**PROVISIONAL TRANSLATION**

# National Action Plan on Antimicrobial Resistance (AMR)

## 2023-2027

**April 7, 2023**

**The Government of Japan**

*The translation in this document is to be considered solely as a reference. In the event of any conflict or inconsistency between the Japanese and English versions, the original Japanese version shall prevail.

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# INTRODUCTION

## ANTIMICROBIAL RESISTANCE: A HEALTH THREAT

The term "Antimicrobial Resistance (AMR)" refers to the state in which certain types of antimicrobials such as antibiotics and antivirals become less effective or ineffective. As the number of such bacteria and viruses with antimicrobial resistance increases, conventional drugs become ineffective, making it difficult to treat infectious diseases that were previously treatable with mild illnesses, and increasing the likelihood of serious illness and death. Therefore, it is important to control the outbreak of antimicrobial resistance (AMR) wherever possible and prevent the spread of infectious diseases caused by antimicrobial-resistant organisms (AROs). Since the 1980s, antimicrobial-resistant (AMR) bacteria that do not respond to conventional antibiotics have been identified around the world, making it increasingly difficult to prevent and treat infections, and the number of infections that do not respond to antibiotics is expected to continue to increase. In Japan, healthcare-associated infections caused by antimicrobial-resistant Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococci* (VRE), followed by multidrug-resistant *Pseudomonas aeruginosa* (MDRP) and multidrug-resistant *Acinetobacter* (MDRA), have spread, and these infections are still major problems in healthcare facilities. In addition, carbapenem-resistant *Enterobacteriaceae* (CRE), which are resistant to carbapenems, have emerged recently.

Infections caused by antimicrobial-resistant organisms (AROs) are less easily recognized as a crisis than infections that are considered more likely to cause rapid pandemics, such as the coronavirus infectious disease, emerged in 2019 (COVID-19). Meanwhile, the review committee on antimicrobial resistance (AMR) in United Kingdom (O'Neill Commission) estimates that if no action is taken, the number of deaths worldwide will reach 10 million by 2050, exceeding the number of deaths from cancer.[1] In Japan, a 2019 survey reported that more than 8,000 annual deaths in 2017 are estimated from bacteraemia[2] caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and fluoroquinolone-resistant *E. coli* (FQREC), which are the most frequently seen antimicrobial resistant bacteria in Japan.[3]

Furthermore, the economic impact of antimicrobial resistance (AMR) is also considered significant as in a 2017 World Bank study stating that if no action is taken, the world's annual Gross Domestic Product (GDP) could decline by 3.8% by 2050 compared to 2017. Since this figure is comparable to the financial crisis that occurred in 2008, it is also considered obvious that the world economy will be in a critical situation.[4]

For all these reasons, antimicrobial resistance (AMR) has been taken up as a serious health threat worldwide and recognized as one of the priorities for the Group of Seven (G7) to address in health sector, and the World Health Organization (WHO) has placed antimicrobial resistance (AMR) control on its important policy agenda.[5] As a member of the Group of Seven (G7), Japan is in a position to play a leading role in the combat against antimicrobial resistance (AMR) not only domestically but also globally, especially in the Asian region.

[1] Jim O'Neill, "The Review on Antimicrobial Resistance. Tackling Drug-Resistant Infections Globally: Final Report and Recommendations.," May 2016
[2] Bacteremia is a condition in which bacteria enter the bloodstream. Various infections can cause bacteremia, and bacteremia makes condition more severe and increases mortality rate.
[3] S Tsuzuki, et al., National trend of blood-stream infection attributable deaths caused by Staphylococcus aureus and Escherichia coli in Japan. J Infect Chemother. 2020; 26(4): 367-371
[4] World Bank, "Drug-resistant infections: a threat to our economic future: final report", May 2017
[5] World Health Organization, 10 global health issues to track in 2021, 24 December 2020

# ACTION PLAN ON ANTIMICROBIAL RESISTANCE (AMR)

In order to suppress the occurrence of antimicrobial resistance (AMR) as much as possible and to prevent the spread of infectious diseases caused by antimicrobial-resistant organisms (AROs), it is important to improve the knowledge and understanding of the public, especially those engaged in the fields of health care, nursing and welfare, food, livestock and aquaculture, and agriculture, regarding antimicrobial resistance (AMR) and use of antimicrobials. In addition, it is important to understand the occurrence of antimicrobial resistance (AMR) and the actual antimicrobial use (surveillance, monitoring) and to assess risk based on these information; to work towards reducing antimicrobial-resistant organisms (AROs) through appropriate infection prevention and control (IPC) and antimicrobial stewardship (AMS); and to ensure effective means of prevention, diagnosis and treatment of antimicrobial resistant infection (ARI), including research on mechanisms of the occurrence and spread of antimicrobial resistance (AMR) and the socioeconomic impact, and research and development of new methods for prevention, diagnosis and treatment.

The May 2015 World Health Assembly endorsed a global action plan on antimicrobial resistance (AMR), urging member states to develop their own national action plans within two years. In order to promote and strengthen domestic measures and international cooperation regarding antimicrobial resistance (AMR), the "Basic Guidelines for Strengthening Measures on Emerging Infectious Diseases" was formulated at the "Ministerial Meeting on Measures on Emerging Infectious Diseases" held on February 9, 2016, which includes description about the formulation of an action plan on antimicrobial resistance (AMR). Following this, at the "Ministerial Meeting on Measures on Emerging Infectious Diseases" held on April 5, 2016, the "National Action Plan on Antimicrobial Resistance (AMR) (2016-2020) " was formulated, which outlines measures to prevent the spread of infectious diseases caused by antimicrobial-resistant organisms (AROs) while suppressing the occurrence of antimicrobial resistance (AMR) as much as possible, with the aim of achieving a world without the disease burden caused by antimicrobial-resistant (AMR)-infectious diseases. The government has been making concerted efforts on antimicrobial resistance (AMR).

Due to the spread of coronavirus infection disease, emerging in 2019 (COVID-19), the planning period of the "National Action Plan on Antimicrobial Resistance (AMR) (2016-2020)" has been extended to the end of FY2022, and "National Action Plan on Antimicrobial Resistance (AMR) (2023-2027)" has been compiled to outline items to be implemented over the next five years to further promote measures on antimicrobial resistance (AMR).

# ABBREVIATIONS

| | |
|---|---|
| AMED | Japan Agency for Medical Research and Development |
| AMR | Antimicrobial Resistance |
| AMS | Antimicrobial Stewardship |
| AMU | Antimicrobial Use |
| ARG | Antimicrobial-resistant Gene |
| ARI | Antimicrobial-resistant Infection |
| ARISE | ARO Alliance for ASEAN & East Asia |
| ARO | Antimicrobial-resistant Organism |
| ASIARS-Net | Asian Antimicrobial Resistance Surveillance Network |
| ASP | Antimicrobial Stewardship Program |
| ASPIRE | Asia-Pacific One Health Initiative on AMR |
| AST | Antimicrobial Stewardship Team |
| AUD | Antimicrobial Use Density |
| CAUTI | Catheter-associated Urinary Tract Infection |
| CCP | Critical Control Point |
| CDC | Centers for Disease Prevention and Control |
| CDI | *Clostridium difficile* Infection |
| CiCLE | Cyclic Innovation for Clinical Empowerment |
| CLABSI | Central Line-associated Bloodstream Infection |
| CLSI | Clinical & Laboratory Standards Institute |
| COI | Conflict of Interest |
| COVID-19 | Corona Virus Infectious Disease, emerged in 2019 |
| CRE | Carbapenem- resistant *Enterobacteriaceae* |
| DALYs | Disability-adjusted life year |
| DDD | Defined Daily Dose |
| DID | DDD per 1,000 inhabitants per day |
| DOT | Days of Therapy |
| DPC/PDPS | Diagnosis Procedure Combination / Per-Diem Payment System |
| ESBL | Extended-spectrum beta-Lactamase |
| EU | European Union |
| FAO | Food and Agricultural Organization of the United Nations |
| FETP-J | Field Epidemiology Training Program Japan |
| FQREC | Fluoroquinolone resistant *Escherichia coli* |
| G7 | Group of Seven |
| GAIN Act | Generating Antibiotics Incentives Now Act |
| GCP | Good Clinical Practice |
| GDP | Gross Domestic Product |
| GHIT Fund | Global Health Innovation Technology Fund |
| GHSA | Global Health Security Agenda |
| GLASS | Global Antimicrobial Resistance Surveillance System |
| GloPID-R | Global Research Collaboration for Infectious Disease Preparedness |
| HACCP | Hazard Analysis and Critical Control Point |
| HAI | Healthcare-associated Infection |
| Hib | *Haemophilus influenzae* type b |
| ICD | Infection Control Doctor |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICMRA | International Coalition of Medicines Regulatory Authorities |
| ICT | Infection Control Team |
| ICU | Intensive Care Unit |
| IDES | Infectious Disease Emergency Specialist (Training Program) |
| IHR | International Health Regulation |

| | |
|---|---|
| IPC | Infection Prevention and Control |
| JARBB | Japan Antimicrobial Resistant Bacterial Bank |
| JARBS | Japan Antimicrobial Resistant Bacterial Surveillance |
| JANIS | Japan Nosocomial Infections Surveillance |
| JICA | Japan International Cooperation Agency |
| JPIAMR | Joint Programming Initiative on Antimicrobial Resistance |
| JSAC | Japan Surveillance of Antimicrobial Consumption |
| J-SIPHE | Japan Surveillance for Infection Prevention and Healthcare Epidemiology |
| JVARM | Japanese Veterinary Antimicrobial Resistance Monitoring System |
| J-VEG | Japanese Veterinary Epidemiology and Genomics |
| MALDI-TOF MS | Matrix-assisted Laser Desorption/Ionization Time Of Flight Mass Spectrometry |
| MBL | Metallo-beta-lactamase |
| MEPM-R | Meropenem Resistance |
| MDRA | Multidrug-resistant *Acinetobacter spp.* |
| MDRP | Multidrug-resistant *Pseudomonas aeruginosa* |
| MRC | Medical Research Council |
| MRSA | Methicillin-resistant *Staphylococcus aureus* |
| NCGM | National Center for Global Health and Medicine |
| NDB | National Database for Prescription and National Health Check-up |
| NICU | Neonatal Intensive Care Unit |
| NIH | National Institutes of Health |
| NOAR | Nippon AMR One Health Report |
| NTDs | Neglected Tropical Diseases |
| OECD | Organisation for Economic Co-operation and Development |
| PCR | Polymerase Chain Reaction |
| PCU | Population-corrected Unit |
| PK/PD | Pharmacokinetics/Pharmacodynamics |
| POC | Point of Care |
| POT | PCR-based Open Reading Frame Typing |
| PPP | Public Private Partnership |
| PPS | Point Prevalence Survey |
| QALYs | Quality-adjusted life year |
| SMA | Sodium Mercaptoacetate |
| SNS | Social networking service |
| SSI | Surgical Site Infection |
| TATFAR | Transatlantic Task Force on Antimicrobial Resistance |
| UNEP | United Nations Environment Programme |
| VICH | International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products |
| WGS | Whole Genome Sequencing |
| WHO | World Health Organization |
| WOAH | World Organisation for Animal Health |
| WPRO | Regional Office for the Western Pacific |
| VAP | Ventilator-associated *Pneumonia* |
| VRE | Vancomycin-resistant *Enterococci* |
| XDR | Extensively Drug-resistance |
| YLD | Years Lived with Disability |

Note that in the following document, antimicrobial substances and drugs for human and animal use are collectively called "antimicrobials". Antimicrobials used specifically against bacteria are called "antibiotics". With regard to animals, only antimicrobials against bacteria are discussed, of which "veterinary antibiotics" and "antibiotic feed additives" together are referred to as "antibiotics for animals".

# THE EFFORTS AND RESULTS OF THE NATIONAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE (AMR) (2016-2020)

In order to promote measures against antimicrobial resistance (AMR), the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020) sets goals for a total of six areas: (1) Public Awareness and Education, (2) Surveillance and Monitoring, (3) Infection Prevention and Control, (4) Antimicrobial Stewardship, (5) Research and Development, and (6) International Cooperation. The National Action Plan on Antimicrobial Resistance (AMR) (2016-2020) sets numerical targets as outcome indices throughout the entire process, and related ministries, agencies, and organizations have worked together to intensively promote measures against antimicrobial resistance (AMR) from the perspective of a global approach that transcends barriers between humans and animals (One Health approach).

## PUBLIC AWARENESS AND EDUCATION

In order to promote the nationwide public awareness-raising activities on antimicrobial resistance (AMR), we have promoted the establishment of the "Public Awareness Raising Meeting on Promoting Measures against Antimicrobial Resistance (AMR)", the AMR Clinical Reference Center (AMRCRC),[6] which consolidates various information on antimicrobial resistance (AMR) and provides information and training to medical professionals and local government officers, and the "Antibiotic Awareness Month". In addition, for professionals and workers in various fields such as healthcare, nursing and welfare, food, veterinary medicine, livestock and aquaculture, and agriculture, we have been promoting education and training on antimicrobial resistance (AMR) through adding and enhancing items related to antimicrobial resistance (AMR) to curricula of educational programs for medical professionals and other professionals.

On the other hand, the public's awareness of antimicrobial resistance (AMR) is not at a high level, and the level of understanding of the "National Action Plan on Antimicrobial Resistance (AMR)" in clinics nationwide is still insufficient. It is necessary to continue to conduct public awareness-raising activities using various methods.

## SURVEILLANCE AND MONITORING

In order to strengthen the surveillance in the medical and nursing care fields, the establishment of a "Antimicrobial Resistance Research Center" in the National Institute of Infectious Diseases, the operation of the "Japan Surveillance for Prevention and Healthcare Epidemiology (J-SIPHE)" to consolidate information on healthcare-associated infections (HAIs), occurrence of antimicrobial-resistant bacteria, and antimicrobial use at participating facilities nationwide, and the expansion of information collection on antimicrobial resistance rates in ambulatory and elderly care facilities have been worked on.

In the field of livestock and aquaculture, the enhancement of the functions and systems of the National Veterinary Assay Laboratory as a core laboratory, and the expansion of information collection on antimicrobial-resistant bacteria not only in livestock, but also in farm-raised aquatic animals and pets have been promoted.

In addition to these, from the viewpoint of promoting the One Health approach, the AMR Clinical Reference Center (AMRCRC) has been conducting nationwide surveillance and monitoring of antimicrobial resistance (AMR) by disclosing and operating the Antimicrobial resistance (AMR) One Health Platform, which covers data not only in the field of human medicine but also in a wide range of fields including veterinary medicine, animal and marine medicine, agriculture, food hygiene and environment. In addition, the "Antimicrobial Resistance One-Health Surveillance Committee" was established to study the status of the use of antimicrobials for humans and animals and the antimicrobial resistance rates of microorganisms in Japan. The Group holds discussions among experts in the human, animal, and environmental fields, and annually produces a "Nippon AMR One Health Report (NOAR)" that evaluates the current status and understanding of trends in each field.

[6] An organization that consolidates information on antimicrobial resistance (AMR) in healthcare and welfare and provides education and awareness for healthcare professionals, welfare workers, and public health-related local government officials. It develops and produces educational materials, provides online information, and offers training opportunities. Established at the National Center for Global Health and Medicine.

It is necessary to continue to promote understanding of antimicrobial resistance (AMR) trends that transcend the boundaries between humans, animals, and the environment, as well as to expand the number of target microorganisms and participating facilities and strengthen the testing systems necessary for trend surveys in order to implement antimicrobial resistance (AMR) countermeasures tailored to local needs.

## Infection Prevention and Control

With regard to infection control measures at medical institutions, the revision of medical fee in FY2022 established the premium for improvement of infection control measures from the viewpoint of promoting infection control measures at individual medical institutions and infection control measures implemented in cooperation with local medical institutions, while building on the premium for infection control measures. In addition, through the "Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE)," comparisons and evaluations regarding infection prevention and control (IPC) have been conducted. On the other hand, current nosocomial infection control measures mainly target medical institutions, and further promotion and strengthening of efforts in elderly care facilities are needed.

In the livestock and aquaculture field, we have supported the development and commercialization of vaccines, immunostimulants, in vitro diagnostics, and reagents, and also made efforts to ensure compliance with the biosecurity standards and to disseminate the guidebook for the biosecurity standards for each livestock species in order to promote production systems that do not rely on antimicrobials. Furthermore, in the food field, we have been providing support to all food businesses that manufacture, process, prepare, and sell food, etc., so that they can smoothly engage in Hazard Analysis and Critical Control Point (HACCP)[7].

## Antimicrobial Stewardship

To promote antimicrobial stewardship, the Ministry of Health, Labour and Welfare (MHLW) has formulated and disseminated the Manual of Antimicrobial Stewardship. Also, in the revision of medical fee in FY2018, the premium for support for appropriate use of antibiotics and the premium for support for appropriate use of pediatric antibiotics were established to support efforts to promote appropriate use of antimicrobials. In particular, the introduction of the premium for support for appropriate use of pediatric antibiotics has resulted in a decrease of approximately 20% in the administration of antibiotics to pediatric patients in outpatient clinics.[8] On the other hand, there are reports that the guidelines are not always followed in the use of broad antimicrobials in the medical field,[9] [10] and further efforts are required to promote their appropriate use.

In the livestock and aquaculture field, guidelines for prudent use have been established to promote the thorough implementation of prudent use. In addition, the risk assessment concerning the impact of antimicrobial-resistant bacteria on human health through food has been completed for all antibiotic feed additives designated in Japan, and the designation of five antibiotic feed additives[11] that were assessed as potentially having adverse effects on human health has been withdrawn. On the other hand, understanding of actual use of antimicrobials at production sites is an issue, and a mechanism needs to be established.

[7] Methods of food hygiene management that control particularly important processes that prevent foodborne bacterial contamination and foreign material contamination that may occur from the time of arrival of raw materials to the time of shipment.

[8] Okubo Y, Nishi A, Michels KB, et al. The consequence of financial incentives for not prescribing antibiotics: a Japan's nationwide quasi-experiment. Int J Epidemiol. 2022;51(5):1645-1655. doi:10.1093/ije/dyac057

[9] Jung-ho Shin, Noriko Sasaki, Susumu Kunisawa, Yuichi Imanaka. Influence of criteria for nosocomial use of antimicrobial agents on the selection of antimicrobial agents recommended in practice guidelines for patients with community-acquired pneumonia, and the impact of its antimicrobial selection on outcomes. The 58th Annual Congress of Japan Society for Healthcare Administration in Fukuoka and online, October 2-4, 2020 (Journal of the Japan Society for Healthcare Administration Vol.57 Suppl. p.172)

[10] 2018 Ministry of Health, Labour and Welfare commissioned project: Evidence Based Medicine (EBM) Dissemination and Promotion Project "Medical Guideline Handbook" p3

[11] Virginiamycin, colistin sulfate, tyrosin phosphate, chlortetracycline, alkyl trimethyl ammonium calcium oxytetracycline

## Research and Development

With regard to research and development and drug discovery related to antimicrobial resistance (AMR) control measures, in addition to the development of the Japan antimicrobial resistant bacterial bank (JARBB), the expansion of genome databases of human, animal, and environmental origin, and the promotion of clinical and epidemiological studies on health economic evaluation and appropriate use of antimicrobials, Japan agency for medical research and development (AMED) has been promoting it through the "Research Project for the Promotion of Innovative Drug Development for Emerging and Re-emerging Infections" and "Cyclic Innovation for Clinical Empowerment (CiCLE)" under an industry-academia-government collaboration system.

Although these efforts have produced some results, such as progress in research on antimicrobial resistance (AMR) control measures, the development of new antibiotics in Japan has been stagnant since the 1990s. On the other hand, even if the number of drugs successfully developed and distributed in the market increases, inappropriate use of such drugs will lead to an increase in the number of antimicrobial-resistant bacteria and, consequently, a weakening of their effectiveness, so it is necessary to control their use to an appropriate level. In the U.S., U.K., Sweden, market incentives are being introduced on a trial basis to increase the predictability of post-marketing profits while separating "usage (sales volume)" from "sales (profits)" (de-linking). In Japan, it is necessary to consider on a specific method to secure drugs for the treatment of antimicrobial resistant bacteria, such as market incentives. In addition, shortages of antibiotics are occurring all over the world, and Japan is also experiencing a large-scale shortage of antibiotics. A stable supply of antibiotics is an important issue to promote their appropriate use and to control the spread of antimicrobial resistance (AMR). In addition to promote research and development of new antibiotics, measures to maintain a stable supply of antimicrobials are required.

## International Cooperation

Japan has supported the efforts of the World Health Organization (WHO), the Group of Seven (G7) process, the World Organisation for Animal Health (WOAH) and others by submitting data to the Global Antimicrobial Resistance Surveillance System (GLASS) of the World Health Organization (WHO), holding the AMR One Health Tokyo Conference jointly with the Western Pacific Regional Office (WPRO), and providing data and advice for the establishment of a database for the use of antibiotics for animals by the World Organisation for Animal Health (WOAH). In addition, Japan has been engaged in the discussion of the human field on the regulatory response required to be implemented by regulatory authorities in the framework of the International Cooperation of Medicines Regulatory Authorities (ICMRA), including Japan, the U.S., and the EU, and in the discussion of the animal field on the development of common global study guidelines in the framework of the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medical Products (VICH). In addition, we have been engaged in international cooperation, mainly in Asian countries, in the areas of infection prevention and control (IPC), support for surveillance systems, development of a system infrastructure for collecting information on antimicrobial-resistant bacteria, and transfer of antimicrobial resistant (AMR) testing technology. Antibiotic use in Japan has remained below the Organization for Economic Cooperation and Development (OECD) average, Japan continues to play a leading role in the world, especially in the Asian region, in addressing antimicrobial resistance (AMR).

