%) from those specializing in small animals. Among the industrial animal clinicians, 251 (79.7%) provided care for dairy cattle, 274 (87.0%) for beef cattle, 51 (16.2%) for swine, 13 (4.1%) for broiler chickens, and 15 (4.8%) for laying hens (note that multiple selections were allowed, resulting in overlaps).

The awareness level for various items was as follows: 70% of industrial animal clinicians and about 65% of small animal clinicians were aware of Japan's Antimicrobial Resistance (AMR) Action Plan (Table 99).

Additionally, when asked how often they "make a conscious effort in daily practice to limit antibiotic use to cases where it is truly necessary, based on proper diagnosis", about 50% of industrial animal clinicians and around 60% of small animal clinicians answered as often as 61% or more of their consultations. Regarding "administering appropriate vaccinations," about 75% of industrial animal clinicians and around 60% of small animal clinicians responded positively (Table 102). Compared to surveys conducted in fiscal years 2017 and 2018 among industrial animal veterinarians, the awareness levels showed a decline.

Furthermore, awareness of "selecting antibiotics with a narrow spectrum of activity initially" was low, raising concerns about the easy use of broad-spectrum antibiotics. While awareness of "conducting antimicrobial susceptibility testing" (Table 102) exceeded 70%, more than half of the respondents reported that the "percentage of cases in daily practice where antimicrobial susceptibility testing was performed" (Table 103) was between 0% and 20%. This suggests that although there is knowledge about the prudent use of antibiotics, the proportion of such practices in daily clinical settings remains low, indicating that there has been no change since fiscal year 2018.

Table 102 Awareness of the "Basic Principles on the Prudent Use of Veterinary Antimicrobial Medicines in Livestock Production" (%)

	Veterinary clinicians specializing in livestock (n=315)	Veterinary clinicians specializing in small animals (n=279)
To prevent infectious diseases through appropriate husbandry and hygiene management	82.5	71.0
To administer appropriate vaccinations	75.6	59.9
To provide appropriate feeding and nutritional management	67.0	51.6
To conduct antimicrobial susceptibility testing	71.7	84.6
To use antibiotics for the minimum necessary duration	81.3	91.0
To select antibiotics with a narrow spectrum of activity initially	49.2	56.3
To use antibiotics critical for human health only when the initial antibiotic was ineffective.	73.7	62.7
Where possible, to select antibiotics with minimum exposure to enteric bacteria	34.9	40.5
To avoid administering antibiotics to healthy livestock animals	81.3	90.0
To avoid using more than one antibiotic in combination	54.6	36.9
To consider providing symptomatic treatment in combination to improve or alleviate symptoms in livestock animals	58.7	58.4
To assess the effect of the antibiotic agent prescribed at the initial consultation to determine whether to continue or change the use of antibiotics diagnosis	78.7	82.1

Table 103: Frequency of Antimicrobial Susceptibility Testing in the Past Year When Using Antibiotics in Daily Practice (Including Testing Commissioned to External Organizations) (%)

	Veterinary clinicians specializing in livestock (n=315)	Veterinary clinicians specializing in small animals (n=279)
0~20%	56.8	63.1
21~40%	24.4	20.4
41~60%	13.3	11.1
61~80%	2.9	3.6
81%~	2.5	1.8

(3) Survey of veterinary medicine students

The Ministry of Agriculture, Forestry and Fisheries has been conducting lectures and awareness surveys on antimicrobial resistance measures for veterinary students nationwide since 2019. Until 2020, awareness surveys were conducted after lectures, but since 2021 surveys have also been conducted before lectures in order to assess the effectiveness of the lectures. The 2023 survey was conducted in the form of a questionnaire survey via the Internet; 530 students from 14 universities (2nd and 3rd year students: 327, 4th year students: 97, 5th year students: 106) responded to the 2022 survey.

In the awareness survey conducted prior to the lecture, 93.6% of the students answered "effective against bacterial infections" in the question about antimicrobial agents (Table 104), indicating that the number of students with correct knowledge has remained stable. It was suggested that veterinary education has successfully imparted a certain level of knowledge about antibiotics, which has been retained over time. However, a certain number of students chose "effective against a common cold" or " effective against viral infection," with a response rate of 33.6% and 17.4%, respectively, suggesting that continued efforts should be made to ensure the dissemination of correct knowledge.

Similarly, in the awareness survey conducted before the lecture, the question "What do you know about antimicrobial resistance control in the veterinary field?" (Table 105) revealed that 54.5% of students were aware of “the existence of antibiotics referred to as second-line drugs," showing an increase compared to the previous year. In contrast, although a high percentage of students chose " Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) is being conducted." and "Partnership between the veterinary and human medicine fields," the number of students was less than a half, showing a slight decrease from the previous year. In addition, only approximately 30% of the students were aware of the important knowledge for practicing drug resistance countermeasures in the field, such as Reduction of infection opportunities through vaccination contributes to antimicrobial resistance control" is slightly increased, the trend has not changed over the past four years.

Because veterinarians play a key role in antimicrobial resistance control in the veterinary field, it is important to continue to educate veterinary students on the correct knowledge and prudent use of antimicrobial agents.