# THE CURRENT STATE AND CHALLENGES OF ANTIMICROBIAL RESISTANCE IN JAPAN

The National Action Plan on Antimicrobial Resistance (AMR) (2016-2020) set numerical targets throughout the plan as performance indicators and has been working on antimicrobial resistance (AMR) measures to achieve the targets.

Table 1 National Action Plan on Antimicrobial Resistance (AMR) (2016-2020) Outcome Indices

## HUMAN-RELATED INDICES

| 1. Lower the penicillin resistance of *Streptococcus pneumoniae* to 15% or less in 2020 |
|---|
| • The penicillin resistance (hereinafter "resistance" refers to the proportion of isolates that are classified as "resistant" or "intermediate" in a standardized antimicrobial susceptibility test) of pneumococcus remains at a higher level than in other developed countries. Since this index is lowering at an annual rate of approx. 2%, it is aimed to accelerate the lowering of the index at an annual rate of 5 to 6%, by promoting the stewardship of oral cephalosporin and other antimicrobials, thereby achieving the resistance rate of the same level as in other developed countries in 2030. |

| 2. Lower the methicillin resistance of *Staphylococcus aureus* to 20% or less in 2020 |
|---|
| • The methicillin (oxacillin) resistance of *Staphylococcus aureus* remains at a higher level than in other developed countries, and this index is lowering at an annual proportion of approx. 2%. The U.K. achieved the annual lowering rate of 5% through the strengthened measures from 2006 to 2011. In Japan as well, by ensuring infection prevention and control and promoting the stewardship of antimicrobials, it is aimed to accelerate the lowering of the index at a rate of approx. 5%, thereby achieving the resistance rates of the same level as in other developed countries. |

| 3. Lower the fluoroquinolone resistance of *Escherichia coli* to 25% or less in 2020 |
|---|
| • The fluoroquinolone resistance of *Escherichia coli* is highly correlated to the use of fluoroquinolones and the resistance is on the increase at an annual rate of 1.5%, which is a higher level than in other developed countries. By promoting the stewardship of oral fluoroquinolones and other antimicrobials, it is aimed to take a downturn in this trend, and achieve the resistance rates of the same level as in other developed countries. |

| 4. Lower the carbapenem (imipenem) resistance of *Pseudomonas aeruginosa* to 10% or less in 2020 |
|---|
| • The carbapenem resistance of *Pseudomonas aeruginosa* stands at 20% as of 2014, which is not a high level compared to other countries. Since this index is lowering at an annual rate of 0.5%, it is aim to achieve the resistance rate of 10% or less, by accelerating the lowering rate to 1 to 2%. |

| 5. Maintain the carbapenem resistance of *Escherichia coli* and *Klebsiella pneumoniae* at 0.2% or less in 2020 |
|---|
| • The carbapenem-resistant *Enterobacteriaceae* (CRE) infection globally expanding and forms a serious health threat, due to the few treatment choices. Fortunately, the carbapenem-resistance of *Escherichia coli* and *Klebsiella pneumoniae* remain low in Japan, respectively at 0.1% and 0.2% as of 2014. It is aimed to maintain these resistance rates at the same level through adequate measures. |

| |
|---|
| 6. Reduce the antimicrobial use per day per 1,000 inhabitants in 2020 to two-thirds of the level by 2013<br>7. Reduce the use of oral cephalosporins, quinolones, and macrolides per day per 1,000 inhabitants in 2020 by 50% from the level in 2013<br>8. Reduce the use of intravenous antimicrobials per day per 1,000 inhabitants in 2020 by 20% from the level in 2013 |
| • The antimicrobial use per day per 1,000 inhabitants (antimicrobial use density) is estimated at 15.8 as of 2013. This is a relatively small figure compared to Europe (see Figure 0.1). However, in the Netherlands, where the antimicrobial use density is the smallest in Europe, the figure stands at 11.3, approximately two-thirds the level in Japan. In the meantime, it is characteristic in Japan that the share of use of oral broad-spectrum antibiotics is very high.<br>• Among the oral antibiotics used in Japan in 2013, macrolides accounted for 33%, cephalosporins for 27% (of which third generation took up 80%), and quinolones for 19% (approx. 80% in total). By reducing the use of these antibiotics by half, and reducing the use of intravenous antibiotics by 20% through the promotion of antimicrobial stewardship, it is aimed to reduce the use of all oral antibiotics to two-thirds. |

## ANIMAL-RELATED INDICES

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|---|
| 1. Lower the tetracycline resistance of *Escherichia coli* to 33% or less |
| • The tetracycline resistance of *Escherichia coli* in livestock in Japan was lowered from 59.0% in 2001 to 45.2% in 2014 (Figure 0.4, Trends in antimicrobial resistance in *Escherichia coli* of farm animal origin in Japan (2001-2014)). This was considered to have been achieved through measures for ensuring appropriate antibiotic use. Therefore, it is deemed possible to accelerate the lowering of resistance rate by implementing this action plan, and the target is set at 33% or less in 2020. |

| |
|---|
| 2. Maintain the third-generation cephalosporin resistance of *Escherichia coli* at the same level as in the other G7 countries as of 2020<br>3. Maintain the fluoroquinolone resistance of *Escherichia coli* at the same level as in the other G7 countries as of 2020 |
| • In the "Ranking of the Importance of Antimicrobials against Bacteria which Affect Human Health through Food Commodities", established by the Food Safety Commission (FSC), the third-generation cephalosporins and fluoroquinolones are rated as critically important in human medicine. In Japan, the resistance rates of *Escharichia coli* derived from cattle, swine and meat poultry to the third-generation cephalosporins and fluoroquinolones were mostly at the same levels as in the other G7 countries (Figure 0.3, International comparison of antimicrobial resistance in *Escherichia coli* of farm animal origin (2013)). This was considered to have been achieved through the specific risk management measures in Japan, including the requirement for prescription by veterinarians for the use of these antibiotics for animals, the use thereof only in cases where other veterinary antibiotics are ineffective, and the mandatory post-marketing reporting periodically concerning the emergence of resistant bacteria. While figures in Japan are already at the same level as in the other G7 countries at present, it is aimed to maintain them at the same level as in the other G7 countries as of 2020 by implementing this action plan, because each G7 country is expected to implement their own action plan to improve their levels in 2020. |

Regarding the antimicrobial resistance rates in 2020, the carbapenem resistance rates of *Escherichia coli* and *bacillus pneumoniae* has been increasing in recent years in many countries around the world, while in Japan the rate remains at or below the 2013 level through the efforts based on the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020). In addition, the carbapenem resistance rate of *Pseudomonas aeruginosa* is decreasing, and progress is being made, although numerical targets have not been achieved. On the other hand, fluoroquinolone resistance ratein *E. coli* and methicillin resistance rate in *Staphylococcus aureus* continue to increase, with a slight decrease in 2021. Penicillin non-susceptibility rates of *Streptococcus pneumoniae* in cerebrospinal fluid (CSF) specimens remain high.

Antibiotic use based on sales of human antibiotics was 9.77 DID in 2021, a decrease of 32.7% compared to 2013.

Injectable antibiotics also decreased by 1.1% compared to 2013. Antibiotic use based on sales of oral antibiotics, including oral cephalosporins, oral macrolides, and oral fluoroquinolones, decreased compared to 2013, but none of the targets have been achieved, and continued efforts are needed.

Table 2 Human-related outcome indices of the National Action Plan: Isolation rate of specific antimicrobial-resistant bacteria (%)＊[12]

| | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2020 (Target) |
|---|---|---|---|---|---|---|---|---|---|---|
| *Streptococcus pneumoniae* penicillin non-susceptibility rate, CSF specimens§ | 47.4 | 47.0 | 40.5 | 36.4 | 29.1 | 38.3 | 32.0 | 33.3 | 59.5 | 15% or less |
| *Streptococcus pneumoniae* penicillin non-susceptibility rate, other than CSF specimens§ | 3.2 | 2.5 | 2.7 | 2.1 | 2.1 | 2.2 | 2.2 | 3.5 | 3.4 | |
| *Escherichia coli* fluoroquinolone resistance rate | 35.5 | 36.1 | 38.0 | 39.3 | 40.1 | 40.9 | 41.4 | 41.5 | 40.4 | 25% or less |
| *Staphylococcus aureus* methicillin resistance rate | 51.1 | 49.1 | 48.5 | 47.7 | 47.7 | 47.5 | 47.7 | 47.5 | 46.0 | 20% or less |
| *Pseudomonas aeruginosa* carbapenem resistance rate (imipenem) | 17.1 | 19.9 | 18.8 | 17.9 | 16.9 | 16.2 | 16.2 | 15.9 | 15.8 | 10% or less |
| *Pseudomonas aeruginosa* carbapenem resistance rate (meropenem) | 10.7 | 14.4 | 13.1 | 12.3 | 11.4 | 10.9 | 10.6 | 10.5 | 10.3 | 10% or less |
| *Escherichia coli* carbapenem resistance rate (imipenem) | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.2% or less (same level) ¶ |
| *Escherichia coli* carbapenem resistance rate (meropenem) | 0.1 | 0.2 | 0.2 | 0.2 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.2% or less (same level) ¶ |
| *Klebsiella pneumoniae* carbapenem resistance rate (imipenem) | 0.3 | 0.3 | 0.3 | 0.2 | 0.2 | 0.3 | 0.2 | 0.2 | 0.2 | 0.2% or less (same level) ¶ |
| *Klebsiella pneumoniae* carbapenem resistance rate (meropenem) | 0.6 | 0.6 | 0.6 | 0.5 | 0.4 | 0.5 | 0.4 | 0.4 | 0.4 | 0.2% or less (same level) ¶ |

Reference: Nippon AMR One Health Report (NOAR) 2021

* Created based on Japan Nosocomial Infections Surveillance (JANIS) data. Data posted every two years starting in 2013 and every year since 2017.

§ The 2014 *Streptococcus pneumoniae* penicillin non-susceptibility rate follows the Clinical & Laboratory Standards Institute (CLSI) 2007 criteria, with penicillin MICs of 0.125 μg/ml or greater as resistant. However, in 2008, Clinical & Laboratory Standards Institute (CLSI) changed its criteria and separated spinal fluid and non-spinal fluid specimens, and since 2015, Japan Nosocomial Infections Surveillance (JANIS) has also published separate tabulations for spinal fluid and non-spinal fluid specimens.

¶Carbapenem resistance rates for *E. coli* and *Klebsiella pneumoniae* in 2014 were 0.1% and 0.2%, maintaining the same level of resistance rates in 2020.

Table 3 Human-related outcome indices of National Action Plan: Antibiotic use (DID) (sales volume basis)[12]

| | 2013[13] | 2021 | Comparison to 2013 | 2020 (Target) |
|---|---|---|---|---|
| All antimicrobials | 14.52 | 9.77 | 32.7% decrease | 33% decrease |
| Oral cephalosporins | 3.91 | 2.11 | 46.1% decrease | 50% decrease |
| Oral fluoroquinolones | 2.83 | 1.48 | 43.7% decrease | 50% decrease |
| Oral macrolides | 4.83 | 2.72 | 47.5% decrease | 50% decrease |
| Intravenous antimicrobial | 0.90 | 0.89 | 1.1% decrease | 20% decrease |

Reference: Nippon AMR One Health Report (NOAR) 2021

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

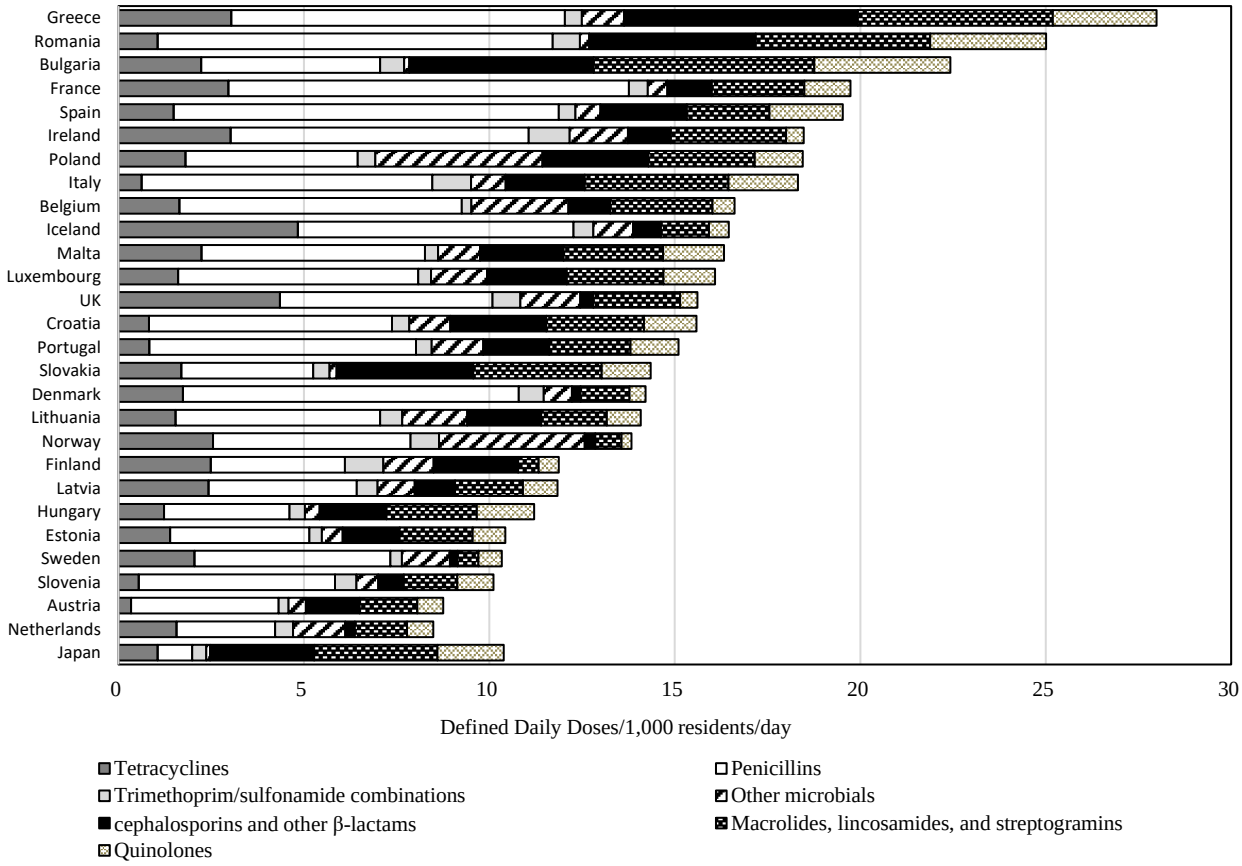
[12] Nippon AMR One Health Report (NAOR) 2021

[13] Muraki Y, et al."Japanese antimicrobial consumption surveillance: first report on oral and parenteral antimicrobial consumption in Japan（2009–2013）" J Glob Antimicrob Resist. 2016 Aug 6;7:19-23.

The inappropriate use of antimicrobials has been indicated as the background to the global spread of antimicrobial resistance (AMR). According to Japan Surveillance of Antimicrobial Consumption (JSAC) report in 2020, total antibiotic use in humans in Japan was approximately 10.8 per day per 1,000 inhabitants in 2020, which is low compared to developed countries in the EU (Figure 1). However, oral cephalosporins, oral fluoroquinolones and macrolides which were effective against a wide range of bacteria were frequently used in Japan, and penicillins were less frequently used compared to other countries.

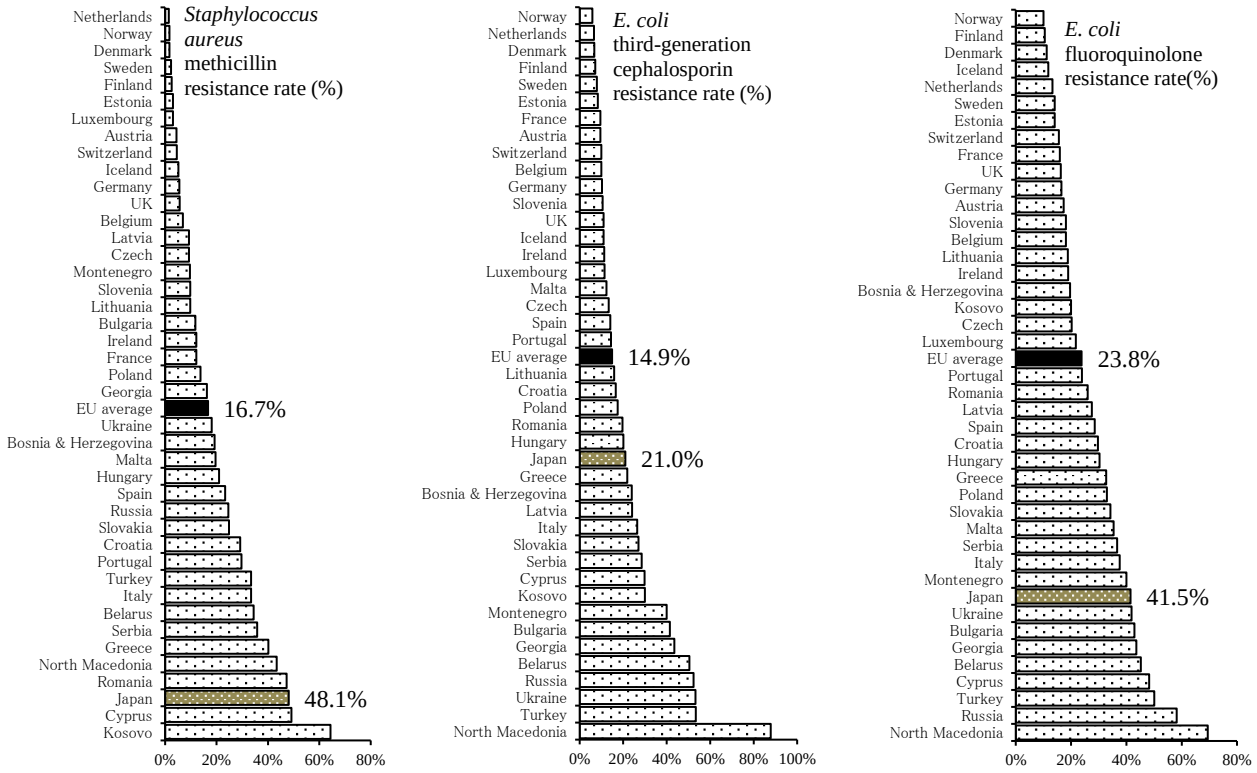
Figure 2 shows that the antimicrobial resistance rates in methicillin-resistant *Staphylococcus aureus* (MRSA) and third-generation cephalosporin-resistant *E. coli* are higher in Japan than in other countries. The prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE), which is of particular concern around the world in recent years, remains low with a percentage of 0.1-0.2% in Japan.

Figure 1. Comparison of antibiotic use for humans in EU countries and Japan[14]




[14] The AMR Clinical Reference Center (AMRCRC) Japan Surveillance of Antimicrobial Consumption (JSAC) https://amrcrc.ncgm.go.jp/surveillance/010/ref/NDB_2013-2020_comparison_ecdc 20230119.pdf

Figure 2. International comparison of antimicrobial resistance rates in major microorganisms showing tendency toward antimicrobial resistance in humans (2020)[15]




[15] Methicillin resistance rate for *Staphylococcus aureus*, third-generation cephalosporin (cefotaxime) resistance rate for *E. coli*, and fluoroquinolone (levofloxacin) resistance rate for *E. coli* are 2019 data submitted by countries to World Health Organization (WHO) Global Antimicrobial Resistance Surveillance System (GLASS). (The data in Japan are based on the Japan Nosocomial Infections Surveillance (JANIS) compiled by the World Health Organization (WHO) Global Antimicrobial Resistance Surveillance System (GLASS) method, and are in column B of the linked spreadsheet.) (https://docs.google.com/spreadsheets/d/1Ej0a-av4V5uoFw19DfZoDvcLpdvHTscfXoqJgozGiwc/edit#gid=1592777314)

Resistance rates to third-generation cephalosporins and fluoroquinolones in *E. coli* from healthy livestock animals remained low. On the other hand, for tetracyclines, the antimicrobial resistance rate remained higher than the target value even as sales volumes declined after 2018. It is necessary to continue to promote appropriate and prudent use of these antimicrobials and to monitor trends in their antimicrobial resistance rates.

Table 4 Animal- related outcome indices of National Action Plan: Isolation rate of specific antimicrobial-resistant bacteria (%)[16]

| | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2020 (Target) |
|---|---|---|---|---|---|---|---|---|
| *E. coli* tetracycline resistance rate (Farm) | 45.2 | 39.9 | | | | | | 33% or less |
| (Slaughterhouse) | | 39.8 | 47.6 | 40.8 | 43.6 | 44.3 | 45.0 | |
| *E. coli* third generation cephalosporin resistance rate (Farm) | 1.5 | 0.9 | | | | | | Same level as Group of Seven (G7) countries[17, 18] |
| (Slaughterhouse) | | 0.7 | 2.4 | 2.1 | 1.1 | 2.1 | 1.4 | |
| *E. coli* fluoroquinolone resistance rate (Farm) | 4.7 | 3.8 | | | | | | Same level as Group of Seven (G7) countries |
| (Slaughterhouse) | | 2.7 | 5.0 | 4.0 | 4.7 | 5.1 | 5.2 | |

Reference: Nippon AMR One Health Report (NOAR) 2021

The current state of antimicrobial resistance (AMR) in livestock in different countries is not simply comparable because of the differences in target animals and survey methods. Concerning *Escherichia coli*, an indicator bacterium for monitoring antimicrobial resistance (AMR), the prevalence of antimicrobial resistance (AMR) (Figure 3) in the Group of Seven (G7) countries shows that the percentages of isolates resistant to tetracyclines, third-generation cephalosporins, and fluoroquinolones in Japan are at comparable levels to those in Western countries. The resistance rates of Tetracyclines, which are largely used in livestock, and the third-generation cephalosporins and fluoroquinolones, which are ranked by the Food Safety Commission of Japan (FSC) as critically important in human healthcare, in the Ranking of the Importance of Antimicrobials against Bacteria which Affect Human Health through Food Commodities, were similar to those in Western countries.