Table 104. Please give your perceptions about antimicrobials (%)

	2nd and 3rd year (n=327)	4th year (n=97)	5th year (n=106)	Whole (2020) (n=394)	Whole (2021) (n=404)	Whole (2022) (n=530)	Whole (2023) (n=530)
Effective against a common cold	32.1	40.2	32.1	26.6	32.2	32.5	33.6
Effective against viral infections*	16.2	24.7	14.2	4.8	10.4	22.8	17.4
Effective against bacterial infections	93.6	93.8	93.4	92.4	91.0	93.6	93.6
Effective to prevent complications after surgery	52.3	64.9	62.3	58.6	64.9	48.5	56.6
Used as a feed additive to be mixed with feed	36.7	44.3	30.2	53.8	41.6	36.4	36.8
Used in pesticides for vegetables and other produce	16.5	15.5	5.7	8.4	13.6	16.4	14.2

*This had been phrased as "effective against an influenza" until 2021

.**The 2020 awareness survey was conducted only after the lecture, which may have biased the numbers (The years 2021 and 2022 show the results of surveys conducted prior to the lecture).

Table 105. Please select what you know about antimicrobial resistance control in the veterinary sector (%)

	2nd and 3rd year student (n=327)	4th year student (n=97)	5th year (n=106)	Whole (2020) (n=394)	Whole (2021) (n=404)	Whole (2022) (n=530)	Whole (2023) (n=530)
An Action Plan on Antimicrobial Resistance (AMR) has been developed and is being implemented	26.9	34.0	34.9	43.9	18.8	30.9	29.8
The existence of antimicrobial agents called second-line drugs	49.8	50.5	72.6	32.7	33.4	34.3	54.5
Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) is being conducted	40.7	43.3	41.5	21.6	18.6	45.8	41.3
Reduction of infection opportunities through vaccination contributes to antimicrobial resistance control.	33.0	30.9	34.0	28.9	29.0	29.1	32.8
Partnership between the veterinary and human medicine fields	38.8	49.5	40.6	45.9	44.6	46.2	41.1
Determination of risk management measures based on risk assessment	33.9	46.4	39.6	31.7	21.3	37.4	37.4
Do not know	15.3	7.2	6.6	9.9	18.1	12.1	12.1

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9. Way Forward

The National Action Plan on Antimicrobial Resistance (AMR) (2016-2020), published in 2016, aimed to conduct an integrated One Health trend survey on the current status of drug-resistant bacteria and antimicrobial usage in the human, animal, agricultural, food and environmental sectors. This report consolidates the results and contributes to the further promotion of AMR countermeasures. It has allowed for a detailed understanding of the challenge of antimicrobial resistance in Japan and the development of measures on the basis of this understanding. The National Action Plan on Antimicrobial Resistance (AMR) (2023-2027) proposes updated goals and strategies based on the achievements to date and presents a new path forward in the fight against AMR. The importance of a One Health approach to the AMR problem has been reemphasized, and it is expected that information on AMR trends and countermeasures be analyzed and evaluated on a regular basis by linking information from human, animal, agricultural, food, and environmental trends studies and by making international comparisons. It also emphasizes the importance of updating methodologies for collecting and analysing data on trends in drug resistance and antimicrobial use in Japan and abroad, as well as international cooperation and collaboration for AMR countermeasures. Continued efforts to conduct advanced research is considered important for leading the global effort to combat AMR.

In the human field, with reference to the "Manual of Antimicrobial Stewardship" and other guidelines, unnecessary antimicrobial prescriptions should be reduced, particularly for acute respiratory tract infections, and when antimicrobial agents are prescribed, appropriateness is expected. Advancement of appropriate use of antimicrobial agents is dependent on the availability of appropriate antimicrobial agents when they are needed. Given the current circumstances where some antimicrobial agents have become difficult to obtain in clinical settings, it is important to ensure a stable supply of essential antimicrobial agents. Considering that it has become possible to obtain information on antimicrobial resistance and antimicrobial use on a regional basis using various surveillance systems related to AMR, it is advisable to select antimicrobial agents and promote appropriate infection control measures according to local conditions. Furthermore, in promoting the appropriate use of antimicrobial agents, it is necessary to continue and develop educational and awareness-raising activities for the public and healthcare professionals using various methods, including behavioral economics.

In the animal sector, the Veterinary AMR Center at the National Veterinary Assay Laboratory, a core laboratory for AMR, was established in October 2023. Moving forward, the Japan Veterinary Antimicrobial Resistance Monitoring (JVARM) will continue to enhance and conduct ongoing and accurate surveys on antimicrobial resistance trends in livestock, aquaculture, and companion animals, as well as antimicrobial usage. It is crucial to provide scientific knowledge essential for various AMR measures, such as AMR risk assessment, risk management, public awareness campaigns, international efforts, and initiatives based on the One Health approach.

The resistance rates of *E. coli* from healthy livestock, outcome indices in the "National Action Plan on Antimicrobial Resistance (AMR) (2023-2027)," are expected to remain low against third-generation cephalosporins and fluoroquinolones, which are critically important for human medicine. However, for tetracyclines, widely used in animals, while a decrease in sales has been observed in swine, the resistance rates have not shown significant changes. The "National Action Plan on Antimicrobial Resistance (AMR) (2023-2027)" has newly set the usage levels of antimicrobial agents for livestock and second-line drugs as outcome indices.