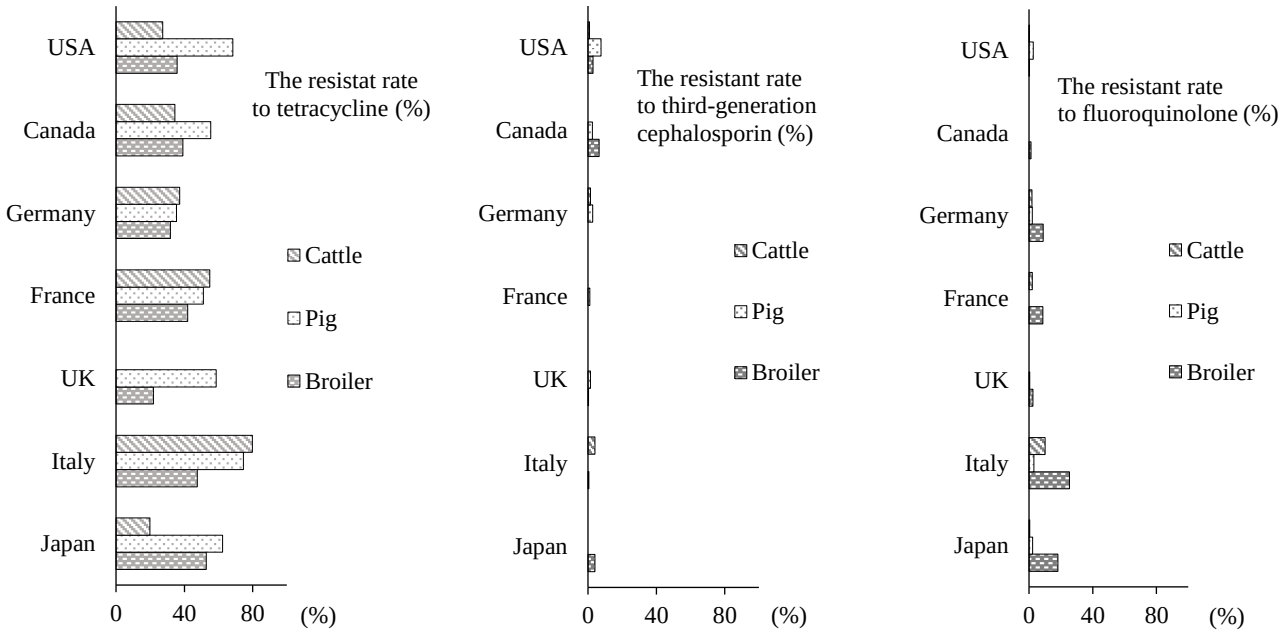
As for the current status of antimicrobial use in the livestock field, a simple international comparison cannot be made because each country's number of livestock, weight of livestock, surveyed agents, and survey methods are different, but looking at the amount of antimicrobials used in livestock in the Group of Seven (G7) countries (Figure 4), the United States has the highest use, while Japan is at the same level as Germany and Italy.

[16] Compiled and partly modified from "Monitoring of AMR" by the National Veterinary Assay Laboratory, Ministry of Agriculture, Forestry and Fisheries. JVARM, "Results of Antimicrobial Resistance Monitoring of Livestock-Derived Bacteria on Farms" https://www.maff.go.jp/nval/yakuzai/yakuzai_p3.html

[17] NARMS: https://www.fda.gov/animal-veterinary/national-antimicrobial-resistance-monitoring-system/narms-now-integrated-data

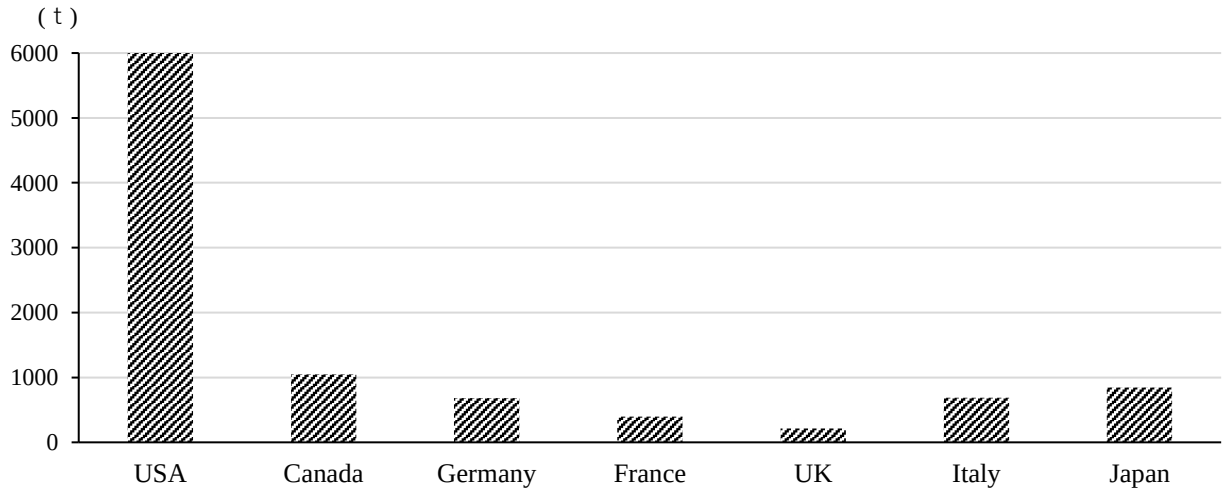
[18] EFSA: https://www.efsa.europa.eu/en

Figure 3. International comparison of antimicrobial resistance rates in *Escherichia coli* of livestock origin (2020)[19]




Data for the U.S. is at 2019, data for Canada is at 2018, and the data for cattle and swine for Germany, France, the U.K. and Italy is at 2019.

Figure 4. International comparison of antibiotic use in the animal field (2020) [20]




[19] Ministry of Agriculture, Forestry and Fisheries National Veterinary Assay Laboratory "Monitoring of AMR" The European Union Summary Report
on Antimicrobial Resistance in zoonotic and indicator bacteria from humans, animals and food in 2019–2020, Canadian Integrated Program for Antimicrobial Resistance Surveillance(CIPARS)2018, National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS)

[20] U.S.: Summary Report On Antimicrobials Sold or Distributed for Use in Food-Producing Animals (fda.gov); Canada: Canadian Antimicrobial Resistance Surveillance System Report; U.K., Italy, Germany and France: Sales of veterinary antimicrobial agents in 31 European countries in 2016-2020; Japan: Annual Report of Sales Amount and Sales Volume of Veterinary drugs
Note that some of the data in the U.S., Canada, EU, and Japan include data of pets and horses, etc. Data in each country show the total amount of antimicrobials used for the total number of livestock in each country.

# NATIONAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE (AMR) (2023-2027)

To date, based on the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020), relevant ministries, agencies, and organizations have been working closely together to achieve a world free from the disease burden caused by infectious diseases due to antimicrobial resistance (AMR), taking measures to reduce the occurrence of antimicrobial resistance (AMR) as much as possible and to prevent the spread of infectious diseases caused by antimicrobial-resistant organisms (AROs). Some of the outcome indicators have shown improvements in response to these efforts, however, there are indicators that have shown little improvements and newly emerging issues. Continued efforts to combat antimicrobial resistance (AMR) in coordination with international movements are needed.

In order to promote seamless antimicrobial resistance (AMR) control measures, it is important to continue to set goals related to the following six areas: (1) Public awareness and education, (2) Surveillance and monitoring, (3) Infection prevention and control, (4) Antimicrobial stewardship, (5) Research and development, and (6) International cooperation, and promote antimicrobial resistance (AMR) control measures toward achieving these goals.

Furthermore, at the 2021 Group of Seven (G7) Climate and Environment Ministers' meeting, for the first time, antimicrobial resistance (AMR) was included in the meeting communiqué, and at the 2021 Group of Seven (G7) Carbis Bay Leaders' Communiqué, the Health Declaration was endorsed that agreed to strengthen an One Health approach. By appropriately responding to the global promotion of the One Health approach and continuing its advanced efforts, Japan can play a leading role in international actions, thereby contributing to protecting the health and lives of its citizens and leading the world in the combat against antimicrobial resistance (AMR).

Therefore, "National Action Plan on Antimicrobial Resistance (AMR) (2023-2027)" has been established to further promote antimicrobial resistance (AMR) control measures.

The National Action Plan on Antimicrobial Resistance (AMR) (2023-2027) sets goals (major items) in the six areas and, in each area, establishes strategies (medium items) to achieve the goals and specific actions (minor items) to implement the strategies. For the strategies to achieve the goals, the objectives, background, specific action items, relevant government agencies and organizations, and evaluation indices for each strategy should be described (Figure 5). In addition, numerical targets throughout the National Action Plan are set as outcome indices.

Figure 5. The Framework of the National Action Plan on antimicrobial resistance (AMR) and the Description of Each Strategy

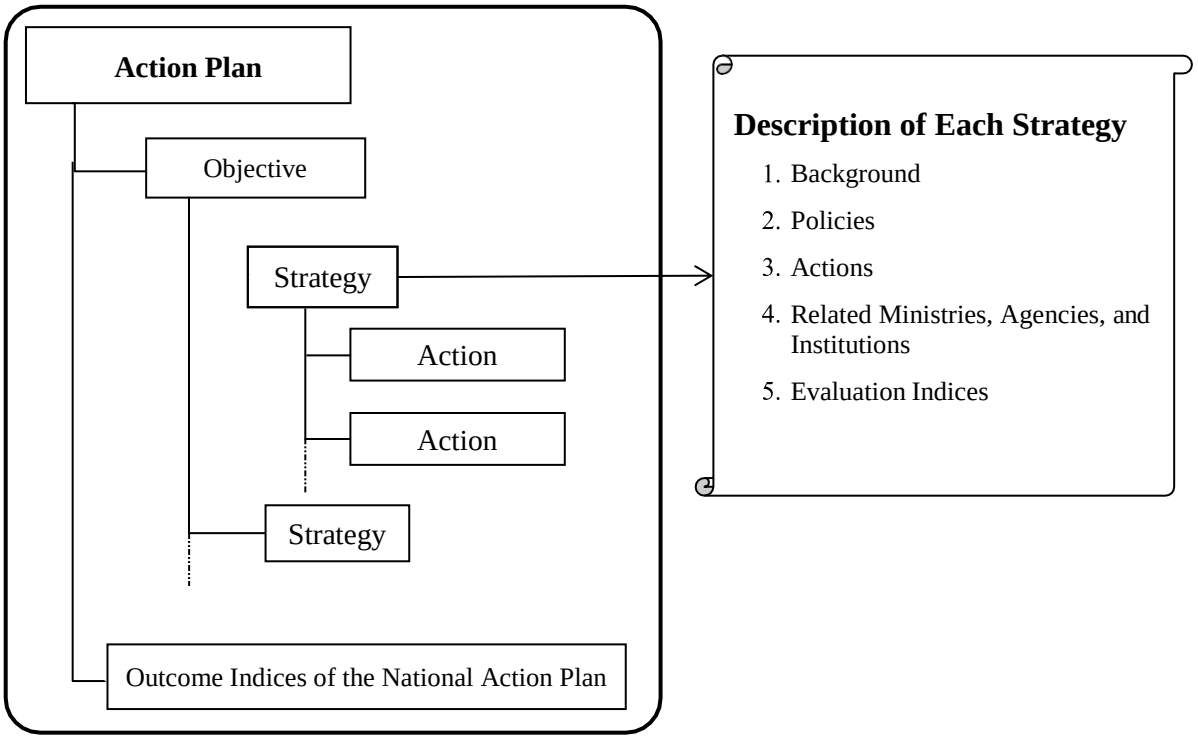


Table 5 Goals and Strategies in Six Areas of Countermeasures on Antimicrobial Resistance (AMR)

| | | |
|---|---|---|
| Goal 1 Public Awareness and Education | | Improve Public Awareness and Understanding, and Promote Education and Training of Professionals |
| | Strategy 1.1 | Promote Public Awareness-raising Activities to Improve Public Knowledge and Understanding of AMR |
| | Strategy1.2 | Promote Education and Training on AMR of Professionals Involved in Related Fields |
| Goal 2 Surveillance and Monitoring | | Continuously Monitor Antimicrobial Resistance and Use of Antimicrobials, and Appropriately Understand the Signs of Change and Spread of Antimicrobial Resistance |
| | Strategy 2.1 | Strengthen the Surveillance of Antimicrobial Resistance in Healthcare and Nursing Care |
| | Strategy 2.2 | Monitor the Trend of the Antimicrobial Use at Medical Institutions |
| | Strategy 2.3 | Strengthen Antimicrobial Resistance Surveillance in the Fields of Veterinary Medicine, Livestock and Aquaculture, and others |
| | Strategy 2.4 | Standardize Methods of Laboratory Testing and Strengthen Testing Functions of Antimicrobial Resistance at Clinical, Commercial and Public Health Laboratories |
| | Strategy 2.5 | Implement Integrated One Health Surveillance Including Humans, Animals, Food, and the Environment |
| Goal 3 Infection Prevention and Control | | Prevent the Spread of Antimicrobial-resistant Organisms by Implementing Appropriate Infection Prevention and Control |
| | Strategy 3.1 | Infection Prevention and Control in Healthcare and Nursing Care and Promotion of Regional Cooperation |
| | Strategy 3.2 | Promote Infection Prevention and Control in Livestock and Aquaculture, Veterinary Medicine and Food Chain |
| | Strategy 3.3 | Strengthen the Outbreak Response Capacity against Antimicrobial-resistant Infections |
| Goal 4 Antimicrobial Stewardship | | Promote Appropriate Use of Antimicrobials in the Fields of Healthcare, Livestock and Aquaculture |
| | Strategy 4.1 | Promote Antimicrobial Stewardship at Medical Institutions |
| | Strategy 4.2 | Ensure Prudent Use of Antibiotics for Animals in the Field of Livestock and Aquaculture and Veterinary Medicine |
| Goal 5 Research and Development | | Promote Research on Antimicrobial Resistance and Foster Research and Development to Secure the Means to Prevent, Diagnose and Treat the Antimicrobial-resistant Infections |
| | Strategy 5.1 | Promote Research to Elucidate the Mechanism of the Emergence and Transmission of Antimicrobial Resistance and its Socioeconomic Impact |
| | Strategy 5.2 | Promote Research on Public Awareness/Education on Antimicrobial Resistance, Infection Prevention and Control, and Antimicrobial Stewardship |
| | Strategy 5.3 | Promote Clinical Research on the Optimization of Existing Methods for Prevention, Diagnosis and Treatment of Infectious Diseases |
| | Strategy 5.4 | Promote Research and Development of Novel Methods for Prevention, Diagnosis and Treatment and Promote the Cooperation of Industry, Academia and Government |
| | Strategy 5.5 | Promote Global Research Collaboration on Antimicrobial Resistance and Research and Development of |

| | | |
|---|---|---|
| | | Novel Methods for Prevention, Diagnosis and Treatment of Antimicrobial-resistant Infections |
| | Strategy 5.6 | Sustainable Research and Development of Antimicrobials and Enhancement of Stable Supply |
| Goal 6 International Cooperation | | Enhance Global Multidisciplinary Countermeasures against Antimicrobial Resistance |
| | Strategy 6.1 | Strengthen Japan's Leadership for Global Policies on Antimicrobial Resistance |
| | Strategy 6.2 | Promote International Cooperation to Achieve the Global Action Plan on Antimicrobial Resistance |

Table 6 National Action Plan on Antimicrobial Resistance (AMR) (2023-2027) Outcome Indices

## HUMAN-RELATED INDICES

1. Maintain the number of patients with vancomycin-resistant *Enterococci* (VRE) infections in 2027 at 80 or less (the level as of 2019)
2. Lower the methicillin resistance of *Staphylococcus aureus* to 20% or less by 2027
3. Maintain the fluoroquinolone resistance of *E. c*oli at 30% or less in 2027
4. Lower the carbapenem (MEPM=R) resistance of *Pseudomonas aeruginosa* to 3% or less by 2027
5. Maintain a carbapenem resistance of *E. coli* and *Klebsiella pneumoniae* at 0.2% or less in 2027
6. Reduce antimicrobial use per day per 1,000 inhabitants by 15% from 2020 levels by 2027
7. Reduce the use of oral third generation cephalosporins, oral fluoroquinolones, and oral macrolides per day per 1,000 inhabitants by 40%, 30%, and 25%, respectively, from 2020 levels by 2027
8. Reduce the use of intravenous carbapenems per day per 1,000 inhabitants by 20% from 2020 levels by 2027

## ANIMAL-RELATED INDICES

1. Lower the tetracycline resistance of *E. coli* to 20% or less in cattle, 50% or less in swine, and 45% or less in chickens by 2027.
2. Lower the third-generation cephalosporin resistance of *E. coli* to 1% or less in cattle, 1% or less in swine, and 5% or less in chickens by 2027.
3. Lower the fluoroquinolone resistance of *E. coli* to 1% or less in cattle, 2% or less in swine, and 15% or less in chickens by 2027.
4. Reduce the total use of veterinary antibiotics in the livestock field by 15% from 2020 levels by 2027.
5. Reduce total use of second-line drugs (third-generation cephalosporins, 15-membered macrolides (tulathromycin and gamithromycin), fluoroquinolones, and colistin) in the livestock field to 27 t or less in 2027.

# GOAL 1
## IMPROVE PUBLIC AWARENESS AND UNDERSTANDING, AND PROMOTE EDUCATION AND TRAINING OF PROFESSIONALS

### Strategies

(1.1) Promote Public Awareness-raising Activities to Improve Public Knowledge and Understanding of AMR

(1.2) Promote Education and Training on AMR of Professionals Involved in Related Fields

# STRATEGY 1.1 PROMOTE PUBLIC AWARENESS-RAISING ACTIVITIES TO IMPROVE PUBLIC KNOWLEDGE AND UNDERSTANDING OF AMR

## BACKGROUND

- Promotion of nation-wide measures against antimicrobial resistance (AMR) requires public awareness and understanding of antimicrobial resistance (AMR) and antimicrobials. Since the formulation of the "National Action Plan on Antimicrobial Resistance (AMR) (2016-2020) ", various educational materials and tools have been distributed in various regions, information has been disseminated through websites and media, and educational awareness-raising activities have been held for the public through some awareness-raising events.
- Junior high school and senior high school students learn about infectious disease control and the importance of using medicines appropriately, as part of their health education at schools.[21]
- However, in an awareness survey conducted in Japan in 2020, only 40% to 50% of all respondents had heard of the term "antimicrobial resistance", indicating that the awareness of antimicrobial resistance (AMR) is not at a high level.[22] [23] In addition, in an awareness survey conducted in Japan in 2022, only 16.4% of respondents correctly answered that "the statement 'Antibiotics knock out viruses' is wrong" and only 28.3% correctly answered that "the statement 'Antibiotics should be stopped as soon as the patient is cured' is wrong".[24]
- In the above awareness survey, 27.4% of respondents indicated that they have antibiotics kept at home, and 25.5% of respondents indicated that they have taken the antibiotics they kept at their own discretion, indicating that there are a certain number of people who take antimicrobials using their own judgment. Furthermore, in the 2020 awareness survey, 34.6% of respondents said they did not finish their medication correctly when they were prescribed with antibiotics.[25] Such inappropriate use of antimicrobials in amounts and duration can encourage the emergence of antimicrobial resistance (AMR).
- Therefore, it is important to promote public awareness and education regarding knowledge and understanding of antimicrobial resistance (AMR). In particular, targeted outreach for specific audience, including young children and their guardians, and elderly people, to whom antimicrobials are often prescribed, will continue to be important.[26] Moreover, it is important to acknowledge people, not discriminating against patients with antimicrobial-resistant infections (ARI) in awareness-raising activities.

## POLICIES

- Create tools which aid proper awareness and understanding of antimicrobial stewardship (AMS), infection prevention and control (IPC), and global efforts that transcend the boundaries between humans and animals (One Health approach), for the purpose of raising the public awareness of antimicrobial resistance (AMR).
- Develop a national campaign against the threat of antimicrobial resistance (AMR) in cooperation with relevant agencies, organizations, and media organizations throughout the year and ensure that appropriate drugs are used when necessary and in appropriate quantities and for appropriate durations for the purpose of increasing nationwide public awareness and understanding of antimicrobial resistance (AMR).
- Implement targeted awareness raising activities for specific audience, including young children and their guardians, and elderly people, to whom antimicrobials are often prescribed, as well as companies with business related to antimicrobial resistance (AMR) and academic groups in healthcare, animal health, and food hygiene.