Therefore, continued efforts are required to reduce the overall use of antimicrobial agents through the development and commercialization of vaccines, the promotion of their use, and the improvement of husbandry hygiene standards. In addition to ensuring appropriate and prudent use, it is essential to analyze and evaluate the factors that contribute to resistance rates being maintained, as well as the trends in resistance rates to various antimicrobial agents, and to respond accordingly.

In the field of companion animals, there has been a noticeable presence of bacterial strains derived from diseased animals with high resistance rates to third-generation cephalosporins and fluoroquinolones. Therefore, in addition to further promoting the "Guide for Antimicrobial Prudent Use in Companion Animals," it is essential to continue and strengthen AMR measures in the companion animal sector.

This report presents the status of antimicrobial-resistant bacteria in various sectors, the usage (or sales volume) of antimicrobial agents in humans, animals, and agriculture, as well as the differences in antimicrobial usage by class across these sectors. Additionally, it highlights significant progress in the collection of data on antimicrobial-resistant bacteria in the food sector and the environment, as well as the analysis of cross-sector genomic data. These advancements indicate considerable progress, and further developments are anticipated in the trend surveys across various sectors in the coming years.

Furthermore, in the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020), the annual Nippon AMR One Health Report has been playing an important role as a one-stop hub to confirm drug susceptibility data of drug-resistant bacteria in humans, animals, and foods. In the future, the analysis of drug-resistant genes and drug-resistant bacteria genome data will be extremely crucial in understanding whether and to what extent specific drug-resistant bacteria and drug-resistant genes increase or decrease and migrate between different sectors within the One Health framework, and in applying this information to risk assessment and risk management. It is also vital to

steadily implement this point based on the National Action Plan on Antimicrobial Resistance (AMR) (2023-2027). Industry, government, and academia will work closely together to promote collaboration among organizations in charge of different fields, while conducting cross-sectional assessments of risks to humans, animals, and the environment. These efforts will facilitate effective responses to the AMR challenge both domestically and internationally and will also play an important role in Japan's leading role in the global AMR control effort. In addition, the collection and analysis of data on antimicrobial resistance is an indispensable foundation for AMR countermeasures, and progress is expected to be made in these efforts in the future. These efforts are anticipated to make a significant contribution to AMR countermeasures in Japan and to improve the people's health and public health.

Appendix

(1) Japan Nosocomial Infections Surveillance (JANIS)

1) Overview

JANIS 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 JANIS (https://janis.mhlw.go.jp/english/index.asp). A result of the analysis is reported back to each institution so that such feedback can be utilized for the formulation and evaluation of infection control measures at each institution. JANIS participation is voluntary with approximately 3,200 medical institutions participating as of December 2023.

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. As of December 2023, 3,074 hospitals participated in the laboratory section. Bacteria that are isolated from specimens from inpatients as well as outpatients at participating hospitals are included in aggregated data. 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. 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 (However, some of them are under Japan's Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases).

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. Antimicrobial Resistance Research Center (AMR-RC), 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 bacteria 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 2022 have already been submitted. 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 H

ealth 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 the status of isolates of antimicrobial resistant bacteria. 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 bias based on this sampling policy in JANIS should be addressed. With regard to clinics that were not previously covered by JANIS, clinics that perform at least one bacterial culture test per month will be able to participate in the JANIS laboratory section beginning in 2022, and discussions are in progress to compile and publish this data.

(2) National Epidemiological Surveillance of Infectious Disease

1) Overview

The National Epidemiological Surveillance of Infectious Disease 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 National Epidemiological Surveillance of Infectious Disease 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 this program 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 National Epidemiological Surveillance of Infectious Disease, 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*Enterobacteriales* 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 108 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. In the case of antimicrobial-resistant bacterial infections classified as Category 5 infectious diseases, carriers are excluded from the scope of reporting.

Table 106. Reporting criteria

Reportable disease	Summary of reporting criteria
VRE	*Enterococcus* is isolated and identified, and the MIC of vancomycin is ≥ 16 μg/mL.
VRSA	*Staphylococcus aureus* is isolated and identified, and the MIC of vancomycin is ≥ 16 μg/mL.
CRE	*Enterobacterales* is isolated and identified, and either A) or B) below is satisfied: A) The MIC 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 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 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 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 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 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 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 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 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 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 of ciprofloxacin is ≥ 4 μg/mL,
or the diameter of the inhibition circle of the ciprofloxacin susceptibility disk (KB) is ≤ 15 mm.

3) System

Physicians/Hospitals directly input and register the information into National Epidemiological Surveillance of Infectious Disease, or Public Health Centers input and register the information into National Epidemiological Surveillance of Infectious Disease after confirming the details notified by physicians/hospitals. 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 National Epidemiological Surveillance of Infectious Disease, 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 National Epidemiological Surveillance of Infectious Disease 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) Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE)

1) Overview

In 2017, the governance of the Regional Infection Control Support System (RICSS) was transferred to the AMR Clinical Reference Centre to utilize the system for AMR control as a surveillance platform for infection control at regional as well as national levels. The system was renamed to Japan Surveillance for Infection Prevention and Healthcare Epidemiology: J-SIPHE.

The system has been launched as a system that can be utilized for AMR measures in hospitals as well as for the promotion of regional cooperation, and a large amount of data has been accumulated and an annual report is published annually to return the data to the facilities using the system. The J-SIPHE 2022 Annual Report covers a total of 1,876 participating medical institutions. The system is designed to collect information on the status of infectious disease treatment, infection control measures and the appropriate use of antimicrobials, the occurrence of healthcare-associated infections, the occurrence of major bacteria and drug-resistant bacteria, the occurrence of bloodstream infections caused by them, and the use of antimicrobials at participating facilities, and to make use of this information at the facilities themselves and in regional networks. With these as its purpose, the system also to establish indicators as an indicator for AMR control.

2) System

This system is based on participation in a regional cooperation network within the framework of the medical fee premium for infection prevention measures. In order to support AMR measures by utilizing the regional cooperation network, etc., information can be shared within the group based on unified standards, and the system visualizes data that are necessary and adequate for AMR measures by making secondary use of existing information such as returned JANIS laboratory section data and integrated inpatients EF files, while reducing the burden on participating facilities.

3) Prospects

The system needs to be further renovated so that it can be utilized for activities such as regional collaborative conferences, and to make it more accessible and meaningful for facilities that lack human resources for infection control. The system aims to make the system more effectively used in building infection control networks at the regional level and in decision-making on infection control.

(4) Trend surveillance of antimicrobial-resistant Mycobacterium tuberculosis

1) Overview

registered tuberculosis patient information system is a part of National Epidemiological Surveillance of Infectious Disease 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, agent-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 agent-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 agent-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. Agent-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 National Epidemiological Surveillance of Infectious Diseases.

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 agent-susceptibility testing results (approximately 80% at present); the establishment of a system for nationwide quality assurance for agent-susceptibility testing; and the quality control of data entry are warranted.

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

1) Overview

JVARM is a nationwide system for monitoring antimicrobial-resistant bacteria among animals. This monitoring has been conducted by the Ministry of Agriculture, Forestry and Fisheries since 1999 through its network of connections with livestock hygiene service centers across Japan. JVARM provides globally important information and is cited as an example of a monitoring system in the WHO report “Antimicrobial resistance: global report on surveillance 2014.”

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 and foodborne pathogens derived from healthy animals; and (3) monitoring of antimicrobial resistance in 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 21). 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 AMR. Antimicrobial resistance surveillance in diseased dogs and cats was launched in FY2017 and in healthy dogs and cats in FY2018. In FY2021, discussion about methodologies for antimicrobial resistance monitoring in the livestock environment started.

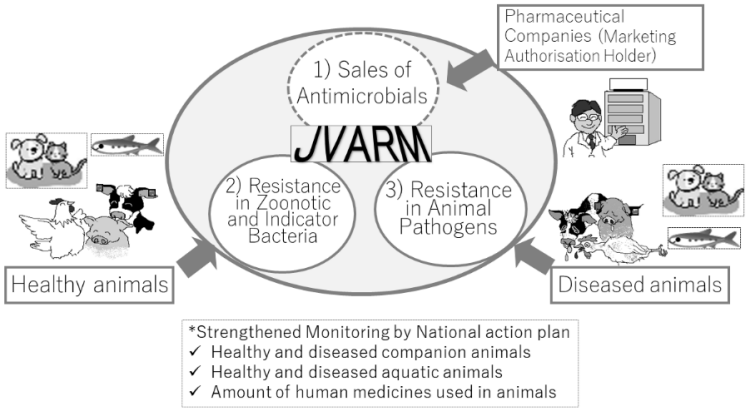

Figure 21. Overview of veterinary antimicrobial resistance monitoring

2) System for the antimicrobial resistance monitoring

When JVARM first began, surveillance of foodborne pathogenic bacteria and indicator bacteria from healthy animals was carried out using samples of strains isolated and identified from the feces of food-producing animals collected at farms by livestock hygiene service centers. Surveillance using strains isolated and identified by the contracted testing agency from feces collected at animal and poultry slaughterhouses was launched in 2012, as this facilitated more intensive sampling at a stage closer to the final food product. In 2016, as it had been confirmed that there was no major difference in the findings of both surveys, JVARM shifted completely from sampling at farms to sampling at animal and poultry slaughterhouses (Figure 22). Bacteria were isolated from faecal samples collected from slaughterhouses (five sites nationwide) and poultry slaughterhouses (13 sites nationwide), using species-selective media and data are based on one strain per bacterial species per farm (the farm's representative strain).

In the case of clinical isolates from food-producing animals, bacterial strains isolated and identified from materials for pathological appraisal by livestock hygiene service centers across the country were collected. One or two strains isolated from a different individual affected in a single case of infectious disease were collected for the monitoring. The MIC values for these strains are measured by the National Veterinary Assay Laboratory using a broth microdilution method based on the CLSI Criteria (Figure 22). The scope of antimicrobial monitoring includes a broad range of active ingredients that are considered important in antimicrobials used exclusively for animals, antimicrobials used for both animals and humans, and antimicrobial feed additives, among others. Antimicrobial agents subject to monitoring are selected for each bacterial species, according to the past monitoring results and Chapter 6.7 of the WOAH Terrestrial Animal Health Code.[3]