[21] Ministry of Education, Culture, Sports, Science and Technology “For the Healthy Life” (Senior High School Edition, 2020)
[22] Cabinet Office, Public Opinion Poll on Infectious Diseases for which Drugs Do Not Work (Antimicrobial resistance), August, 2019
[23] Health and Labor Sciences Research Ohmagari Group, Health, Welfare and Labor Administration Promotion Survey Project Fund Research, Research on the Implementation of National Action Plan on Antimicrobial Resistance (AMR), May 2020
[24] Antibiotic Awareness Survey Report 2022 (Online survey, August, 2022), National Center for Global Health and Medicine AMR Clinical Reference Center (https://amr.ncgm.go.jp/pdf/20220930_report_press.pdf)
[25] Antibiotic Awareness Survey Report 2020 (Online survey, August, 2020), National Center for Global Health and Medicine AMR Clinical Reference Center (https://amr.ncgm.go.jp/pdf/20201006_report.pdf)
[26] Plan national d’alerte sur les antibiotiques 2011-2016, Ministère du Travail, de L’emploi et de la Santé, France, 2011

**Key Messages to Raise Public Awareness**

- **State of Antimicrobial Resistance**: Seriousness of the problem, the world situation, the reality in Japan and its position in the world.
- **Antimicrobial Stewardship**: Antibiotics are not effective for most cases of the common cold, and unnecessary use of antimicrobials breeds the emergence of antimicrobial-resistant organisms (AROs).
- **Infection Prevention and Control**: Practicing the etiquette of covering coughs, handwashing, and receiving vaccination (*Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), and influenza) are key to prevent infections.
- **One Health approach**: Integrated efforts across the areas, including human healthcare, veterinary medicine, livestock and aquaculture, food hygiene, and environment, are important to combat antimicrobial resistance (AMR).

## ACTIONS

### For General Population

- Conduct government-wide conferences and other activities related to awareness-raising
- Develop and provide awareness-raising tools
- Run a platform (website) to communicate information on antimicrobial resistance (AMR) and disseminate information through social networking services (SNS) and media
- Implement awareness-raising events in collaboration with the Antibiotic Awareness Month
- Make thorough risk communication [27] in the areas of human, veterinary medicine, livestock and aquaculture, and food hygiene
- Implement regular surveys on the knowledge, attitude, and practice regarding antimicrobial resistance (AMR)

### For Specific Populations

Scope: Inpatients and outpatients, young children and their guardians, elderly people, and care facility residents

- Develop and provide awareness-raising tools tailored to the nature and needs of each audience

Scope: Junior high school and high school students

- Promote education regarding infectious disease control and the importance of using medicine appropriately

Scope: Travelers to overseas destinations

- Provide information regarding antimicrobial resistance (AMR) through websites for travelers to overseas destinations[28]

[27] In the entire process of risk analysis, stakeholders such as the general public (consumers, consumer organizations), government (risk management organizations, risk assessment organizations), media, businesses (primary producers, manufacturers, distributors, industry associations, etc.), and experts (researchers, research and educational institutions, medical institutions, etc.) exchange information and opinions about risks and risk factors from their respective perspectives mutually. Risk communication can deepen the knowledge of the characteristics of the risks to be considered and their effects, and in the process deepen mutual understanding among the parties involved, building trust and allowing risk management and risk assessment to function effectively. The purpose of risk communication is an activity of "dialogue, co-consideration, and collaboration" (engagement), not persuasion. This is based on the idea that the public should be involved as stakeholders in decisions.

[28] The examples are: Overseas Safety HP, Ministry of Foreign Affairs (MOFA) (http://www.anzen.mofa.go.jp), Ministry of Health, Labour and Welfare (MHLW) website (http://www.mhlw.go.jp), For Traveler's Health (FORTH), Ministry of Health, Labour and Welfare (MHLW) (http://www.forth.go.jp)

Scope: Companies with business related to antimicrobial resistance (AMR) or antimicrobials and academic groups in healthcare, animal health, and food hygiene

- Develop guidance for non-public sectors to implement their own awareness-raising activities (with consideration of conflict of interest (COI))
- Request a statement of cooperation for countermeasures against antimicrobial resistance (AMR)

## RELATED MINISTRIES, AGENCIES, AND INSTITUTIONS

Office for COVID-19 and Other Emerging Infectious Disease Control, Cabinet Secretariat (CAS); Food Safety Commission of Japan (FSC), Cabinet Office (CAO); Ministry of Foreign Affairs (MOFA); Ministry of Education, Culture, Sports, Science and Technology (MEXT); Ministry of Health, Labour and Welfare (MHLW); Ministry of Agriculture, Forestry and Fisheries (MAFF); Ministry of the Environment (MOE)

## EVALUATION INDICES

- Level of antimicrobial resistance (AMR) awareness and comprehension
- Number of antimicrobial resistance (AMR) awareness-raising tools distributed
- Number of accesses to the antimicrobial resistance (AMR) information platform (website) and social networking services (SNS)

## STRATEGY 1.2 PROMOTE EDUCATION AND TRAINING ON AMR OF PROFESSIONALS INVOLVED IN RELATED FIELDS

### BACKGROUND

- Reducing the emergence and spread of antimicrobial resistance (AMR) requires antimicrobial stewardship (AMS) and infection prevention and control (IPC). To foster antimicrobial stewardship (AMS) and infection prevention and control (IPC) among professionals dealing with antimicrobials and infectious diseases, their behavioural change based on increased knowledge and understanding of antimicrobial resistance (AMR) is critical in addition to the strengthening regulations.
- Educational interventions for health care workers have had some impact. For example, a workshop-based intervention for community general practices in the United Kingdom was shown to reduce antimicrobial prescribing by 6.1% in these practices.[29] Another study found that online training of general practitioners in the Netherlands resulted in a 21% antimicrobial prescription rate in the intervention group, compared to a 33% rate in the control group.[30]
- Japan, however, has only a small number of experts of infectious disease control. For example, there are 1,554 physicians specialized in infectious disease, which are approximately 1/15$^{th}$ of board-certified surgeons and 1/3$^{rd}$ of acute care surgeons, as of July 2022. Moreover, there are 531 physicians working in infectious disease departments, which is only 0.2% of total working physicians in hospitals and clinics.[31] Number of other certified healthcare professions in infectious disease control is significantly limited; there are 3,312 Certified Nurses in Infection Control, 100 Certified Nurse Specialists in Infection Control Nursing, 1,045 Certified Pharmacists in Infection Control, and 776 Infection Control Microbiological Technologists, as of December 2021.[32]
- In addition, according to an awareness survey conducted among clinics nationwide in 2020, only 31.3% of respondents said they "can explain/understand the "National Action Plan on Antimicrobial Resistance (AMR)" to others," 54.4% said that "antimicrobial stewardship has a great effect in reducing antimicrobial resistance," and only 71.1% of the respondents said that they "rarely prescribe antibiotics when diagnosing a common cold (0-20%)".[33]
- The roles of veterinarians and those engaged in livestock and aquaculture industry who use veterinary antibiotics or antibiotic feed additives are especially significant in reducing risk in the field of livestock and aquaculture. They need to use antibiotics with correct understanding of antimicrobial resistance (AMR) and appropriate and prudent use of antibiotics.
- These efforts to promote and educate those who use these antimicrobials and those involved in infection prevention and control (IPC) of microorganisms regarding antimicrobial resistance (AMR) need to be further enhanced.

[29] McNulty C, Hawking M, Lecky D, et al. Effects of primary care antimicrobial stewardship outreach on antibiotic use by general practice staff: pragmatic randomized controlled trial of the TARGET antibiotics workshop. J Antimicrob Chemother. 2018;73(5):1423-1432. doi:10.1093/jac/dky004

[30] Dekker ARJ, Verheij TJM, Broekhuizen BDL, et al. Effectiveness of general practitioner online training and an information booklet for parents on antibiotic prescribing for children with respiratory tract infection in primary care: a cluster randomized controlled trial. J Antimicrob Chemother. 2018;73(5):1416-1422. doi:10.1093/jac/dkx542

[31] List of physicians specialized in infectious disease (July 1, 2022) (https://www.kansensho.or.jp/uploads/files/senmoni/meibo_220701.pdf)

[32] Japanese Nursing Association Credentialing system (http://nintei.nurse.or.jp/nursing/qualification/), Certified nurse specialists in infection control nursing (http://www.ncn.ac.jp/examination/grad/050/026advanced.html), Certified Pharmacist in Infection Control (https://www.jshp.or.jp/snmon/senmon2.html), Infection Control Microbiological Technologist (ICMT) system (http://www.jscm.org/icmt_new/index.html)

[33] Gu, et al., The Japanese Association for Infectious Diseases Joint Commission of Inquiry for Outpatients Antimicrobial Use, The 2nd Nationwide Questionnaire Survey on Antimicrobial Stewardship with Clinic Physicians, Japanese Journal of Chemotherapy 69(Suppl.A)195, April 2021

## POLICIES

- ○ Accumulate the necessary knowledge, enrich practical education programs, and promote their use in relevant organizations in order to improve knowledge on antimicrobial resistance (AMR), and promote education on infection prevention and control (IPC) and antimicrobial stewardship (AMS) among professionals and workers in various areas, including healthcare, nursing care, food, veterinary medicine, livestock and aquaculture, and agriculture
- ○ Enhance and promote a continuous antimicrobial resistance (AMR) educational system covering undergraduate education and post-graduate training
- ○ Put in place a system for shared access to infectious disease experts in regions, and create a platform for relevant professionals to easily access information

## ACTIONS

### ■ Undergraduate/Graduate Education

Scope: Undergraduate/Graduate students pursuing careers in human healthcare[34], veterinary medicine[35], nursing care and public welfare[36], agriculture, livestock and aquaculture and food hygiene

- Continue to promote the educational activities in related institutions as the contents related to antimicrobial resistance (AMR), infection prevention and control (IPC), and antimicrobial stewardship (AMS) in the basic education for various professions

### ■ National Qualification

Scope: Examinees to be qualified as professionals in healthcare, veterinary medicine, nursing care, and public welfare

- Establish and continue the subjects on antimicrobial resistance (AMR), infection prevention and control (IPC), and antimicrobial stewardship (AMS) in standard questions for qualifying examinations, as appropriate

### ■ Post-Graduate Education and Training

Scope: Physicians and dentists

- Implement antimicrobial stewardship (AMS) education in residency systems for physicians and dentists, as appropriate (see Strategy 4.1)

Scope: Pharmacists

- Develop and introduce standard training programs on antimicrobial resistance (AMR), infection prevention and control (IPC), and antimicrobial stewardship (AMS) in clinical training

Scope: Veterinarians

- Implement training programs related to antimicrobial resistance (AMR) in post-graduate clinical training
- Improve and implement seminars and training for livestock health inspectors and clinical veterinarians

Scope: Healthcare professionals other than physicians, dentists, and pharmacists, and other workers in medical institutions[37]

- Develop and improve training programs related to infection prevention and control (IPC) in post-graduate introductory training

[34] Physicians, dentists, pharmacists, registered nurses, licensed practical nurses, midwives, public health nurses, medical technologists, radiological technologists, clinical engineering technologists, speech-language-hearing therapists, physical therapists, occupational therapists, dental hygienists, registered dietitians, etc.
[35] Veterinarians, veterinary nurses for companion animals, etc.
[36] Social workers, certified care workers, psychiatric social workers, care managers, home care workers, etc.
[37] Those who work in medical institutions and may directly contact patients or patients' biological fluids, including nursing assistants, health fitness programmers, health information managers, medical assistants, physician administrative assistant, clinical research coordinator, linen keepers, janitors, and guards

■ **Continuing Education**

Scope: Healthcare professionals, other workers in medical institutions, professionals in veterinary medicine, and professionals in livestock and aquaculture, and agriculture

- Continue and improve training programs related to infection prevention and control (IPC) (such as the importance of hand hygiene) and antimicrobial stewardship (AMS) in continuing education
- Promote appropriate administration of antibiotics by disseminating educational programs utilizing the antimicrobial susceptibility table (antibiogram) for healthcare professionals
- Encourage relevant groups including academic societies to use the training programs and enhance relevant training
- Support education and training through the infectious disease education professional network (Infectious Disease Education Consortium)[38]
- Implement seminars and training for livestock producers, aquaculture farmers, and feed manufacturers, and ensure prefectures to instruct on-site practices in veterinary medicine and livestock production, and to raise thorough awareness thereon

Scope: Responsible local government officers

- Continue and improve training programs related to outbreaks of antimicrobial-resistant infections (ARIs) as a part of professional education and training (see Strategy 3.3)
- Promote use of the training programs and enhancement of relevant training
- Enhance relevant seminars and training (see Strategy 3.3)

■ **Professional Education**

Scope: Qualified professionals[39] and examinees for qualification by health care groups, academic associations, and certification authorities regarding infectious diseases

- Encourage relevant groups to include antimicrobial resistance (AMR)-related training in the requirements for qualification and renewing of qualification
- Enhance training systems for field epidemiology within hospitals (hospital epidemiology) (see Strategy 2.1and Strategy 3.3)

Scope: Physicians, dentists, pharmacists, medical technologists, and nurses other than those described above

- Provide support to promote antimicrobial resistance (AMR)-related requirements to be included in existing relevant qualifications

Scope: Veterinarians

- Consider instituting a certification system for the appropriate management of infectious diseases in veterinary medicine

[38] A network across disciplines (medical, animal, food, infection prevention and control, appropriate use of antimicrobials, etc.) that brings together human resources capable of providing education on infectious diseases. Since the number of personnel who can provide education and training on antimicrobial resistance (AMR) is limited, the network will develop educational tools and train personnel for education and training activities

[39] Qualifications related to infection prevention and control: Infection Control Doctor (Japanese College of Infection Control Doctors), Certified Nurse Specialist in Infection Control Nursing and Certified Nurse in Infection Control (Japanese Nursing Association), Board Certified Infection Control Pharmacy Specialist and Board Certified Pharmacist in Infection Control (Japanese Society of Hospital Pharmacists), Infection Control Microbiological Technologist (Japanese Society for Clinical Microbiology), Board Certified Physician and Dental Hygienist in Nosocomial Infection Prevention and Control (Japanese Association for Oral Infectious Diseases), Certified Sterilisation Specialist (Japanese Society of Medical Instrumentation), and other private qualifications

Qualifications by academic associations related to infectious disease consultation: Certified Infectious Disease Specialist (The Japanese Association for Infectious Diseases), Japanese Antimicrobial Chemotherapy Physician (JACP), Fellow of JACP (Japanese Society of Chemotherapy), Japanese Antimicrobial Chemotherapy Dentist (JACD), Fellow of JACD (Japanese Society of Chemotherapy), and Japanese Antimicrobial Chemotherapy Pharmacist (Japanese Society of Chemotherapy)

Outpatient Anti-infective Agent Pharmacist (Japanese Society of Chemotherapy), Board certified Pharmacotherapy Specialist (The Japanese Society of Pharmaceutical Health Care and Sciences), Board certified Local Pharmaceutical Health Care Specialist (The Japanese Society of Pharmaceutical Health Care and Sciences)

■ **Ensuring Capacity for Awareness Raising and Education**

Scope: People involved in human healthcare, nursing care, public welfare, and food

- Promote activities of the infectious disease education professional network (Infectious Disease Education Consortium) by experts in each field in order to promote educational and awareness-raising activities through collaboration among various fields (related professional associations, academic societies, local governments, etc.)

Scope: Workers engaged in healthcare, nursing care, and public welfare, and local government officers

- Provide information and promote awareness and education centered on the AMR Clinical Reference Center (AMRCRC)

Scope: Workers engaged in veterinary medicine, livestock and aquaculture, agriculture, and food

- Improve a platform to provide information regarding antimicrobial resistance (AMR) in the veterinary medicine, livestock, aquaculture and agriculture fields

## RELATED MINISTRIES, AGENCIES, AND INSTITUTIONS

Ministry of Education, Culture, Sports, Science and Technology (MEXT); Ministry of Health, Labour and Welfare (MHLW); Ministry of Agriculture, Forestry and Fisheries (MAFF); National Institute of Infectious Diseases (NIID); National Veterinary Assay Laboratory (NVAL); National Agriculture and Food Research Organization (NARO); Food and Agricultural Materials Inspection Center (FAMIC); and National Center for Global Health and Medicine (NCGM)

## EVALUATION INDICES

- Types and performance of seminars and training conducted
- Numbers of qualifications which require training related to antimicrobial resistance (AMR)

# GOAL 2
## CONTINUOUSLY MONITOR ANTIMICROBIAL RESISTANCE AND USE OF ANTIMICROBIALS, AND APPROPRIATELY UNDERSTAND THE SIGNS OF CHANGE AND SPREAD OF ANTIMICROBIAL RESISTANCE

### Strategies

(2.1) Strengthen the Surveillance of Antimicrobial Resistance in Healthcare and Nursing Care

(2.2) Monitor the Trend of the Antimicrobial Use at Medical Institutions

(2.3) Strengthen Antimicrobial Resistance Surveillance in the Fields of Veterinary Medicine, Livestock and Aquaculture, etc.

(2.4) Standardize Methods of Laboratory Testing and Strengthen Testing Functions of Antimicrobial Resistance at Clinical, Commercial and Public Health Laboratories

(2.5) Implement Integrated One Health Surveillance Including Humans, Animals, Food, and the Environment

# STRATEGY 2.1 STRENGTHEN THE SURVEILLANCE OF ANTIMICROBIAL RESISTANCE IN HEALTHCARE AND NURSING CARE

## BACKGROUND

- Japan recognizes the importance of surveillance on antimicrobial resistance (AMR) and has systems dedicated to the surveillance in healthcare: the Japan Nosocomial Infections Surveillance (JANIS) which monitors the trends of antimicrobial resistance (AMR) and the National Epidemiological Surveillance of Infectious Diseases based on the Act on Prevention of Infectious Diseases and Medical Care for Patients Suffering Infectious Diseases (Act No. 114 of 1998) and the nationwide computerized tuberculosis (TB)surveillance system which tracks trends in antimicrobial-resistant *Mycobacterium tuberculosis* (MTB) bacteria, and the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) established in April 2017 to consolidate antimicrobial resistance (AMR)-related data for use by medical institutions and regional networks. In addition, the revision of medical fee in FY2022 established the premium for enhanced surveillance to evaluate medical institutions that participate in regional and national surveillance.
- However, the prevalence of certain antimicrobial-resistant organisms (AROs) is not monitored because none of the systems is applied for these antimicrobial-resistant organisms (AROs) and whose spread has not been fully confirmed.[40] Japan Nosocomial Infections Surveillance (JANIS) is a voluntary survey, and most of the participating facilities are relatively large medical institutions with more than 200 beds,[41] but elderly care facilities do not participate. Therefore, the challenge is to understand the actual situation of antimicrobial resistance (AMR) in medical institutions with less than 200 beds.
- Regarding healthcare-associated infection (HAI) surveillance, in addition to the Japan Nosocomial Infections Surveillance (JANIS), the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE)[42] is expected to collect and consolidate information on the medical examination status of infection diseases, infection control measures and appropriate use of antibiotics at participating facilities, the occurrence of healthcare-associated infections (HAIs), major bacteria and antimicrobial-resistant organisms (AROs), bloodstream infections caused by them, and antibiotic use, and to use this information for collaboration among individual facilities and facilities in the region. On the other hand, the lack of participating facilities is an issue, and opportunities for utilization needs to be increased.
- The impact of coronavirus infectious disease, emerged in 2019 (COVID-19) on the number of patients and isolation rates of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* in 2019 and 2020 were compared using the Japan Nosocomial Infectious Surveillance (JANIS) data. The number of patients and isolation rates for each bacteria decreased slightly for methicillin-susceptible and resistant *Staphylococcus aureus*, decreased by 60% for penicillin-susceptible and resistant *Streptococcus pneumoniae*, and increased for third-generation cephalosporin-resistant *Klebsiella pneumoniae*. For the remaining bacteria, the number of patients decreased but the isolation rate increased.[43]

[40] The national systems do not collect data on certain antimicrobial-resistant organisms (AROs), including multidrug-resistant *Neisseria gonorrhoeae*, antimicrobial-resistant tuberculosis, and fluoroquinolone-resistant species in *Salmonella* and *Shigella*. Multidrug-resistant *Neisseria gonorrhoeae* and antimicrobial-resistant *Mycobacterium tuberculosis* (MTB) have been monitored by individual research groups.

[41] Among the total of 3,016 medical institutions participating in Japan Nosocomial Infectious Surveillance (JANIS), 177 organizations submitted their data on intensive care units(ICUs), 120 organizations on neonatal intensive care units (NICUs), and 945 organizations on surgical site infections (SSIs), as of January 2023.

[42] Among the total of 1,870 medical institutions (excluding clinics) participating in Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE), 866 organizations participate in the antimicrobial stewardship team (AST) unit, 1,730 organizations in the antimicrobial use (AMU) unit, 1,240 organizations in the infection control team (ICT) unit, 1,069 organizations in the healthcare-associated infection (HAI) unit, and 1,441 organizations in the Microorganisms and Resistant Bacteria unit as of January 2023.

[43] Hirabayashi A, Kajihara T, Yahara K, et al. Impact of the COVID-19 pandemic on the surveillance of antimicrobial resistance J Hosp Infect. 2021 Nov;117:147-156. doi: 10.1016/j.jhin.2021.09.011. Epub 2021 Sep 22.