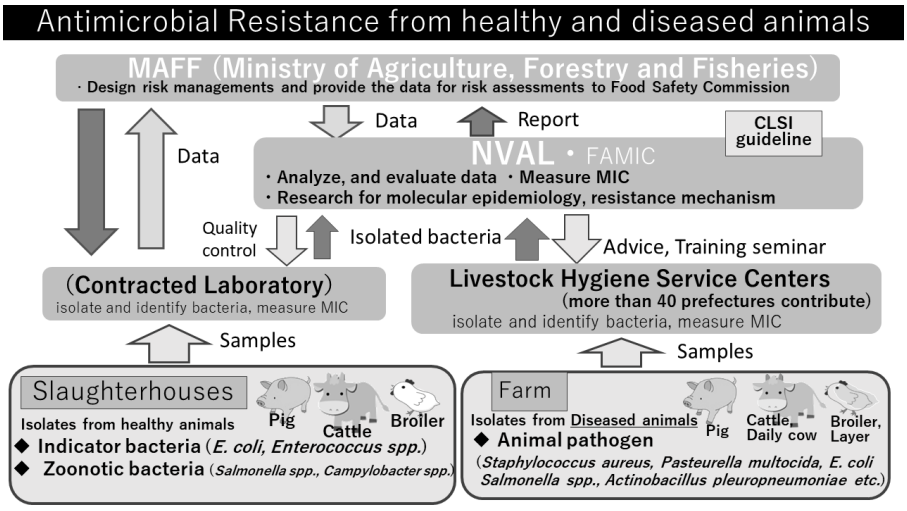

Figure 22. Monitoring system for drug-resistant bacteria from healthy livestock (slaughterhouses and poultry slaughterhouses) and from diseased livestock (farms).

For the companion animal survey, the survey method was determined based on the results of the discussion at the Working Group on Companion Animal AMR Surveillance, and from 2017, strains derived from diseased dogs and cats were collected from clinical laboratories. Also, from 2018, healthy dogs and cats were targeted, and specimens were collected from veterinary hospitals nationwide with the cooperation of the Japan Veterinary Medical Association (Fig. 23).

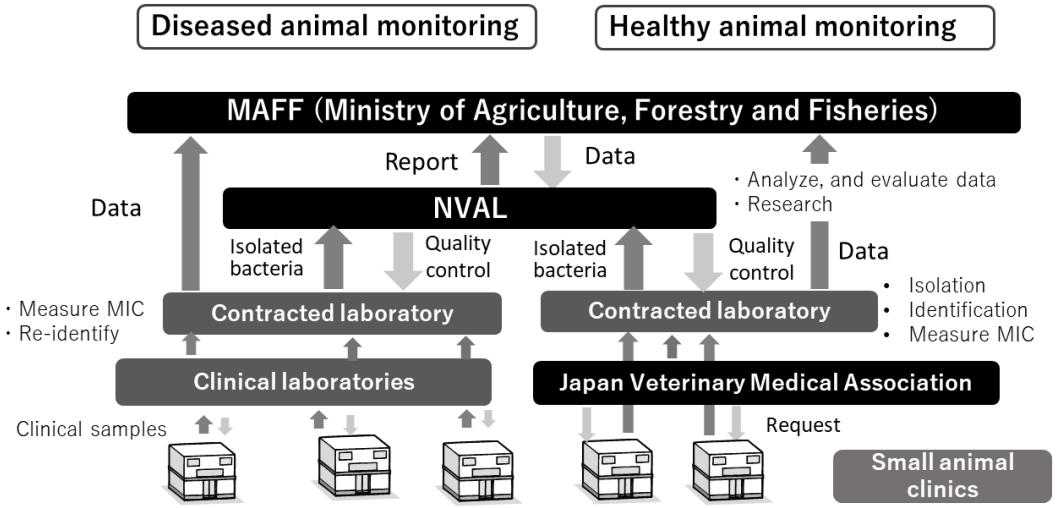

Figure 23. System for antimicrobial resistance monitoring in healthy and diseased dogs and cats

Isolation of bacteria from specimens was carried using selective media in all cases, with one strain of one species per hospital. The MICs of the collected strains were determined at the contract laboratory using the micro-broth dilution method according to CLSI. Antimicrobial substances to survey were selected for each species of bacteria, taking into account the drugs used in clinical settings for companion animals in addition to those targeted in the livestock survey.

Efforts are made to achieve standardization in the isolation and identification of strains and antimicrobial susceptibility testing, by such means as training sessions for the staff of livestock hygiene service centers who carry out this work at the National Veterinary Assay Laboratory each year and checks of quality control at the contracted testing agency. In addition, a parallel survey of the origin of the samples and the date on which they were collected is carried out. 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. Antimicrobial feed additives are analyzed by the 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.