## POLICIES

- Strengthen the surveillance of antimicrobial resistance (AMR) in the medical field through reviewing and expanding target facilities and subjects of the "Japan Nosocomial Infection Surveillance (JANIS)" to work towards understanding the trend of antimicrobial resistance (AMR) in small medical institutions and clinics with less than 200 beds. Particularly consider notifiable disease surveillance for antimicrobial-resistant *Mycobacterium tuberculosis* (MTB), antimicrobial-resistant *Neisseria gonorrhea* infections and understanding antimicrobial-resistant (AMR) fungi, which are spreading globally and becoming an issue.
- Work towards understanding the trend of antimicrobial resistance (AMR) among residents of small medical institutions and elderly care facilities by reviewing target facilities and subjects of Japan Nosocomial Infections Surveillance (JANIS).
- Develop efficient healthcare-associated infection (HAI) surveillance methods, which are based on physicians' consultations. Link data obtained from the healthcare-associated infection (HAI) surveillance with data from Japan Nosocomial Infections Surveillance (JANIS) and antimicrobial use (AMU) data from receipt information by using Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) to promote assessment and management of the risk of healthcare-associated infections (HAIs) caused by antimicrobial-resistant organisms (AROs) within hospitals and regional networks.
- Strengthen comprehensive think-tank function regarding antimicrobial resistance (AMR), including collection of various information on antimicrobial resistance (AMR) inside and outside Japan, provision of the information to the forefront clinicians and researchers, and policy recommendation to the government and international organizations such as the World health Organization (WHO)

## ACTIONS

### ■ Strengthen the National Epidemiological Surveillance of Infectious Diseases

- Promote monitoring of antimicrobial-resistant *Mycobacterium tuberculosis* (MTB) and multidrug-resistant *Neisseria gonorrhoeae* infections, etc.
  - ✓ Standardize the methods and subjects of antimicrobial susceptibility testing
  - ✓ Conduct molecular epidemiological research on multidrug-resistant *Neisseria gonorrhoeae*
  - ✓ Discuss the necessity and relevance of notifiable disease surveillance of antimicrobial-resistant (AMR) *Pseudomonas aeruginosa* infections
- Implement supportive measures to facilitate the mandatory reporting on infectious diseases
  - ✓ Support the development and introduction of a disease notification support system for electronic medical records
  - ✓ Support and standardize full digitalization of reporting of medical institutions to public health centers
- Promote data link with the data collected by Japan Nosocomial Infections Surveillance (JANIS) regarding antimicrobial-resistant infections (ARIs)[44], which are included in Category V infectious diseases, and infectious diseases facing the problem of antimicrobial resistant (AMR), and review reporting standards, as appropriate
- Discuss methods to provide feedback on the risk assessment results to the local health laboratories, public health centers, etc. after National Institute of Infectious Disease conduct risk assessment on antimicrobial resistance (AMR) in each region based on the notifications of infections and the data of pathogens from National Epidemiological Surveillance of Infectious Diseases

### ■ Strengthening the Japan Nosocomial Infections Surveillance (JANIS)

- Conduct research to aid the review of target facilities and subjects of Japan Nosocomial Infections Surveillance (JANIS) (see Strategy 3.1)

[44] Carbapenem-Resistant *Enterobacteriaceae* (CRE) infection, antimicrobial-resistant *Acinetobacter* infection, antimicrobial-resistant *Pseudomonas aeruginosa*, vancomycin-resistant *Enterococci* (VRE) infection, vancomycin-resistant *Staphylococcus aureus* infection, penicillin-resistant *Streptococcus pneumoniae* infection, methicillin-resistant *Staphylococcus aureus* infection

- Support implementation of antimicrobial resistant (AMR) surveillance in medical institutions without an in-house clinical microbiological laboratory, in partnership with off-site contract laboratories for testing
- Further expand targets of surveillance to include bacteria required according to the updated specifications of the World Health Organization (WHO) Global Antimicrobial Resistance Surveillance System (GLASS)[45]
- Accelerate data collection and analysis on key antimicrobial-resistance genes (ARGs)[46] and clinical information
- Consider adding antimicrobial-resistant (AMR) fungi[47] to the scope of the Japan Nosocomial Infections Surveillance (JANIS)
  - ✓ Standardize the methods and subjects of antimicrobial susceptibility testing
- Introduce a system to analyze Japan Nosocomial Infections Surveillance (JANIS) data at the regional level[48] and promote the application of Japan Nosocomial Infections Surveillance (JANIS) data to surveillance activities through the Regional Network for Infectious Diseases Prevention and Control (tentative name) (see Strategy 3.1)

■ **Enhancement of the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE)**

- Continue to conduct surveillance through the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) in addition to the Japan Nosocomial Infections Surveillance (JANIS)
  - ✓ Conduct collection of healthcare-associated infection (HAI) data as part of the work of the antimicrobial stewardship team (AST) in medical institutions and regions
  - ✓ Consider investigating the disease burden, including the number of patients, deaths, disability-adjusted life years (DALYs), quality-adjusted life years (QALYs), and other economic burden, including treatment costs, of bloodstream infections caused by antimicrobial-resistant organisms (AROs)
- Conduct study on automated system to detect suspected healthcare-associated infection (HAI) carriers symptoms from electronic medical records (see Strategy 4.1)
- Conduct analysis by linking healthcare-associated infection (HAI) data with Japan Nosocomial Infections Surveillance (JANIS)[49]
- Provide training to provide necessary knowledge and techniques to implement Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) (see Strategy 1.2 and Strategy 3.3)

■ **Establish a Comprehensive Think-tank Organization for Antimicrobial Resistance (AMR)**

- Strengthen antimicrobial resistance (AMR) control measures from basic research to clinical through the collaboration between the Antimicrobial Resistance Research Center in the National Institute of Infectious Diseases (NIID) and the AMR Clinical Reference Center (AMRCRC) of the National Center for Global Health and Medicine (NCGM)

[45] Strains (*Acinetobacter spp.*, *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. aureus*, *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, *Salmon*ella *spp.*(non-typhoidal), *S. enterica serovar Typhi*, *S. enterica serovar Paratyphi A*, *Shigella spp.*, *N. gonorrhoeae*), Specimen information (blood, CSF spinal fluid, urine, stool, and lower respiratory tract-derived specimens), antimicrobial resistance factors (NDM, OXA, VIM, IMP, GES, KPC, mcr 1-10, CTX-M, TEM, SHV, NDM, OXA, VIM, mecA/mecC, cfr)

[46] Includes genes for extended-spectrum beta-lactamases (ESBL), third-generation cephalosporin resistance such as AmpC, metallo-beta-lactamase (MBL), carbapenemases such as KPC and OXA, and other important antimicrobial resistance such as MCR-1

[47] *Candida albicans; C. glabrata*; *C. parapsilosis*; *C. tropicalis*; *C. krusei*

[48] A system to analyze Japan Nosocomial Infections Surveillance (JANIS) data at the regional level has already been designed through the development of a Regional Infection Control Support System (mentioned below), supported by the Health and Labour Sciences Research Grants (Grants-in-aid for Scientific Research).

[49] The Regional Infection Control Support System is designed to enable the collaboration with Japan Nosocomial Infections Surveillance (JANIS). By interchanging its data with healthcare-associated infection (HAI) surveillance data, the System can identify the antimicrobial-resistant organisms (AROs) that contribute to cause healthcare-associated infections (HAIs) and analyze the degree thereof.

## RELATED MINISTRIES, AGENCIES, AND INSTITUTIONS

Ministry of Health, Labour and Welfare (MHLW); National Institute of Infectious Diseases (NIID); National Center for Global Health and Medicine (NCGM); public health centers; and prefectural and municipal public health institutes

## EVALUATION INDICES

- Number of reports on antimicrobial-resistant *Mycobacterium tuberculosi*s (MTB), multidrug-resistant *Neisseria gonorrhoeae* infections, etc.
- Number of medical institutions participating in antimicrobial resistance (AMR) surveillance and its research

Table 7. Major Healthcare-associated Infections (HAIs) (the surveillance targets of the U.S. Centers for Disease Prevention and Control)

| Healthcare-associated Infections (HAIs) | |
|---|---|
| Central line-associated Bloodstream Infections (CLABSIs) | Bacteraemia and sepsis triggered by infection in central line-associated bloodstream, and their complications |
| Catheter-associated Urinary Tract Infections (CAUTIs) | Urinary tract infections developed in patients with a urinary catheter, including bladder catheterization |
| Ventilator-associated Pneumonia (VAP) | Pneumonia developed in patients using a medical ventilator |
| Surgical Site Infections (SSIs) | Infections developed at surgical sites after operation |
| *Clostridium difficile* Infections (CDIs) | Enteral infections caused by *Clostridium difficile*<br>(CDIs may be facilitated by selective proliferation of the strain by antibiotic use.) |

Reference: The U.S. Centers for Disease Prevention and Control (National Healthcare Safety Network and Emerging Infections Program)

## STRATEGY 2.2 MONITOR THE TREND OF THE ANTIMICROBIAL USE AT MEDICAL INSTITUTIONS

### BACKGROUND

- Antimicrobial use (AMU) in medical institutions is known to be closely associated with antimicrobial resistance (AMR). [50] It is demonstrated that reduction of antimicrobial use (AMU) represses the emergence of antimicrobial-resistant organisms (AROs).[51]
- Antimicrobial use (AMU) surveillance in medical institutions leads to understand antimicrobial use (AMU) indicators[52], and conduct quantitative and qualitative evaluation of antimicrobial stewardship (AMS) between medical institutions by linking antimicrobial resistance (AMR) surveillance data collected by Japan Nosocomial Infections Surveillance (JANIS), and research on utilization of antimicrobial use (AMU) surveillance has been conducted.[53]
- Furthermore, using the antimicrobial use (AMU) indicators, which are of international standards, enables comparison of antimicrobial use (AMU) status in Japan with the world.
- Considering that antimicrobial use varies by region as well as dosage and number of days of administration depending on the type of infection, patient age, organ function, etc., it is necessary to develop a system that enables detailed trend monitoring at each medical institution.
- Currently, inpatient and outpatient monitoring of antimicrobial use (AMU) using sales volume and medical billing information.[54] The results of this survey revealed that antimicrobial prescriptions are used more in clinics than in hospitals. In particular, 90% of prescriptions are for outpatient use, and it has become clear that many antibiotics are used for diseases such as upper respiratory tract infections and diarrhea, which are not considered to require antibiotics.[55,56,57] In order to further promote appropriate use, it is important to conduct a surveillance targeting clinics where a large number of prescriptions are made.
- The online monitoring system for antimicrobial stewardship at clinics was established to promote the antimicrobial stewardship (AMS) at clinics by analyzing and visualizing information on antimicrobial prescriptions and names of injuries and diseases at clinics nationwide, and to consolidate and utilize information on the status of antibiotic use at participating medical institutions and in local networks. Although a Point Prevalence Survey (PPS) on antibiotic use was conducted in health care facilities for the elderly requiring long-term care, participation has been limited to a small number of facilities, and it is necessary to expand the number of participating facilities.

[50] Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infect Dis. 2014;14:13. Published 2014 Jan 9. doi:10.1186/1471-2334-14-13

[51] Dancer SJ, Kirkpatrick P, Corcoran DS, Christison F, Farmer D, Robertson C. Approaching zero: temporal effects of a restrictive antibiotic policy on hospital-acquired Clostridium difficile, extended-spectrum β-lactamase-producing coliforms and meticillin-resistant Staphylococcus aureus. Int J Antimicrob Agents. 2013;41(2):137-142. doi:10.1016/j.ijantimicag.2012.10.013

[52] The combination of antimicrobial use density (AUD) , the days of therapy (DOT) and their combination

[53] 2021 Health and Labour Sciences Research Grant, Research on Implementation of National Action Plan on Antimicrobial Resistance (AMR)

[54] Japan Surveillance of Antimicrobial Consumption (JSAC)
http://amrcrc.ncgm.go.jp/surveillance/010/ref/NDB_2013-2020.pdf

[55] Hashimoto H, Saito M, Sato J, et al. Indications and classes of outpatient antibiotic prescriptions in Japan: A descriptive study using the national database of electronic health insurance claims, 2012-2015. Int J Infect Dis. 2020;91:1-8. doi:10.1016/j.ijid.2019.11.009

[56] Kimura Y, Fukuda H, Hayakawa K, et al. Longitudinal trends of and factors associated with inappropriate antibiotic prescribing for non-bacterial acute respiratory tract infection in Japan: A retrospective claims database study, 2012-2017. PLoS One. 2019;14(10):e0223835. Published 2019 Oct 16. doi:10.1371/journal.pone.0223835

[57] Ono A, Aoyagi K, Muraki Y, et al. Trends in healthcare visits and antimicrobial prescriptions for acute infectious diarrhea in individuals aged 65 years or younger in Japan from 2013 to 2018 based on administrative claims database: a retrospective observational study. BMC Infect Dis. 2021;21(1):983. Published 2021 Sep 21. doi:10.1186/s12879-021-06688-2

○ Antimicrobial use (AMU) had been gradually decreasing since 2016, with an even larger decrease starting in 2020.[58] The reduction in the incidence of acute respiratory tract infections and the number of patients seen in clinics as a result of infection control measures taken against Corona Virus Infectious Disease, emerged in 2019 (COVID-19) may have contributed to decrease antimicrobial use (AMU). Preventive measures against infections in addition to the antimicrobial stewardship (AMS) contributed to the reduction of antimicrobial use (AMU).

## POLICIES

○ Develop surveillance methods to monitor antimicrobial use (AMU) in medical institutions (inpatient and outpatient departments)

○ Monitor antimicrobial use (AMU) indicators at individual medical institutions, and conduct quantitative and qualitative comparison and evaluation of antimicrobial stewardship (AMS) continually by linking antimicrobial use (AMU) indicators with antimicrobial resistance (AMR) surveillance data from Japan Nosocomial Infections Surveillance (JANIS)

○ Monitor the actual status of antimicrobials prescribed in nursing care facilities

## ACTIONS

■ **Antimicrobial Use Surveillance in Medical Institutions by Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE)**

- Promote participation of small and medium-sized hospitals and clinics in the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE). Enhance utilization through collaboration with Japan Nosocomial Infections Surveillance (JANIS)
- Promote securing a system capable of a quantitative and qualitative evaluation using Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE), etc. in the framework between medical institutions, etc., and consider a method to feed back the multicenter comparisons to each medical institution.
- Promote utilization of the antimicrobial use (AMU) surveillance system in hospital outpatient departments and clinics
- Promote utilization of the National Database for Prescription and National Health Check-up (NDB)
- Encourage participation of medical institutions in the antimicrobial use (AMU) surveillance system
- Conduct research on the integration of antimicrobial use (AMU) surveillance systems in inpatient and outpatient departments
- Conduct research studies to explore infection incidence, antimicrobial use rates, descriptions of prognosis and risk factors for each department
- Explore collaboration of the antimicrobial use (AMU) surveillance systems between inpatient and outpatient departments

■ **Apply Antimicrobial Use (AMU) Surveillance to Risk Assessment and Risk Management**

- Continue quantitative and qualitative evaluation of antimicrobial stewardship (AMS) (benchmarking) in individual medical institutions, and conduct research studies for utilization of antimicrobial stewardship by linking antimicrobial use (AMU) indicators of some medical institutions with Japan Nosocomial Infections Surveillance (JANIS) data (see Strategy 4.1)
- Revise guidelines to evaluate the quality of antimicrobial stewardship (AMS) using antimicrobial use (AMU) indicators

[58] Japan Surveillance of Antimicrobial Consumption (JSAC)

- Promote securing a system capable of quantitative and qualitative evaluation using antimicrobial use (AMU) indicators in the framework in the Regional Network for Infectious Diseases Prevention and Control (tentative name) (see Strategy 3.1), between medical institutions, etc., and consider a method to feed back the multicenter comparisons to each medical institution.
- Enhance the "One Health Platform for Antimicrobial Resistance (AMR)" with information on antimicrobial use, antimicrobial resistance rates, information on medical practices[59], and other information in each prefecture, using Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) and Japan Nosocomial Infections Surveillance (JANIS) data

■ **Monitor the Actual Status of Antimicrobial Prescription in Nursing Care Facilities**

- Monitor the use of antimicrobials prescribed in nursing care facilities

## RELATED MINISTRIES, AGENCIES, AND INSTITUTIONS

Ministry of Health, Labour and Welfare (MHLW); National Institute of Infectious Diseases (NIID); National Center for Global Health and Medicine (NCGM); public health centers; and prefectural and municipal public health institutes

## EVALUATION INDICES

- Antimicrobial use (AMU) in medical institutions
- Number of organizations participating in antimicrobial use (AMU) surveillance for inpatient and outpatient departments
- Number of local governments conducting systematic evaluation of local antimicrobial use (AMU) indicators

[59] The examples are: blood culture status (multiple set rate), hand hygiene use/adherence rate

# STRATEGY 2.3 STRENGTHEN ANTIMICROBIAL RESISTANCE SURVEILLANCE IN THE FIELDS OF VETERINARY MEDICINE, LIVESTOCK AND AQUACULTURE

## BACKGROUND

- In 1999, the Government of Japan started a system to monitor nation-wide trends of antimicrobial resistance (AMR) in livestock, called the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM), and its core laboratory, the National Veterinary Assay Laboratory (NVAL), conducts surveillance of antimicrobial-resistant organisms (AROs) in partnership with prefectures, the Food and Agricultural Materials Inspection Center (FAMIC), and other organizations. For its part, it collects data on antimicrobial use (AMU) converted from sales volume of antibiotics for animals, and the results are published annually, and data is provided to the "Nippon AMR One Health Report (NAOR)" from the perspective of the One Health approach. Furthermore, it is provided as Japanese data to "the Annual Report on Antimicrobial Agents Intended for Use in Animals" compiled and reported by the World Organisation for Animal Health (WOAH).
- Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) conducts survey and research including characterization of various antimicrobial-resistant organisms (AROs) and uses the results as the basis for risk assessment. In order to accumulate and analyze genetic information on antimicrobial resistant bacteria, the genome database (J-VEG) was newly developed in FY2019, and some data was registered to start analysis. In the future, the database should be further enhanced and accurately detect warning signs of changes and expansion of antimicrobial resistance (AMR).
- The Food and Agricultural Organization of the United Nations (FAO) considers that antimicrobial-resistant bacteria of aquacultural origin have a minor impact on human health.[60] Organized surveillance and monitoring systems are not seen overseas in this field. On the other hand, in Japan, surveillance has been conducted on the antimicrobial susceptibility of pathogens that are target of efficacy or effects of antibiotics for farm-raised aquatic animals, and the surveillance has been used as a basis for risk assessment.
- In the field of pets, there has been no international surveillance and monitoring of antimicrobial susceptibility, except in some European countries, but in Japan, surveillance of antimicrobial susceptibility in diseased pets started in 2017 and in healthy pets in 2018.
- In the field of agriculture, the Food and Agriculture Organization of the United Nations (FAO) and other organizations are discussing the collection and sharing of data related to surveillance.

## POLICIES

- Continue surveillance on antimicrobial resistance (AMR) in livestock, farm-raised aquatic animals, and pets
- Continue surveillance to estimate the use of antimicrobials used in animal and agriculture fields
- Make outcomes of these efforts widely known. Apply the outcomes for risk assessment and the One Health Surveillance, described in Strategy 2.5. Use them also to develop risk management measures
- Enhance the database of antimicrobial-resistance genes (ARGs) and other genes in the animal field to accurately identify warning signs of changes and expansion of antimicrobial resistance (AMR)

## ACTIONS

### ■ Implement Surveillance on Antimicrobial Resistance (AMR) in Animal Fields

- Enhance the surveillance of antimicrobial resistance (AMR) in livestock, farm-raised aquatic animals, and pets, while reviewing target species and drugs in a timely and appropriate manner
- Develop antimicrobial susceptibility testing manuals, etc. to enable harmonised comparison and evaluation and collect data based on the uniform methods

[60] Improving biosecurity through prudent and responsible use of veterinary medicines in aquatic food production, FAO Fisheries and Aquaculture Technical Paper No. 547, 2012.

- Perform whole genome analysis on the collected strains and continue to accumulate gene information

■ **Implement Surveillance on Antimicrobial Use (AMU)**

- Continue surveillance to estimate the antimicrobial use (AMU) of antibiotics for animals in livestock, farm-raised aquatic animals, and pets
- Continue surveillance to estimate the antimicrobial use (AMU) of human antibiotics in livestock and pets
- Newly establish a system to understand the antimicrobial use (AMU) per farm in the livestock field
- Continue surveillance to estimate the antimicrobial use (AMU) of antibiotic feed additives per target livestock
- Implement surveillance on the antimicrobial use (AMU) in agriculture

■ **Application of Surveillance to Risk Assessment and Risk Management**

- Adequately identify warning signs of change or spread of antimicrobial resistance (AMR) based on the status of antimicrobial resistance (AMR) in different livestock species and outbreaks of livestock diseases
- Analyze the epidemiological relationship between zoonotic and human-derived antimicrobial-resistant bacteria in collaboration with the Japan Nosocomial Infections Surveillance (JANIS), using the results of whole genome analysis of strains collected by the Japan Veterinary Antimicrobial Resistance Monitoring (JVARM)

## RELATED MINISTRIES, AGENCIES, AND INSTITUTIONS

Ministry of Agriculture, Forestry and Fisheries (MAFF); NVAL, National Agriculture and Food Research Organization (NARO); FAMIC; Fisheries Research Agency (FRA); livestock hygiene service centers; and fisheries research and laboratory facilities

## EVALUATION INDICES

- Number of surveillance reports
- Number of obtained strains

# STRATEGY 2.4 STANDARDIZE METHODS OF LABORATORY TESTING AND STRENGTHEN TESTING FUNCTIONS OF ANTIMICROBIAL RESISTANCE AT CLINICAL, COMMERCIAL AND PUBLIC HEALTH LABORATORIES

## BACKGROUND

- Antimicrobial resistance (AMR) testing includes pathogen culture and identification, antimicrobial susceptibility testing, nucleic acid amplification tests, antimicrobial-resistance gene (ARG) tests, and antimicrobial resistance (AMR) rapid diagnosis kits. Epidemiological genome analysis is used to study antimicrobial-resistant infection (ARI) outbreaks. However, quality control measures have not uniformly been applied nationwide to these tests, posing obstacles to the implementation and evaluation of antimicrobial resistance (AMR) surveillance and monitoring. The number of laboratories capable of conducting detailed analysis on antimicrobial resistance (AMR) including antimicrobial-resistance gene (ARG) is still limited, and examination standards, targets, and methods used among them are not standardized.
- In the field of animals, in order to unify the methods used by inspection organizations that participate in the "Japanese Veterinary Antimicrobial Resistance Monitoring (JVARM)" investigation, the National Veterinary Assay Laboratory (NVAL), the core laboratory, has provided training to prefectural livestock health inspectors and quality control to inspection organizations.
- In-house clinical microbiological laboratories play significant roles in antimicrobial resistance (AMR) and healthcare-associated infection (HAI) surveillance and monitoring, and antimicrobial stewardship (AMS). However, examination in medical institutions, particularly microbial examination, have been considered unprofitable. Therefore, many small and medium-sized hospitals have chosen to outsource such testing.