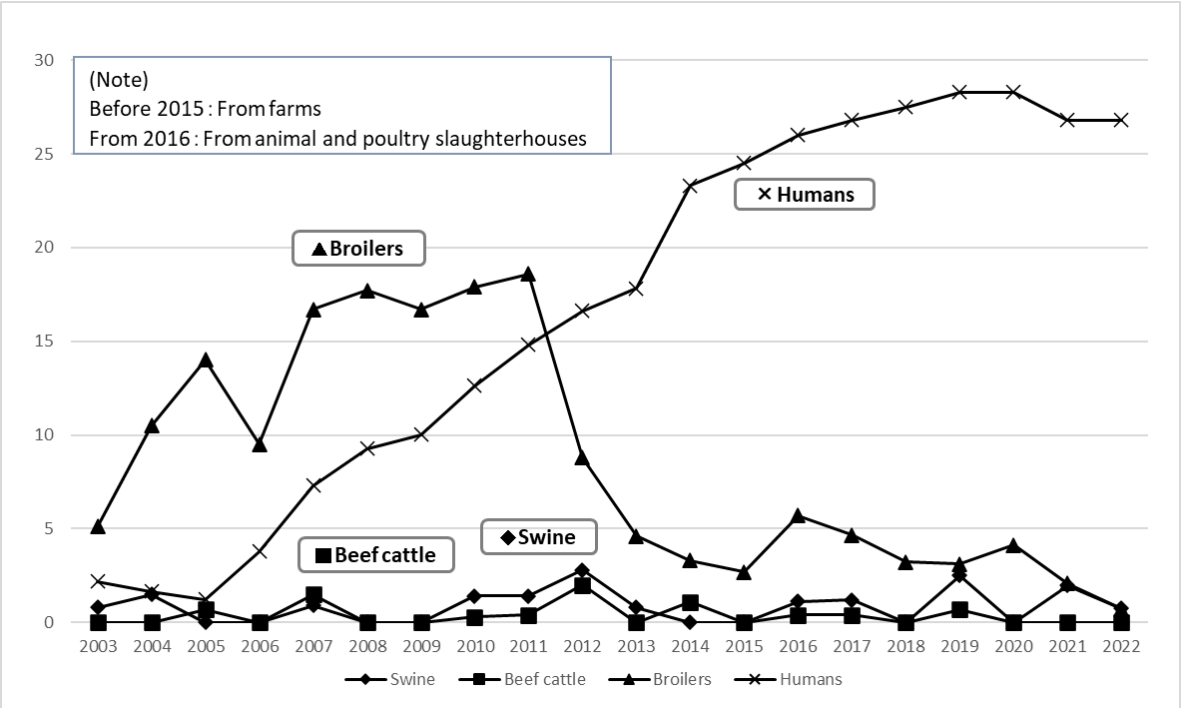

Figure 24. Comparison of the proportion of third generation cephalosporin-resistant *Escherichia coli* derived from humans and food-producing animal

Comparing data from JVARM and JANIS, which monitors resistant bacteria in human medical settings, the resistance rate to third generation cephalosporins had increased until 2011 in both human-derived and broiler-derived *E. coli*, but then has decreased drastically in broiler since 2012. This may be due to the discontinuation of the off-label use of third generation, which had been practiced cephalosporins in some egg hatcheries, in response to the guidance given to the relevant organizations advising to stop it by presenting the JVARM results.[6] In humans, on the other hand, the rate has continued to increase showing different trends in humans broiler (Figure 24).

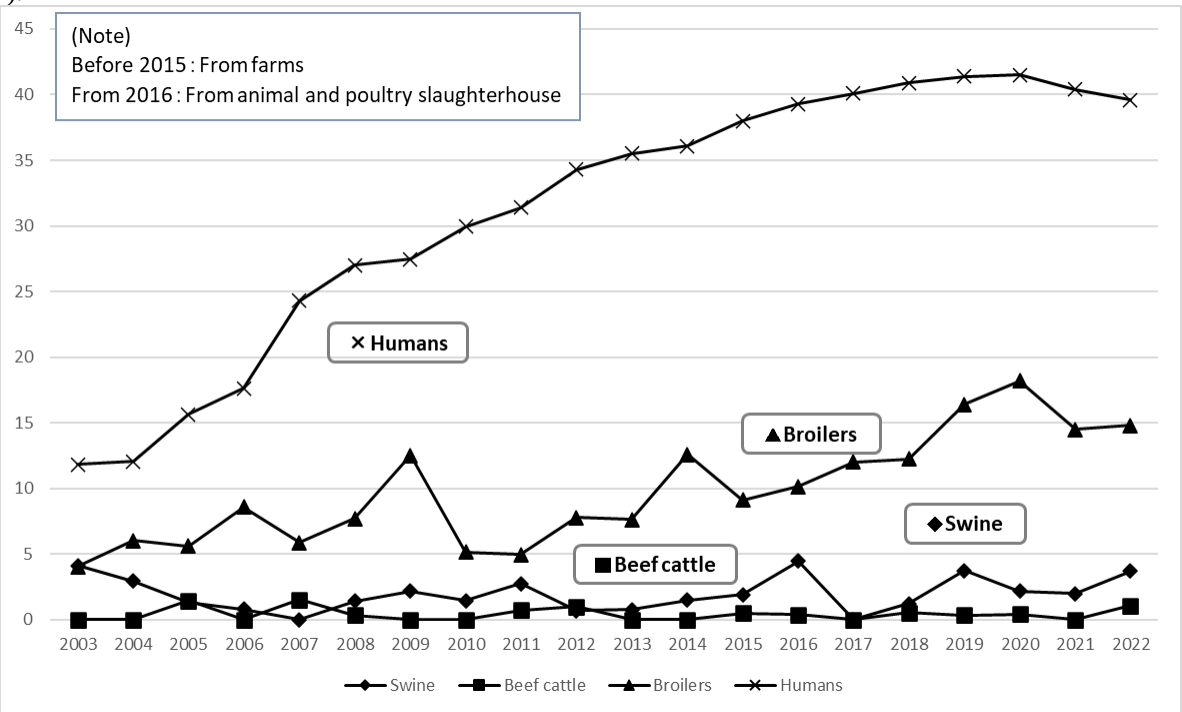

Figure 25. Comparison of the proportion of fluoroquinolone-resistant *Escherichia coli* derived from humans and food-producing animal

While an increasing trend in the fluoroquinolone resistance rate of human *E. coli* has been observed since 2003,

the fluoroquinolone resistance rate of *E. coli* from livestock has remained below 5% for swine and beef cattle-derived strains and below 20% for broiler-derived strains, showing different trends between human and livestock (Figure 25)

3) Monitoring the sales volumes of veterinary antimicrobials

An annual monitoring is conducted on the volumes of sales of veterinary antimicrobials, based on the reported quantities of veterinary agents handled by marketing authorization holders, pursuant to Article 71-2 of the Veterinary Agent Control Regulations (MAFF Ordinance No. 107 of 2004) (Figure 26). Starting 2001, the monitoring has included the volume of sales by active pharmaceutical ingredient, and the estimated percentage of sales by animal species, in addition to the sales volumes by antimicrobial class and route of administration. 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 agents, Quasi-agents and Medical Devices." Under the WOAH Terrestrial Animal Health Code's section on antimicrobial usage (Chapter 6.8), [4] these data are submitted to the WOAH for the activity to understand and compare usage in each country of the world.

Figure 26. Monitoring on the sales volumes of veterinary antimicrobials

4) Future prospects

The main issues to be addressed by JVARM in the future are: 1) further promotion of more advanced investigation and analysis of antimicrobial resistance genes and others through whole-genome analysis of bacteria from livestock and companion animals, and consideration of their use in trend surveys and comparison with the human field; and 2) evaluation of the amount of veterinary antimicrobial use by the biomass weight calculated by the method proposed by WOAH. To promote the One Health surveillance and monitoring, these data accumulated will lay the ground for risk assessment and risk management by clarifying the transmission of process of antimicrobial resistance bacteria through collaborating with other fields.

(6) Trend Surveillance of Antimicrobial Agents in Japan (JSAC, J-SIPHE)

1) Overview

The governance of Japan Antimicrobial Consumption Surveillance (JACS), an antimicrobial use surveillance system established in 2015 through the Ministry of Health, Labour and Welfare (MHLW) Science Research, was transferred to the AMRCRC and it was renamed to Japan Surveillance of Antimicrobial Consumption (JSAC) (Antimicrobial Use Surveillance) in 2022 in order to conduct a monitoring of antimicrobial use in humans in Japan on an annual and continuous basis at national level and utilize it for in AMR measures. Currently, JSAC (http://amrcrc.ncgm.go.jp/surveillance/index.html) investigates antimicrobials use (AMU) in Japan and by prefecture using sales volume information and NDB. In addition, AUDs and DOTs of each participating facility are compiled and published as an annual report in J-SIPHE (https://j-siphe.ncgm.go.jp/).

2) Monitoring methods

The sales volume data is used to calculate the potency for each agent for overall use and by dosage form (oral and parenteral) and by prefecture, and figures are collated based on either the ATC or AWaRe classification advocated by the WHO. In the case of AMU in humans, these figures are shown over time, adjusted by defined daily dose (DDD) as defined by the WHO, then adjusted by population to calculate DID (DDDs/1,000 inhabitants/day). To monitor AMU from a One Health perspective, figures converted into titer values are summarized by weight for each ATC category and are then shown totalled with AMU elsewhere. Figures shown for AMU at medical institutions are the results from J-SIPHE monitoring.

∗ ATC Classification: Anatomical Therapeutic Chemical Classification System, a classification system for pharmaceutical products proposed by WHO.

∗ AWaRe classification: an indicator of appropriate antimicrobial use recommended by WHO (see p. 86)

3) Prospects

The establishment of Japan's first AMU surveillance programs in the form of JSAC and J-SIPHE put in place a system that enables trends in AMU over time to be fed back to the public. Sources of AMU information include both data on the volume of sales and insurance billing data. The sources of information used and the way in which they are presented need to be altered according to their purpose and further consideration is required regarding the form in which they should be collated and fed back on an ongoing basis.

(7) 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] 42 *Campylobacter jejuni* and 3 *Campylobacter coli* strains isolated from feces of diarrhoea patients athospitals in Tokyo in 2021 were tested using five antimicrobials such as ABPC, TC, NA, CPFX, and EM. The number of samples for the 2021 isolates was very small due to the outbreak of novel coronavirus infection. Results were determined by measuring the zone of inhibition and following the susceptibility determination table in the protocol[9].

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. While tests were conducted using the disk method, in accordance with U.S. CLSI standards, judgment criteria are provided for only three agents, namely CPFX and EM. Accordingly, other agents were assessed in accordance with standards unified as part of a Ministry of Health, Labour and Welfare-funded research project concerning the promotion of food safety, with reference to EUCAST breakpoints and various literature. 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, in order to know the emergence of antimicrobial-resistant bacteria nationwide.