## POLICIES

- Endeavor to improve the level of test technologies and ensure the availability of an examination system for standardized comparison and evaluation by supporting the establishment of nation-wide, external evaluation management systems for antimicrobial resistance (AMR) tests
- The National Veterinary Assay Laboratory (NVAL), which is the core laboratory, conducts training and quality control to improve the accuracy of laboratory testing techniques and ensure an examination system that enables unified comparison and evaluation.
- Conduct research on microbial examination systems, which aims to enhance antimicrobial stewardship (AMS) in medical institutions
- Explore the possibilities of introducing new technologies and equipment in public and animal health laboratories[61] to enhance their capacity of antimicrobial resistance (AMR) related information collection and provision

## ACTIONS

### ■ Standardize Testing Methods and Strengthen Quality Control

- Renew the antimicrobial susceptibility testing manual in line with the international standards, which enables harmonised comparison and evaluation in each field and implement training using the manual
- Support the establishment of external evaluation management systems and promote the introduction of the system in medical institutions and laboratories

[61] Public and animal health laboratories include the National Institute of Infectious Diseases (NIID), the National Veterinary Assay Laboratory (NVAL), prefectural and municipal public health institutes, and livestock hygiene service centers

- Develop manuals and guidelines for testing antimicrobial-resistance genes (ARGs) and comparative analysis of antimicrobial-resistant organisms (AROs)
- Consider creating bacterial strains (panels) to be used for quality control of bacteriological assay instruments and providing them to laboratories nationwide, and promote public awareness of them
- Renew the manuals and guidelines for each medical institution to create an antimicrobial susceptibility table (e.g. antibiogram) of major causative microorganisms
- Continuously implement training, quality control, etc. in order to conduct tests using unified methods at inspection organizations involved in investigation by the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

■ **Expand Testing Capacity related to Antimicrobial Resistance and Conduct Research for the Purpose**

- Strengthen and expand the capacity of antimicrobial resistance (AMR) related information collection and provision in public and animal health laboratories
- Conduct clinical research on the use of antimicrobial resistance (AMR)-related tests[62] and basic microbial tests[63], which may contribute to enhance antimicrobial stewardship (AMS) (see Strategy 5.2)

■ **Introduce New Technologies for Surveillance and Monitoring and Apply Them to Control Measures**

- Develop new technologies[64] for surveillance and monitoring based on molecular epidemiology and promote their introduction in public and animal health laboratories
- Strengthen surveillance and monitoring[65] based on molecular epidemiology by expanding the antimicrobial resistance (AMR) genome database and apply the outcomes to risk assessment and risk management

## RELATED MINISTRIES, AGENCIES, AND INSTITUTIONS

Ministry of Health, Labour and Welfare (MHLW); Ministry of Agriculture, Forestry and Fisheries (MAFF); National Institute of Infectious Diseases (NIID); National Veterinary Assay Laboratory (NVAL); National Agriculture and Food Research Organization (NARO); Food and Agricultural Materials Inspection Center (FAMIC); National Center for Global Health and Medicine (NCGM); public health centers; prefectural and municipal public health institutes; and livestock hygiene service centers

## EVALUATION INDICES

- Number of organizations adopting standards
- Number of training seminars implemented for standardization
- Number of samples obtained from surveillance and monitoring based on molecular epidemiology

[62] Antimicrobial resistance (AMR)-related tests include: E-test, Break-point Checkerboard Plate method, multiplex PCR, rapid detection test for antimicrobial-resistant gene products, matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS).
[63] Basic microbial tests include: Gram staining, fluorescent labeling, bacterial culture and identification, anaerobic culture test, bacterial antimicrobial susceptibility testing, acid-fast bacilli culture test, acid-fast bacilli antimicrobial susceptibility testing, yeast-like fungus antifungal susceptibility testing, rapid diagnosis of various bacteria and viruses
[64] New technologies for surveillance and monitoring based on molecular epidemiology include: Whole genome sequencing (WGS), and metagenomic analysis.
[65] Elucidate the transmission pathways of antimicrobial-resistance genes (ARGs) and antimicrobial-resistant organisms (AROs) by interchanging data from antimicrobial-resistant organism (ARO) genome analysis, genome database, and surveillance and monitoring. Apply the findings for developing control measures.

## STRATEGY 2.5 IMPLEMENT INTEGRATED ONE HEALTH SURVEILLANCE INCLUDING HUMANS, ANIMALS, FOOD, AND THE ENVIRONMENT

### BACKGROUND

- Accurate understanding of the antimicrobial resistance (AMR) ecosystem - the variety, spread, and transmission pathways - is essential for eliminating the transmission pathways of antimicrobial resistance (AMR).
- Japan currently has two antimicrobial resistance (AMR) surveillance and monitoring systems, the Japan Nosocomial Infections Surveillance (JANIS) for human health and the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) for animal health, and their collaboration has been promoted. On food, research has been conducted on multidrug-resistant *Enterobacteriaceae* and Vancomycin-resistant *Enterococci*, and data on antimicrobial resistance (AMR) in bacteria of food origin collected by prefectural and municipal public health institutes has been linked with the data from Japan Nosocomial Infections Surveillance (JANIS) and Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) and checked on a regular basis.
- In addition, the antimicrobial resistance (AMR) One Health Platform is operated at the AMR Clinical Reference Center (AMRCRC) to consolidate information on One Health-related AMR, antimicrobial use (AMU) in inpatient and outpatient departments, infectious diseases, and vaccination in order to utilize this information for antimicrobial resistance (AMR) control in each region. This facilitates the use of the data of antimicrobial resistance (AMR) not only in the human field, but also in livestock, farm-raised aquatic animals, and pets.
- Furthermore, in order to examine the status of the antimicrobial use (AMU) for humans and animals and the antimicrobial resistance rates of microorganisms in Japan, the "Antimicrobial Resistance One Health Surveillance Committee" was established and experts in the fields of humans, animals, food and the environment discuss them. The committee prepares the annual "Nippon AMR One Health Report (NOAR)" to evaluate the current status and understanding of trends in antimicrobial resistance (AMR) and antimicrobial use (AMU) in each field in Japan.

### POLICIES

- Data will be consolidated and shared in the network established by the National Institute of Infectious Diseases (NIID), the National Veterinary Assay Laboratory (NVAL), and the National Center for Global Health and Medicine (NCGM) to establish the One Health Surveillance system with world-wide actions beyond barriers between humans and animals, etc., which links data from multiple surveillance and monitoring systems including the Japan Nosocomial Infections Surveillance (JANIS) and Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM). In addition, the "Antimicrobial Resistance One Health Surveillance Committee" will periodically analyze and evaluate the trend of antimicrobial resistance (AMR) and countermeasures by coordinating information from each surveillance and monitoring, while also conducting international comparisons. In addition, the evaluation results will be made public and utilized in the review of the "National Action Plan on Antimicrobial Resistance (AMR) (2023-2027)".
- Conduct research to prepare for establishing surveillance and monitoring systems of antimicrobial-resistant organisms (AROs) in food
- Conduct research on surveillance and monitoring of antimicrobial-resistant organisms (AROs) and residual antimicrobials in aquatic and terrestrial environment, as well as in wild animals

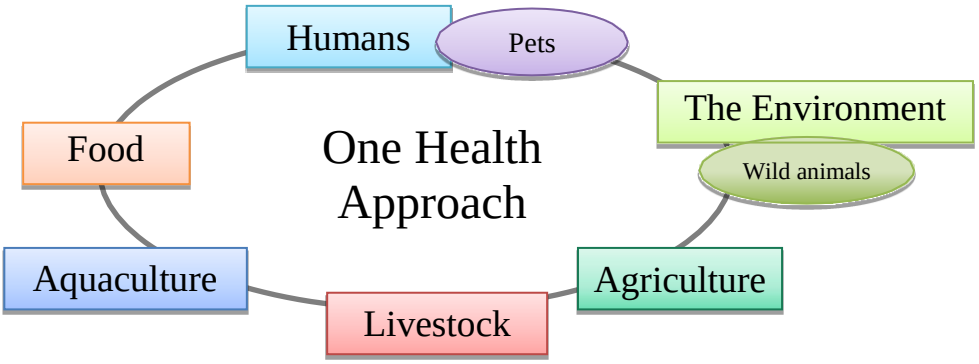



Figure 6 Collaboration under One Health approach

## ACTIONS

- **Promote the One Health Surveillance System**
  - Implement the following measures at the Antimicrobial Resistance One Health Surveillance Committee[66] for antimicrobial resistance (AMR) and antimicrobial use (AMU);
    - ✓ Create the One Health Surveillance Network on Antimicrobial Resistance (AMR) (tentative name), which includes National Institute of Infectious Diseases (NIID), National Veterinary Assay Laboratory (NVAL), National Center for Global Health and Medicine (NCGM) and conduct collecting and sharing data
    - ✓ Continue to promote the analysis and evaluation based on the integrated data from surveillance and monitoring, other scientific studies, and tests conducted by local governments
    - ✓ Continue preparation and publication of the annual "Nippon Antimicrobial Resistance One Health Report (NAOR)"[67] and improve the contents
  - Conduct research to prepare for establishing an antimicrobial resistance (AMR) surveillance and monitoring system on food[68]
  - Analyze transmitting factors of antimicrobial resistance (AMR) in humans, animals, food, and environment. Conduct research to elucidate linkage between their transmission processes
  - Conduct research to monitor antimicrobial resistance (AMR) and residual antimicrobials in aquatic and terrestrial environment
  - Collect information on antimicrobial-resistant bacteria, including their presence in the environmental water and soil and their impact on health
  - Collect basic information on residual antimicrobials in the environment
  - Link data related to antimicrobial resistance (AMR) surveillance/monitoring across humans, animals, food, and environment, and conduct investigation and analysis of antimicrobial-resistant bacteria that are feared to be transmitted to humans using genetic databases
  - Implement surveillance on the antimicrobial use (AMU) in agriculture
  - Modify the national surveillance and monitoring projects to align with changes to the Global Antimicrobial Resistance Surveillance System (GLASS)
  - Conduct surveillance and monitoring in each region regarding antimicrobial resistance (AMR) to facilitate the use of the "AMR One Health Platform" for regional collaboration, and promote the use of the platform by posting their interpretation of data and initiatives in each region

[66] Committee members' areas of expertise : human clinical practice, human resistant bacteria, human antibiotics, animal resistant bacteria, animal antimicrobials, food resistant bacteria, environmental resistant bacteria, environmental residual antibiotics
[67] Nippon AMR One Health Report (NAOR) 2017, NAOR 2018, NAOR 2019, NAOR 2020, NAOR 2021 https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000120172.html
[68] This includes imported food products.

## Related Ministries, Agencies, and Institutions

Food Safety Commission of Japan (FSC), Cabinet Office (CAO); Ministry of Health, Labour and Welfare (MHLW); Ministry of Agriculture, Forestry and Fisheries (MAFF); Ministry of the Environment (MOE); National Institute of Infectious Diseases (NIID); National Veterinary Assay Laboratory (NVAL); National Agriculture and Food Research Organization (NARO); Food and Agricultural Materials Inspection Center (FAMIC); NCGM; public health centers; prefectural and municipal public health institutes; and livestock hygiene service centers

## Evaluation Indices

- Reported number on surveillance under One Health approach
- Number of samples obtained by antimicrobial resistance (AMR) surveillance and research in each field

# GOAL 3
## PREVENT THE SPREAD OF ANTIMICROBIAL-RESISTANT ORGANISMS BY IMPLEMENTING APPROPRIATE INFECTION PREVENTION AND CONTROL

### Strategies

(3.1) Infection Prevention and Control in Healthcare and Nursing Care and Promotion of Regional Cooperation

(3.2) Promote Infection Prevention and Control in Livestock and Aquaculture, Veterinary Medicine and Food Chain

(3.3) Strengthen the Outbreak Response Capacity against Antimicrobial-resistant Infections

# STRATEGY 3.1 INFECTION PREVENTION AND CONTROL IN HEALTHCARE AND NURSING CARE AND PROMOTION OF REGIONAL COOPERATION

## BACKGROUND

- With the amendment of the Medical Care Act (Act No. 205 of 1948) in 2006, all medical institutions became obligated to establish a nosocomial infection control committee to promote nosocomial infection control. With the revision of the medical fee in FY2012, a premium for regional cooperation in infection control was created and regional infection control networks[69] among medical institutions are being established to support infection control of small and medium-sized medical institutions. With the revision of the medical fee in FY2022, the premium for improvement of infection control measures was newly established to further promote efforts for infection prevention and control (IPC).[70]
- Concerning efforts that have been referred to as "infection control", the role of infection prevention has become important, and it is being addressed in an integrated manner as "infection prevention and control (IPC)".
- In the meantime, recently, as antimicrobial resistant organisms (AROs) have become a hot issue in nursing care facilities, efforts to control healthcare-associated infections (HAIs)[71] are being promoted as a broader concept.[72] However, current nosocomial infection control is mainly intended for inpatient and outpatient departments of medical institutions, and it is not clearly stated to cover nursing care facilities.
- The outbreak of Corona virus infectious disease, emerged in 2019 (COVID-19) has increased awareness of infection prevention and control (IPC) and improved the implementation rate and techniques of hand hygiene and wearing protective equipment.[73] These results should be used to further improve the quality of nosocomial infection control measures at medical institutions by applying them to antimicrobial resistance (AMR) control measures as well.

## POLICIES

- Promote a cooperation system in which infection prevention and control (IPC) are addressed in an integrated manner in various clinical settings, such as inpatient and outpatient departments in medical institutions, nursing care facilities, and home care, and promote comprehensive antimicrobial resistance (AMR) control measures, linking the efforts of the existing infection control team (ICT) at the field level with those of antimicrobial stewardship program (ASP)
- Regarding infection prevention and control (IPC), expand activities in cooperation with regional hospitals and related organizations (clinics, pharmacies, nursing care facilities, public health centers, prefectural and municipal public health institutes, etc.), develop concrete activity models of a comprehensive regional infection prevention and control network, and support its sequential establishment all over the country
- Promote research on technical support to promote infection prevention and control (IPC) (automatic analytical system of clinical data, etc.)
- Enhance infection prevention and control (IPC) through promoting vaccination and utilizing the relevant framework of medical care quality evaluation

[69] There is a program of establishing a regional network for nosocomial infection control, which is intended to support the prevention and response of healthcare-associated infections. This is implemented in some prefectures.
[70] Participating medical institutions in 2020 annual report were 778 institutions (eligible for the premium 1 for infection control measures; 539, eligible for the premium 2 for infection control measures; 232, no premium; 7)
[71] Strausbaugh LJ. Emerging health care-associated infections in the geriatric population. Emerg Infect Dis. 2001;7(2):268-271. doi:10.3201/eid0702.010224
[72] Cohen CC, Herzig CT, Carter EJ, Pogorzelska-Maziarz M, Larson EL, Stone PW. State focus on health care-associated infection prevention in nursing homes. Am J Infect Control. 2014;42(4):360-365. doi:10.1016/j.ajic.2013.11.024
[73] Japan Surveillance for Infection Prevention and Healthcare Epidemiology（J-SIPHE）2020/2021 Annual Report

## ACTIONS

### ■ Promote Infection Prevention and Control and Strengthen Regional Cooperation

- Continue to discuss infection prevention and control (IPC) measures at outpatient departments and for home care by the "Antimicrobial resistance (AMR) Subcommittee" and the "Antimicrobial Stewardship(AMS) Working Group" (see Stratety 4.1) established under Ministry of Health, Labour and Welfare (MHLW), as appropriate
- Continue research to review target facilities and subjects to the Japan Nosocomial Infections Surveillance (JANIS) (see Strategy 2.1).
- Based on the implementation of the concrete activity model of regional infection control measures, ("Regional Network for Infectious Diseases Prevention and Control (tentative name))" project, consider the role of prefectures and promote nationwide expansion of the project
- Disseminate concrete application models of the premium for improvement of infection control measures, and promote more effective operation that uses Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE)
- Conduct research to evaluate the thoroughness and compliance rate of daily hand hygiene in hospitals and other institutions
- Introduce antimicrobial stewardship (AMS) and antimicrobial resistance (AMR) screening components into the infection prevention and control (IPC) guidelines and manuals, based on current situation surveys of antimicrobials at nursing care facilities, as appropriate (see Strategy 5.2)

### ■ Development a System of Cooperation among Laboratories, Medical Institutions, and Local Governments

- Create a reporting and consultation system for the detection of clinically important antimicrobial- resistant organisms (AROs) at laboratories
- Promote research to develop a manual for risk assessment and management on antimicrobial resistance (AMR) in cooperation with local stakeholders
- Conduct comparison and evaluation (benchmarking) of infection prevention and control (IPC) at the level of medical institutions, regions and nation, and implement research for promoting infection prevention and control (IPC) measures based on the results

### ■ Promote Infection Prevention

- Continue to promote vaccinations (*Streptococcus pneumoniae*, *Heamophilus influenzae* Type b (Hib), influenza vaccines, etc.) contributing to promote the prevention of antimicrobial-resistant infections (ARIs)
- Continue to promote evaluations related to infection prevention and control (IPC) and antimicrobial stewardship (AMS), etc. in the Quality Health Care Evaluation scheme

## RELATED MINISTRIES, AGENCIES, AND INSTITUTIONS

Ministry of Health, Labour and Welfare (MHLW); National Institute of Infectious Diseases (NIID); National Center for Global Health and Medicine (NCGM); public health centers; prefectural and municipal public health institutes; Japan Council for Quality Health Care

## EVALUATION INDICES

- Number of healthcare-associated infections (HAIs) caused by antimicrobial-resistant organisms (AROs)
- Number of local goverments that have established Regional Network for Infectious Diseases Prevention and Control (tentative name) that meets the requirements
- Vaccination rates of *Streptococcus pneumoniae*, *Haemophilus influenzae* Type b (Hib), and Influenza vaccines

# STRATEGY 3.2 PROMOTE INFECTION PREVENTION AND CONTROL IN LIVESTOCK AND AQUACULTURE, VETERINARY MEDICINE AND FOOD CHAIN

## BACKGROUND

- Improving the level of rearing hygiene management and maintaining the health condition of livestock are extremely important elements of controlling the occurrence and selection of antimicrobial-resistant organisms (AROs), leading to the prevention of the occurrence of infectious diseases in animals, to secure safety production of animal products, as well as to reduce instances of using antibiotics for animals. They are also highly important from the viewpoint of reducing production costs.
- Regarding appropriate rearing hygiene management to prevent infectious diseases at the production sites of animal products, the biosecurity standards were established based on the provisions of the Act on Domestic Animal Infectious Diseases Control (Act No. 166 of 1951). The status of biosecurity for the care of the livestock (cattle, pig, poultry, etc.), the implementation status of the biosecurity instruction plan, the implementation status of instructions, advice, recommendations and orders submitted by the Prefectural Governor, and the status of securing prefectural livestock health inspectors are announced to the public every year by each prefecture, to promote the improvement in the conditions of hygienic control.
- Handbook for Hygienic Practice during Primary Production (beef, pork, poultry and eggs), which describes measures to produce safer animal products as well as to reduce the occurrence of food poisoning, in addition to measures to prevent infectious diseases in livestock provided in the biosecurity standards is publicly available.
- On the other hand, for appropriate hygiene management for the prevention of infectious diseases at the production site of farm-raised aquatic animal, the "Guideline for Disease Control of Aquatic Animals" and the "Basic Plan for Fisheries" require aquaculture producers to take hygiene management measures and to use aquaculture drugs appropriately.
- For food processing and distribution processes, Hazard Analysis and Critical Control Point (HACCP) became mandatory for all businesses in principle in the revision of the Food Sanitation Act (Act No. 233 of 1947) in 2018 in order to promote countermeasures to reduce contamination with antimicrobial-resistant organisms (AROs) and other microorganisms as well as to prevent food poisoning from occurring.
- In all fields of livestock, farm-raised aquatic animals and pets, appropriate vaccination is important to prevent infectious diseases, in addition to thorough hygienic management. Under the present circumstances, the development of vaccines for orphan diseases and farm-raised aquatic animals is hampered due to the small market, even if they are desired.

## POLICIES

- Raise and promote awareness of infection prevention and control (IPC) at facilities related to livestock and aquaculture as well as veterinary medicine through further stringent compliance with the biosecurity standards, appropriate vaccinations, and dissemination of the Handbook for Hygienic Practice during Primary Production
- Raise awareness that the prevention of infectious diseases will result in antimicrobial resistance (AMR) control, reducing the opportunities to use antibiotics for animals
- Embed Hazard Analysis and Critical Control Point (HACCP) in food processing and the distribution process

## ACTIONS

- **Promote Infection Prevention and Control (IPC) of Livestock, Farm-raised Aquatic Animals and Pets**
  - Promote development and commercialization of vaccines and immunostimulants for livestock, farm-raised aquatic animals and pets
  - Ensure compliance with the biosecurity standards based on the provisions of the Act on the Prevention of Infectious Disease in Livestock, and disseminate the Handbook for Hygienic Practice during Primary Production
  - Share good practices in the livestock field with producers, and ensure thorough guidance on the appropriate use of antimicrobials by the officials of Livestock Hygiene Service Centers, etc.
  - Share good practices in rearing management with prefectural governments, and strengthen the system of appropriate guidance on aquaculture hygiene management and aquaculture drugs by fish epidemic prevention officers and others when using veterinary antibiotics for farm-raised aquatic animals.
- **Promote Infection Prevention and Control (IPC) of Food processing and Distribution Process**
  - Embed Hazard Analysis and Critical Control Point (HACCP)

## RELATED MINISTRIES, AGENCIES, AND INSTITUTIONS

Ministry of Agriculture, Forestry and Fisheries (MAFF); Ministry of Health, Labour and Welfare (MHLW); National Veterinary Assay Laboratory (NVAL); National Agriculture and Food Research Organization (NARO); prefectural and municipal public health institutes; livestock hygiene service centers

## EVALUATION INDICES

- Number of veterinary vaccines, immunostimulants, and others put to practical use
- Status of compliance with the biosecurity standards
- Number of views on websites related to the Handbook for Hygienic Practice during Primary Production
- Amount of vaccines used for livestock, farm-raised aquatic animals and pets

## STRATEGY 3.3 STRENGTHEN THE OUTBREAK RESPONSE CAPACITY AGAINST ANTIMICROBIAL-RESISTANT INFECTIONS

### BACKGROUND

- Recently, cases of nosocomial outbreak with Carbapenem-resistant *Enterobacteriaceae* (CRE) or other antimicrobial-resistant organisms (AROs) are increasing. In the meanwhile, regarding the ability to implement epidemiological studies and to take measures for infectious disease containment by a medical institution itself, there are large differences in response capacity between medical institutions. In addition, as there are differences in knowledge and experience with antimicrobial-resistant infections (ARIs) among local governments, it is necessary to strengthen the response capacity to outbreaks by antimicrobial-resistant infections (ARIs) by establishing guidelines and providing training seminars.
- Vancomycin-resistant *enterococci* (VRE) infections are a Category V infectious disease requiring notifiable disease surveillance under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases, and the number of patients reported in the National Epidemiological Surveillance of Infectious Disease has remained below 100 cases annually from 2011 to 2019. However, in 2020, there were 135 cases (as of January 25, 2021), exceeding the previous record of 120 cases in 2010. Overseas, a new epidemic strain (*pts*-deficient *Enterococcus faecium*) was reported to have caused a large outbreak across states in Oceania[74], and a large outbreak of this strain was subsequently reported in Europe. The large outbreak reported in Japan in 2018 in Aomori Prefecture was also caused by this epidemic strain.[75]
- Outbreaks of carbapenem-resistant *Acinetobacter*[76] and multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB)[77] have also been reported overseas. Moreover, outbreaks of antimicrobial-resistant infections (ARIs) have mainly occurred within hospitals, but due to the recent spread of antimicrobial resistance (AMR) in the community, there are growing concerns about the occurrence of community-acquired antimicrobial-resistant infection (ARI) outbreaks. An outbreak of multidrug-resistant group A *streptococcal* infections was reported in Israel in 2017.[78] Since 2016, a large outbreak of ultra-multidrug-resistant typhoid infections has been reported in Pakistan,[79] and outbreaks of multidrug-resistant *Salmonella spp.* have been reported in China, Taiwan, Israel, and elsewhere.[80, 81, 82, 83] An outbreak of ultra-multidrug-resistant *Shigella dysenteriae* (XDR *Shigella sonnei*) occurred in early 2022, mainly in Europe.[84] Strengthening monitoring system and response capacity to epidemic and outbreaks of antimicrobial-resistant organisms (AROs) in these food and waterborne

[74] Carter GP, Buultjens AH, Ballard SA, et al. Emergence of endemic MLST non-typeable vancomycin-resistant Enterococcus faecium. J Antimicrob Chemother. 2016;71(12):3367-3371. doi:10.1093/jac/dkw314
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[83] Cohen E, Kriger O, Amit S, Davidovich M, Rahav G, Gal-Mor O. The emergence of a multidrug resistant Salmonella Muenchen in Israel is associated with horizontal acquisition of the epidemic pESI plasmid. Clin Microbiol Infect. 2022;28(11):1499.e7-1499.e14. doi:10.1016/j.cmi.2022.05.029
[84] Extensively drug-resistant Shigella sonnei infections - Europe - European Region (EURO). 2022 https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON364

infection diseases is also an important issue to be addressed.

- A system that provides the necessary support for infection prevention and control (IPC), medical examination of infectious diseases, and administrative responses needs to be developed, and the deployment of local infectious disease specialists needs to be enhanced.

## POLICIES

- Develop manuals and guidelines to respond to both nosocomial and community outbreaks of antimicrobial-resistant infections (ARIs) at a local level, and establish a system whereby local professionals provide support to respond to an outbreak. Strengthen response capacities and a network through increasing education and training opportunities for those involved in the antimicrobial-resistant infection (ARI) outbreak control measures
- Establish a response system to a large-scale outbreak which causes a serious shortage of human resources by dispatching experts throughout the country regarding epidemiological investigations, clinical management, and public health responses, as appropriate. In addition, the deployment of local infectious disease specialists will be enhanced during normal times, and the response support system from the national level to the local level will be strengthened.

## ACTIONS

### ■ Support Local Responses to Outbreaks of Antimicrobial-Resistant Infections (ARIs)

- Support local response to antimicrobial-resistant infection (ARI) outbreaks by the Regional Network for Infectious Diseases Prevention and Control (tentative name) (see Strategy 3.1)
  - ✓ Update manuals and guidelines[85] to respond to nosocomial antimicrobial-resistant infections (ARIs) outbreaks at a local level
  - ✓ Establish a system at medical institutions during normal times and collaborate with health centers to prepare for outbreaks by disseminating manuals and guidelines.
  - ✓ Discuss a mechanism for requesting assistance from hospitals to health centers, local infectious disease specialists, prefectures, and the national government based on risk assessment in the manual and guidelines
- Conduct training seminars for members of the "Regional Network for Infectious Diseases Prevention and Control (tentative name)" and the responsible persons in local governments (see Strategy 2.1)

### ■ Strengthen the Capacity to Respond to Large Scale Outbreaks

- Enhance the talent pool of antimicrobial resistance (AMR) professionals[86] who can respond in case of an extreme shortage of human resources associated with an antimicrobial-resistant infection (ARI) outbreak

[85] Manual for Infection Control in Nursing Homes, Guidance for responding to outbreaks of antimicrobial-resistant bacteria in small and medium-sized hospitals, Responding to outbreaks of antimicrobial-resistant pathogens in health-care facilities: guidance for the Western Pacific region (https://apps.who.int/iris/handle/10665/363498), Risk Assessment and Response Guidelines for Carbapenem-Resistant Enterobacteriaceae (CRE) Infections by Health Centers - Toward Better Collaboration Between Public Health Centers and Medical Institutions

[86] Graduates of the Field Epidemiology Training Program Japan (FETP-J), antimicrobial-resistant infection (ARI) professionals of the National Center for Global Health and Medicine and the National Institute of Infectious Diseases, Infectious Disease Emergency Specialists (IDES) and antimicrobial-resistant infection (ARI) professionals in the fields of practical epidemiology, clinical management, infection prevention and control (IPC) and public health who belong to other medical institutions and research institutes

## Related Ministries, Agencies, and Institutions

Ministry of Health, Labour and Welfare (MHLW); NIID; National Center for Global Health and Medicine (NCGM); public health centers; and prefectural and municipal public health institutes

## Evaluation Indices

- Number of responses to the outbreak and the number of patients with antimicrobial-resistant infections (ARIs)
- Number of training seminars implemented for relevant parties

# GOAL 4
# PROMOTE APPROPRIATE USE OF ANTIMICROBIALS IN THE FIELDS OF HEALTHCARE, LIVESTOCK AND AQUACULTURE

## Strategies

(4.1) Promote Antimicrobial Stewardship at Medical Institutions

(4.2) Ensure Prudent Use of Antibiotics for Animals in the Field of Livestock and Aquaculture and Veterinary Medicine

## STRATEGY 4.1 PROMOTE ANTIMICROBIAL STEWARDSHIP AT MEDICAL INSTITUTIONS

### BACKGROUND

- While infection prevention and control (IPC) at medical institutions contribute to the prevention of expansion of antimicrobial resistance (AMR), infection prevention and control (IPC) cannot prevent the emergence of antimicrobial-resistant organisms (AROs) and the occurrence of antimicrobial-resistant infections (ARIs) by itself.
- To minimize the occurrence of antimicrobial-resistant infections (ARIs) and to reduce the resultant disease burden, it is extremely important to ensure antimicrobial stewardship (AMS) for inpatient and outpatient.[87] In Japan, the annual cost of inappropriate antibicotics prescribed for upper respiratory tract infection in 2016 was estimated to be USD 297.1 million.[88]
- Antimicrobial stewardship (AMS) has effects to reduce unnecessary prescriptions and minimize the emergence of antimicrobial-resistant organisms (AROs), while suppressing medical expenses. In Japan, there is a report of an estimated cost saving of USD 150 thousand by reducing carbapenem-resistant bacteria through the efforts of an in-house antimicrobial stewardship team (AST),[89] and another report showed a 25.8% reduction in antibiotic treatment costs by providing intervention and feedback on dosing appropriateness, de-escalation, and recommendations for blood culture collection by a team of physicians, pharmacists, and bacteriologists at a local hospital.[90]
- However, some medical institutions in Japan have promoted antimicrobial stewardship measures, including the mandatory pre-authorization or reporting for specified antibiotics[91] use. On the other hand, it is necessary to utilize the Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE) as a comprehensive promotion system that integrates measures to promote antimicrobial stewardship (AMS).
- In response to this situation, in the revision of medical fee in FY2018, the premium for support for appropriate use of antibiotics, which is an evaluation of in-hospital antimicrobial stewardship team (AST), was newly established as well as the premium for support for appropriate use of pediatric antibiotics in the pediatric outpatient clinic fee and pediatric family practice fee to evaluate medical care that contributes to improving patient and family understanding of appropriate use of antibiotics. The introduction of the premium for support for appropriate use of pediatric antibiotics has resulted in a decrease of approximately 20% in the administration of antibiotics to pediatric patients in outpatient clinics. In addition, with the revision of medical fee in FY2022, the premium for support for appropriate use of pediatric antibiotics in otolaryngology was newly established, further promoting the appropriate use of antibiotics.

[87] Society for Healthcare Epidemiology of America; Infectious Diseases Society of America; Pediatric Infectious Diseases Society. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol. 2012;33(4):322-327. doi:10.1086/665010

[88] Tsuzuki S, Kimura Y, Ishikane M, Kusama Y, Ohmagari N. Cost of inappropriate antimicrobial use for upper respiratory infection in Japan. BMC Health Serv Res. 2020;20(1):153. Published 2020 Feb 28. doi:10.1186/s12913-020-5021-1

[89] Akazawa T, Kusama Y, Fukuda H, et al. Eight-Year Experience of Antimicrobial Stewardship Program and the Trend of Carbapenem Use at a Tertiary Acute-Care Hospital in Japan-The Impact of Postprescription Review and Feedback. Open Forum Infect Dis. 2019;6(10):ofz389. Published 2019 Sep 5. doi:10.1093/ofid/ofz389

[90] Fukuda T, Watanabe H, Ido S, Shiragami M. Contribution of antimicrobial stewardship programs to reduction of antimicrobial therapy costs in community hospital with 429 Beds --before-after comparative two-year trial in Japan. J Pharm Policy Pract. 2014;7(1):10. Published 2014 Aug 5. doi:10.1186/2052-3211-7-10

[91] Broad-spectrum antibiotics including anti-methicillin-resistant *Staphylococcus aureus* (MRSA) drugs and carbapenem antibiotics

○ Antimicrobial stewardship (AMS) is an area that essentially requires consideration concerning conflict of interest (COI) with the pharmaceutical companies. In Japan, following the formulation of the National Action Plan on Antimicrobial Resistance (AMR), the Ministry of Health, Labour and Welfare issued the Manual of Antimicrobial Stewardship, The1st Edition on June 1, 2017 and the Manual of Antimicrobial Stewardship, The 2nd Edition on December 5, 2019, while the Japanese Association for Infectious Diseases and the Japanese Society of Chemotherapy issued the "JAID/JSC Guide to Clinical Management of Infectious Diseases 2019," and the Japanese Society of Chemotherapy and the Japan Society for Surgical Infection issued the "Japanese Clinical Practice Guidelines for antimicrobial prophylaxis in surgery"; there are various guidelines and other publications related to infectious disease care. On the other hand, it has been reported that the guidelines are not always followed in the use of broad-spectrum antimicrobials in the clinical settings.[92,93]

## POLICIES

○ Based on the idea that conflict of interest (COI) between medical institutions/pharmacies and related companies, etc. must be thoroughly managed when promoting antimicrobial stewardship (AMS), the "Antimicrobial stewardship (AMS) Working Group" established under Ministry of Health, Labour and Welfare (MHLW) is to update the Manual of Antimicrobial Stewardship as necessary

○ Continuously update and improve the Manual of Antimicrobial Stewardship based on the latest findings and develop guidance to enable each medical institution to formulate its antimicrobial stewardship (AMS) guidelines and manuals for medical examination of infectious diseases based on antimicrobial susceptibility. Promote antimicrobial stewardship (AMS) and appropriate medical examination of infectious diseases for outpatients and inpatients through operation of antimicrobial stewardship teams (ASTs) to promote antimicrobial stewardship (AMS) at medical institutions and the quality evaluation of antimicrobial stewardship (AMS)

○ Promote measures to enhance antimicrobial stewardship (AMS) concerning the prevention, diagnosis and treatment of infectious diseases

## ACTIONS

### ■ Publish guidelines/manuals for Antimicrobial Stewardship

- Continue to promote infection prevention and control (IPC) and antimicrobial stewardship (AMS) through necessary discussion at the "Antimicrobial Resistance (AMR) Subcommittee" and the "Antimicrobial stewardship (AMS) Working Group" established within Ministry of Health, Labour and Welfare (MHLW). (see Strategy 3.1)
- Update the Manual of Antimicrobial Stewardship, enhance its content, and promote its use in clinical practice
- Expand support for antimicrobial stewardship (AMS) for outpatients through the online monitoring system for antimicrobial stewardship at clinics

### ■ Review regulations regarding diagnosis and treatment to promote Antimicrobial Stewardship (AMS)

- Review information included in package inserts (e.g. Precautions for Use) for antimicrobials based on scientific evidence
- Reflect the findings based on the latest scientific evidence in Pharmacokinetics/Pharmacodynamics (PK/PD), etc. into the Manual of Antimicrobial Stewardship[94] and other documents

[92] Jung-ho Shin, Noriko Sasaki, Susumu Kunisawa, Yuichi Imanaka. Influence of criteria for nosocomial use of antimicrobial agents on the selection of antimicrobial agents recommended in practice guidelines for patients with community-acquired pneumonia, and the impact of its antimicrobial selection on outcomes. The 58th Annual Congress of Japan Society for Healthcare Administration in Fukuoka and online, October 2-4, 2020 (Journal of the Japan Society for Healthcare Administration Vol.57 Suppl. p.172)

[93] 2018 Ministry of Health, Labour and Welfare commissioned project: Evidence Based Medicine (EBM) Dissemination and Promotion Project "Medical Guideline Handbook" p3

[94] First Edition (https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000166612.pdf), Second Edition (https://www.mhlw.go.jp/content/10900000/000573655.pdf)

- Conduct research on optimizing appropriate use initiatives in intravenous antibiotics
- Based on related research results, review methods to further promote antimicrobial stewardship (AMS) for outpatients[95] (see Strategy 5.2)

■ **Support establishment of a system to promote Antimicrobial Stewardship (AMS) at medical institutions**

- Strengthen the specific antimicrobial stewardship (AMS) components in professional education and training for physicians, pharmacists, nurses, clinical technologists and particular professionals (see Strategy 1.2)
- Continue to support medical institutions in the formulation of management guidance of conflict of interest (COI)[96] concerning antimicrobial stewardship (AMS), antimicrobial stewardship (AMS) guidelines, and medical examination manuals for infectious diseases based on the institution-specific antimicrobial susceptibility at each medical institution (see Strategy 2.4)
- Establish antimicrobial stewardship teams (ASTs) at medical institutions and continue research on securing dedicated employees, based on receipt information, etc.
- Consider expanding to small and medium sized hospitals for the addition of antimicrobial stewardship (AMS) implementation based on the research results
- Establish systems to dispatch experts, conduct education and to provide consultation services (see Strategy 1.2) through the Regional Network for Infectious Diseases Prevention and Control (tentative name) (see Strategy 3.1), and promote infection control measures implemented through cooperation among medical institutions based on the premium for improvement of infection control measures
- Conduct research on the development of the Antimicrobial Stewardship Support System (tentative name)[97] and the utilization of pharmacists (see Strategy 5.3)

## RELATED MINISTRIES, AGENCIES AND INSTITUTIONS

Ministry of Health, Labour and Welfare (MHLW); National Center for Global Health and Medicine (NCGM)

## EVALUATION INDICES

- The number of medical institutions that implement a comprehensive antimicrobial stewardship (AMS) program
- The number of antimicrobial stewardship (AMS) support systems in each region

[95] It has been demonstrated in the Cochrane Systematic Reviews that the prohibition of prescription of antibiotics to patients with acute upper respiratory tract infection in their first visit has no association with prognosis, proving that this is one of the most substantiated antimicrobial stewardship (AMS) strategies. Spurling GK, Del Mar CB, Dooley L, Foxlee R, Farley R. Delayed antibiotics for respiratory infections. Cochrane Database Syst Rev. 2013;(4):CD004417. Published 2013 Apr 30. doi:10.1002/14651858.CD004417.pub4
Dar OA, Hasan R, Schlundt J, et al. Exploring the evidence base for national and regional policy interventions to combat resistance. Lancet. 2016;387(10015):285-295. doi:10.1016/S0140-6736(15)00520-6.

[96] Self-regulation of antimicrobial promotion activities by pharmaceutical companies and others at medical institutions, refrain from accepting research funding for research related to antimicrobial stewardship (AMS), etc.

[97] Develop a system to ensure that the appropriate dose and frequency of antibiotics are administered and conduct research on their effectiveness in antimicrobial stewardship and improving prognosis.

## STRATEGY 4.2 ENSURE PRUDENT USE OF ANTIBIOTICS FOR ANIMALS IN THE FIELD OF LIVESTOCK AND AQUACULTURE AND VETERINARY MEDICINE

### BACKGROUND

- Veterinary antibiotics and antibiotic feed additives used in livestock are important materials to protect the health of livestock and to ensure the stable production of safe food. On the other hand, their use always involves a risk of selecting antimicrobial resistant bacteria that might bring adverse effects to human medicine, veterinary medicine, and food safety.
- Therefore, in Japan, based on the principles of risk analysis established by the international standards of the World Organisation for Animal Health (WOAH) and the Codex Alimentarius Commission, the Food Safety Commission of Japan (FSC) conducts risk assessment concerning the impact of antimicrobial resistant bacteria on human health through food. Based on the results, the Ministry of Agriculture, Forestry and Fisheries (MAFF) formulates and implements risk management measures in accordance with the extent of risks.
- Regarding veterinary antibiotic use, compliance with various regulatory systems under related laws and regulations[98] is promoted through the monitoring and guidance by prefectural pharmaceutical inspectors, etc., thereby promoting appropriate use of veterinary antibiotics. In addition, guidelines for the prudent use of veterinary antibiotics in the livestock industry have been established, and the government is working to promote the prudent use of veterinary antibiotics by educating veterinarians and producers and providing guidance on the use of veterinary antibiotics by prefectural governments.
- In addition, the testing materials and criteria for antimicrobial susceptibility testing that veterinarians require for the prudent use of veterinary antibiotics have been developed and enhanced.
- Veterinary antibiotics for farm-raised aquatic animals are not currently included in the scope of the directions or the prescription system for veterinary medicinal products that involves veterinarians. However, in each prefecture, guidance for appropriate use of such antibiotics is provided by experts at fisheries research and laboratory facilities and other organizations.
- Appropriate use of antibiotic feed additives is ensured by specifying applicable feed products (targeted animal species and breeding stages (products for lactation period, for fattening period, etc.)) and standard amounts to be added in feed.[99] Products that may negatively affect human medicine are not to be designated as feed additives.
- Steady progress was made on the risk assessments concerning the impact of antimicrobial-resistant bacteria on human health through food, and risk assessment was completed for all designated antibiotic feed additives. Based on the experience of the risk assessment and international trends, the "Assessment Guideline for the Effect of Food on Human Health regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food Producing Animals" and "Ranking of the Importance of Antimicrobials against Bacteria which Affect Human Health through Food Commodities" were revised in March 2022.
- For pets, the "Working Group on the Prudent Use of Antimicrobials for Pets" has prepared a "Guidebook for the Prudent Use of Antimicrobials for Pets" and is working to promote and educate clinical veterinarians for pets to ensure the prudent use.