(8) 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 2021. 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. The susceptible discs were ABPC, GM, KM, SM, TC, ST, CP, CTX, CAZ, and CFX, FOM, NA, CPFX, NFLX, AMK, IPM and MEPM 17 agent disks were used. 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 zone would not be coalesced. The diameters of inhibition zone was 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.

(9) 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 *N. 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 six 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 CTRX and spectinomycin as recommended agents; for AZM, which was used as part of the two-agent combination therapy overseas; and for PCG, CFIX, and CPFX, which had been used as recommended agents in the past. The EUCAST standards were used for susceptibility and resistance assessment (Table 107). For reference, the proportion of resistant strain based on CLSI Guidelines (M100- S25) (Table 108) is indicated in Table 109. 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, CTRX and SPCM are the only recommendable agents in Japan. Because *N. gonorrhoeae* that are present in the pharynx are an important source of infection, *N. gonorrhoeae* in pharynx should be treated. Due to its *in vivo* pharmacokinetics, SPCM does not have effect on *N. gonorrhoeae* present in the pharynx. Therefore, CTRX 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. CTRX is administered by intramuscular injection overseas, and therefore subject to dose limitation. Therefore, if strains that indicate the CTRX MIC of 0.5 μg/mL are transmitted overseas, it is likely that CTRX 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 107. Antimicrobial susceptibility assessment criteria based on EUCAST (μg/mL) for *N. 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 108. Antimicrobial susceptibility assessment criteria based on CLSI (μg/mL) for *N. 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 109. The proportion (%) of antimicrobial-resistant *N. 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.

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

1) Overview

For typhoid and paratyphoid fever, 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, *Salmonella* Paratyphi A, and *Shigella* spp. in 2022 and after, and using a disk diffusion method for *Shigella* spp. in 2021 and before.

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.

(11) Antimicrobial Resistance (AMR) One Health Platform

1) Overview

In October 2019, the AMRCRC published the “Antimicrobial Resistance (AMR) One Health Platform"（https://amr-onehealth-platform.ncgm.go.jp/home）, a website that provides easy-to-understand information related to infectious diseases in the human, animal and environmental fields.

This system allows users to freely view trends in agent resistance rates, antimicrobial use, and other AMR-related indicators by field, prefecture, and year. The information handled is mainly secondary use from outputs of this report, AMED research and other deliverables.

In November 2021, prefectural homepage was newly established, which allows users to view various indicators in one place from the homepage of each prefecture. We hope that this platform will be utilized to further promote AMR measures in each region.

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Websites of Key Trend Surveys

AMR Clinical Reference Center

http://amrcrc.ncgm.go.jp/

Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE)

https://j-siphe.ncgm.go.jp/

Nippon AMR One Health Report

https://amr-onehealth.ncgm.go.jp/

Antimicrobial Resistance (AMR) One Health Platform

https://amr-onehealth-platform.ncgm.go.jp/home

Japan Surveillance of Antimicrobial Consumption (JSAC)

http://amrcrc.ncgm.go.jp/surveillance/index.html

Japan Nosocomial Infections Surveillance (JANIS), Ministry of Health, Labour and Welfare

https://janis.mhlw.go.jp/

National Epidemiological Surveillance of Infectious Disease

https://www.niid.go.jp/niid/ja/allarticles/surveillance/2270-idwr/nenpou/

Infectious Disease Surveillance Program: Request for Physician Reporting Under the Infectious Diseases Control Law (Ministry of Health, Labour and Welfare)

https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou/kekkaku-kansenshou11/01.html

Infectious Disease Surveillance Program: Infectious Diseases and Animals Reportable by Veterinarians Under the Infectious Diseases Control Law (Ministry of Health, Labour and Welfare)

https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/kenkou/kekkaku-kansenshou/kekkaku-kansenshou11/02.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/

The Antimicrobial Resistance One Health Surveillance Committee: Terms of References

January 16, 2017
Partially amended on October 4, 2023

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) (2023-2027), enacted on April 7, 2023, also requires promoting 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 Department of Infectious Disease Prevention and Control, Public Health Bureau, Ministry of Health, Labour and Welfare (MHLW), in order to review necessary technical matters that pertain to One Health AMR surveillance and prepare annual reports.

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 of the Department of Infectious Disease Prevention and Control, Public Health 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 Department of Infectious Disease Prevention and Control, Public Health Bureau, HLW.
(2) Clerical affairs for the Committee should be handled by the Division of Infectious Disease Prevention and Control, Department of Infectious Disease Prevention and Control, Public Health 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

The annual Nippon AMR One Health Report was created 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, 7th meeting on 10/17/2019, and 8th meeting on 11/6/2020, 9th meeting on 1/17/2022, 10th meeting on 11/21/2022, and 11th meeting on 12/13/2023. And this report has been created through discussion at a series of the AMR One Health Surveillance committee in cooperation with additional experts and cooperating governmental agencies:12th meeting on 1/8/2025.

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Cooperating governmental agencies

Food Safety Commission Secretariat	Ministry of the Environment
Ministry of Agriculture, Forestry and Fisheries	Ministry of Land, Infrastructure, Transport and Tourism

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