[98] To ensure the appropriate and limited use of veterinary antibiotics, measures are taken with regard to the use and sales of veterinary antibiotics through the requirement for examination by veterinarians (Veterinarians Act, Law No. 186 of 1949), and the prohibition of sale to persons without prescriptions by veterinarians and the specification of standards for use (Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, Law No. 145 of 1960).
[99] Measures are taken to promote the appropriate and limited use of antibiotic feed additives, based on the Act on Safety Assurance and Quality Improvement of Feeds (Act No. 35 of 1953).

## POLICIES

- ○ Continue to formulate risk management measures in accordance with the extents of risks and appropriately implemented, based on the results of risk assessment concerning the impact of antimicrobial-resistant bacteria on human health through food, conducted by Food Safety Commission of Japan (FSC), in accordance with the principles of risk analysis established by the international standards of the World Organisation for Animal Health (WOAH) and the Codex Alimentarius Commission.
- ○ Establish and enhance methods required for ensuring the prudent use of veterinary antibiotics by veterinarians.
- ○ Examine and promote the expanded and strengthened involvement of experts in the use of veterinary antibiotics for farm-raised aquatic animals.

## ACTIONS

- ■ **Promote risk assessment and risk management of the effects on human health via food of antimicrobial resistance (AMR) due to use of antibiotics for animals**
  - Formulate and appropriately implement risk management measures based on the guidelines for developing risk management measures, taking into account the results of risk assessment conducted by Food Safety Commission of Japan (FSC) (such measures may include the revocation of designation, temporary prohibition of use, narrowed scope of applicable animal species and breeding stages, and strengthened surveillance.)
  - Adequately promote food safety risk assessment for antimicrobial-resistant bacteria; review, as needed, the "Assessment Guideline for the Effect of Food on Human Health regarding Antimicrobial-Resistant Bacteria Selected by Antimicrobial Use in Food Producing Animals", which describes the methods and criteria for the said food safety risk assessment, and the "Ranking of the Importance of Antimicrobials against Bacteria which Affect Human Health through Food Commodities", which is ranking of importance of antibiotics for humans to conduct risk assessment
  - Review, as needed, the guidelines for developing risk management measures concerning veterinary antibiotics and antibiotic feed additives.
- ■ **Establish a veterinary antimicrobial stewardship system**
  - Grasp and analyze the total amount of human antibiotics and antibiotics for animals used in veterinary medicine by "Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)".
  - Implement calculation and international comparisons of the amount of antibiotics for animals per livestock species based on appropriate use unit of antibiotics for animals
  - Establish a system to grasp the actual use of antimicrobials on each farm and utilize it for veterinarian's medication guidance, etc.
- ■ **Strengthen the system for ensuring the prudent use of antibiotics for animals**
  - Among veterinarians and producers, ensure thorough implementation of prudent use in accordance with and gear up guidance as per "Basic Concepts concerning the Prudent Use of Antibiotics for Animals in Livestock Production", "Guidance concerning the Appropriate Use of Aquaculture Drugs", and "Guidebook for the Prudent Use of Antimicrobials for Pets"; and improve contents of promotional and educational tools targeted at veterinarians, producers, and pet owners (brochures, leaflets, etc) to promote the prudent use of veterinary antibiotics
  - Create leaflets concerning the appropriate use of antibiotic feed additives, targeted at producers and feed manufacturers.
  - Establish and strengthen test materials, determination methods and criteria and indices concerning the effectiveness of treatment for antimicrobial susceptibility, as the basis for the prudent use of veterinary antibiotics
  - Strengthen the leadership of experts (e.g. veterinarians, pharmaceutical inspectors, fish epidemic prevention officers) in the use of veterinary antibiotics for farm-raised aquatic animals

## Related Ministries, Agencies and Institutions

Food Safety Commission of Japan (FSC), Cabinet Office (CAO); Ministry of Agriculture, Forestry and Fisheries (MAFF); National Veterinary Assay Laboratory (NVAL); Food and Agricultural Materials Inspection Center (FAMIC); livestock hygiene service centers; fisheries research and laboratory facilities

## Evaluation Indices

- The number of risk management measures that are formulated and/or implemented

# GOAL 5
# PROMOTE RESEARCH ON ANTIMICROBIAL RESISTANCE AND FOSTER RESEARCH AND DEVELOPMENT AND OTHER MEASURES TO SECURE THE MEANS TO PREVENT, DIAGNOSE AND TREAT THE ANTIMICROBIAL-RESISTANT INFECTIONS

## Strategies

(5.1) Promote Research to Elucidate the Mechanism of the Emergence and Transmission of Antimicrobial Resistance and its Socioeconomic Impact

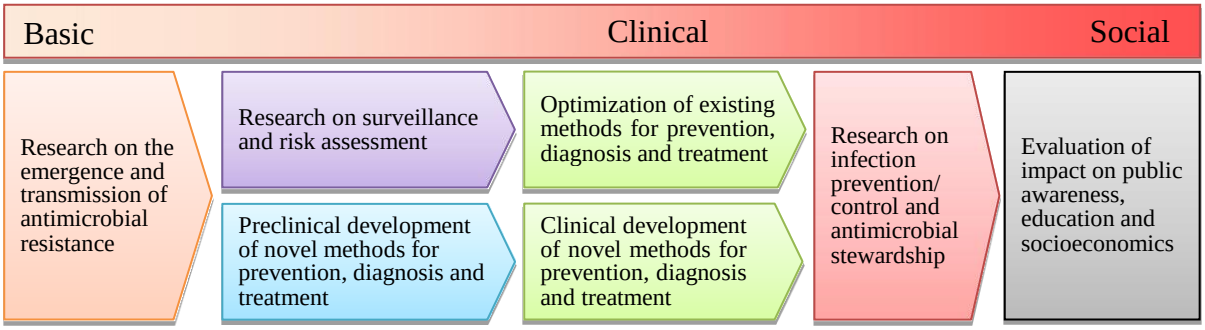
(5.2) Promote Research on Public Awareness/Education on Antimicrobial Resistance, Infection Prevention and Control, and Antimicrobial Stewardship

(5.3) Promote Clinical Research on the Optimization of Existing Methods for Prevention, Diagnosis and Treatment of Infectious Diseases

(5.4) Promote Research and Development of Novel Methods for Prevention, Diagnosis and Treatment and Promote the Cooperation of Industry, Academia and Government

(5.5) Promote Global Research Collaboration on Antimicrobial Resistance and Research and Development of Novel Methods for Prevention, Diagnosis and Treatment of Antimicrobial-resistant Infections

(5.6) Sustainable Research and Development of Antimicrobials and Enhancement of Stable Supply



# STRATEGY 5.1 PROMOTE RESEARCH TO ELUCIDATE THE MECHANISM OF THE EMERGENCE AND TRANSMISSION OF ANTIMICROBIAL RESISTANCE AND ITS SOCIOECONOMIC IMPACT

## BACKGROUND

- To break the transmission chain of antimicrobial resistance (AMR), it is required to accurately elucidate the entire ecosystem of antimicrobial resistance (AMR), specifying the types of organisms that acquire antimicrobial resistance (AMR), the mechanism of acquisition, and the channels and extent of the spread. Activities have been enhanced globally to figure out this entire ecosystem of antimicrobial resistance (AMR).[100]
- It is important to preserve strains isolated from antimicrobial-resistant organisms (AROs) and to accumulate genome data including antimicrobial-resistant genes (ARGs) to promote antimicrobial resistance (AMR)-related research and development (R&D), including the research on antimicrobial resistance (AMR) mechanisms and the development of new methods for prevention, diagnosis and treatment. Identification of epidemiological risk factors leading to the acquisition of antimicrobial resistance (AMR) and their linkage to antimicrobial resistance (AMR) mechanisms is also important to promote effective and implementable antimicrobial resistance (AMR) measures. In Japan, the National Institute of Infectious Diseases established the Japan Antimicrobial Resistant Bacteria Bank (JARBB) in 2019 and is building a cooperative system with overseas partners to collect antimicrobial-resistant strains that are rare in Japan.
- Estimation of the impact of antimicrobial resistance (AMR) on society and economy, including disease burden (e.g. mortality, incidence of complications, prolonged hospitalization) and economic burden (e.g. increased medical expenses, opportunity costs) have been performed in the U.S., Europe and other regions, and based on the data, the review committee on antimicrobial resistance (AMR) in United Kingdom (O'Neill Commission) has estimated that deaths due to antimicrobial resistance (AMR) would reach 10 million worldwide by 2050, and Gross Domestic Product of 1,000 trillion dollars would be lost if no measures will be taken in the future.[101]
- According to the estimates made by Ministry of Health, Labour and Welfare (MHLW) study group using Diagnosis Procedure Combination (DPC) data, hospitalization cost for a methicillin-resistant *Staphylococcus aureus* (MRSA) infection was approximately 3.4 times higher than that for a non-methicillin-resistant *Staphylococcus aureus* (MRSA) infection, hospitalization days approximately 3.0 times longer, and mortality rate 3.7 times higher. Extrapolating these results to all 1,584 hospitals that had introduced the Per-Diem Payment System based on Diagnosis Procedure Combination (DPC/PDPS) in 2014, the disease burden due to methicillin-resistant *Staphylococcus aureus* (MRSA) infections was estimated to increase hospitalization costs by 210 billion yen (3.41% of all impatient medical expenses), increase hospital stays by 4.34 million days (3.02% of all hospitalization days), and increase deaths by 143,000 (3.62% of all deaths).[102] In addition, a study conducted by the same group, with the cooperation of hospitals that have experienced outbreaks of antimicrobial-resistant bacteria in the past, showed that economic losses due to outbreaks can be as high as 69.8 million yen in containment costs and 476 million yen in productivity losses, and that measures including early information disclosure may limit these losses.[103]

[100] D.G. Joakim Larsson & Carl-Fredrik FlachNature Reviews Microbiology 20, 257-269, 2022 (https://www.nature.com/articles/s41579-021-00649-x)

[101] Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. The Review on Antimicrobial Resistance Chaired by Jim O'Neill, December 2014.

[102] Uematsu H, Yamashita K, Kunisawa S, Fushimi K, Imanaka Y. Estimating the disease burden of methicillin-resistant Staphylococcus aureus in Japan: Retrospective database study of Japanese hospitals. PLoS One. 2017;12(6):e0179767. Published 2017 Jun 27. doi:10.1371/journal.pone.0179767 Health and Labour Sciences Research Grants (Research on Emerging and Re-emerging Infectious Diseases and Immunization) 2016, "Assessment of Risks in Health and Economics Caused by Epidemic of Antimicrobial Resistant Organisms".

[103] Morii D, Tomono K, Imanaka Y. Economic impact of antimicrobial-resistant bacteria outbreaks on Japanese hospitals. Am J Infect Control. 2020;48(10):1195-1199. doi:10.1016/j.ajic.2019.12.006 Health, Labour and Welfare Policy Research Grants (Research on Emerging and Re-emerging Infectious Diseases and Immunization) 2019, "Research on Implementation of National Action Plan on Antimicrobial Resistance (AMR)"

## POLICIES

- Promote research to elucidate the emergence and transmission of antimicrobial resistance (AMR) based on the genome analysis
- Promote antimicrobial resistance (AMR) genome surveillance to figure out mechanisms of the emergence and transmission of antimicrobial resistance (AMR) and drug discovery by promoting the preservation of antimicrobial-resistant organism (ARO) strains, and utilizing the pathogen genomics database that contains Japan Antimicrobial Resistant Bacterial Bank (JARBB) and antimicrobial resistance (AMR) provided by the National Institute of Infectious Diseases (NIID).
- In the fields of agriculture and aquaculture, utilize the genome database of antimicrobial resistant bacteria (J-VEG) developed by the National Veterinary Assay Laboratory (NVAL), to contribute to antimicrobial resistance (AMR) measures in collaboration with the antimicrobial resistance (AMR) genome database (GenEpid-J) of the National Institute of Infectious Diseases (NIID) and Japan Antimicrobial Resistant Bacterial Bank (JARBB).
- Conduct research on estimating the impact of Antimicrobial-resistant Infections (ARIs) on health, society and economy and publish the results in plain language to raise awareness.

## ACTIONS

### Promote research on the emergence and transmission of antimicrobial resistance

- Promote research to elucidate the mechanisms of emergence and transmission of antimicrobial resistance (AMR) , the transmission process of antimicrobial-resistant organisms (AROs)/ antimicrobial resistance genes (ARGs), and the ecosystem of antimicrobial-resistant organisms (AROs)/ antimicrobial resistance genes (ARGs) including their spread and interaction in general society and the environment (see Strategy 2.1)
- Promote preservation of isolates in JARBB available to industry, academia, and medicine (see Strategy 2.4 and Strategy 5.4)
- Promote surveillance on pathogen trends using Japan Antimicrobial Resistant Bacterial Bank (JARBB)[104]; elucidate the mechanisms of emergence and transmission of antimicrobial resistance (AMR); promote R&D including drug discovery, etc.; and collect genomic information on isolates in Japan and overseas (Japan Antimicrobial Resistant Bacterial Surveillance (JARBS))
- Promote research on one-health antimicrobial resistance (AMR) surveillance using *E. coli* (tricycle surveillance)[105] in collaboration with the World Health Organization (WHO)
- Promote research to establish and utilize a system to collectively manage strains and clinical information of antimicrobial-resistant organisms (AROs)
- Promote research on the relevance of the process of antimicrobial resistance (AMR) transmission between humans and animals utilizing the genome database (J-VEG)
- Conduct research to elucidate the mechanisms of emergence and transmission of antimicrobial resistance (AMR), and Critical Control Points (CCP) in livestock and aquaculture, and veterinary medicine
- Conduct research on the environmental impact of antimicrobials and antimicrobial-resistant organisms (AROs) in sewage

### Promote research on the health and socioeconomic burdens of antimicrobial resistance

- Promote research on the disease burden[106] and economic burden of antimicrobial-resistant infections (ARIs) at healthcare institutions[107] (see Strategy 2.1)

[104] Antimicrobial resistance (AMR) genome database included
[105] Surveillance targeting *E. coli* producing extended-spectrum beta-lactamases (ESBLs) in humans, animals, and environment based on a multidisciplinary integrated surveillance protocol developed by the World Health Organization (WHO)
[106] Incidence rate, mortality, rate of sequelae, hospitalization days, disease burden indices (e.g. Disability-adjusted life years (DALYs), Years lived with disability (YLD)), etc.
[107] Research is in progress under Health and Labour Sciences Research Grants 2015, "Assessment of Risks in Health and Economics Caused by Epidemic of Antimicrobial Resistant Organisms".

- Promote research concerning the effect of antimicrobial resistance (AMR) measures on the reduction of medical expenses
- Promote research on systematic risk assessment based on surveillance results
- Support utilization of Diagnosis Procedure Combination (DPC) and the National Database for Prescription and National Health Check-up (NDB)

## Related Ministries, Agencies and Institutions

National Healthcare Policy Secretariat, Cabinet Office; Ministry of Education, Culture, Sports, Science and Technology (MEXT); Ministry of Health, Labour and Welfare (MHLW); Ministry of Agriculture, Forestry and Fisheries (MAFF); Ministry of the Environment; NIID; NVAL; National Agriculture and Food Research Organization (NARO); Food and Agricultural Materials Inspection Center (FAMIC); National Center for Global Health and Medicine (NCGM); Japan Agency for Medical Research and Development (AMED)

## Evaluation Indices

- The number of papers funded by national grants in the relevant areas
- The number of genomes accumulated in the genome database

## STRATEGY 5.2 PROMOTE RESEARCH ON PUBLIC AWARENESS/EDUCATION ON ANTIMICROBIAL RESISTANCE, INFECTION PREVENTION AND CONTROL, AND ANTIMICROBIAL STEWARDSHIP

### BACKGROUND

- To implement policies for combating antimicrobial resistance (AMR), it is important not only to accumulate existing scientific evidence and incorporate it into public health measures, but also to create new scientific evidence in Japan, and share it with society and the international community.
- For effective public awareness and education, research on identifying people's knowledge, attitudes and practices concerning antimicrobial use and antimicrobial resistance (AMR), and messages leading to behavior modification is crucial. At home and overseas, research has been undertaken regarding effective campaign methods targeted at people and at healthcare professionals.[108,109]
- Regional cooperation in infection prevention and control (IPC) is one of the areas where Japan is leading, and research is in progress concerning its effectiveness.[110]
- With respect to antimicrobial stewardship (AMS), the total amount of antimicrobial use is relatively small in Japan; however, the proportion of broad-spectrum third-generation oral cephalosporins, fluoroquinolones, and macrolides is high. In addition, according to a survey conducted in 2018 by the Health and Labour Sciences Research Group, while many hospitals have a working infection control team (ICT), the content of its activities varies from hospital to hospital, with only about 70% of hospitals having standards for the number of days or antimicrobial agents administered, and only 60% and 50% having standards for the use of anti-methicillin-resistant *Staphylococcus aureus* (MRSA) drugs and wide-spectrum antibiotics, respectively.[111]
- In the fields of livestock and aquaculture, surveillance and research have been conducted to find indices and scientific evidence required for the appropriate and prudent use of veterinary antibiotics.
- For the effective implementation of antimicrobial resistance (AMR)-related measures, it is required to specify process indicators to identify progress in measures, as well as outcome indices to evaluate effectiveness. It is also necessary to examine the validity of such indices. The Health and Labour Sciences Research Group conducted an international comparison of measures in their study.[112] In the UK, which has experienced significant reductions in the number of bloodstream infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in the past, a number of systematic policy interventions were implemented to combat healthcare-associated infections (HAIs), combining outcome-based incentives and interventions based on the number of healthcare-associated infections (HAIs), and interventions by multidisciplinary hospital infection control teams (ICT). On the other hand, Japan uses voluntary surveillance and focuses on recommendations and persuasive interventions, thus presenting different interventions/appropriate combinations for future consideration.

[108] Gu Y, Fujitomo Y, Soeda H, et al. A nationwide questionnaire survey of clinic doctors on antimicrobial stewardship in Japan. J Infect Chemother. 2020;26(2):149-156. doi:10.1016/j.jiac.2019.12.005

[109] Kamata K, Tokuda Y, Gu Y, Ohmagari N, Yanagihara K. Public knowledge and perception about antimicrobials and antimicrobial resistance in Japan: A national questionnaire survey in 2017. PLoS One. 2018;13(11):e0207017. Published 2018 Nov 5. doi:10.1371/journal.pone.0207017

[110] Research is in progress under Health and Labour Sciences Research Grants (Grants-in-aid for Scientific Research) 2014, "Research concerning Infection Control at Medical Institutions" and under Health and Labour Sciences Research Grants 2013, "Establishment of a Surveillance System for Nationwide Trends in the Use of Antibiotics, and Evaluation of Infection Prevention Premiums".

[111] Shin JH, Mizuno S, Okuno T, et al. Nationwide multicenter questionnaire surveys on countermeasures against antimicrobial resistance and infections in hospitals. BMC Infect Dis. 2021;21(1):234. Published 2021 Feb 27. doi:10.1186/s12879-021-05921-2 Health, Labour and Welfare Policy Research Grants (Research on Emerging and Re-emerging Infectious Diseases and Immunization) 2019, "Research on Implementation of National Action Plan on Antimicrobial Resistance (AMR)"

[112] Mizuno S, Iwami M, Kunisawa S, et al. Comparison of national strategies to reduce meticillin-resistant Staphylococcus aureus infections in Japan and England. J Hosp Infect. 2018;100(3):280-298. doi:10.1016/j.jhin.2018.06.026 Health, Labour and Welfare Policy Research Grants (Research on Emerging and Re-emerging Infectious Diseases and Immunization) 2018, "Research on Implementation of National Action Plan on Antimicrobial Resistance (AMR)"

## POLICIES

- ○ Conduct research on effective intervention methods and benchmarking methods to measure the effectiveness to promote public awareness and education, infection prevention and control (IPC), and antimicrobial stewardship (AMS)

## ACTIONS

- ■ **Research on behavior change**
  - Promote surveys on people's knowledge, attitudes and practices to identify, evaluate and improve the effects of activities aimed at public awareness-raising and education
- ■ **Promote clinical and epidemiologic research concerning antimicrobial stewardship (AMS) and infection prevention and control (IPC) in human medicine**
  - Promote research to evaluate progress in antimicrobial stewardship (AMS) and its effectiveness and cost-effectiveness at medical institutions (see Strategy 4.1)
  - Promote clinical research on the utilization of basic microbiological tests that contributes to antimicrobial stewardship (AMS) (see Strategy 2.4)
  - Review research on the effectiveness of antibiotic prescription regulation for outpatients with acute upper respiratory tract infection (see Strategy 4.1)
  - Review research on the risk of colonization by antimicrobial-resistant organisms (AROs) and the relevant screening methods at medical institutions
  - Review research on the detection status of antimicrobial-resistant bacteria and antimicrobial use at nursing care facilities (see Strategy 3.1)
  - Conduct research to examine the way in which local experts and local governments in outbreak areas should be involved in each healthcare institution in order to effectively prevent healthcare-associated infection (HAI) outbreak cases or prevent their spread, and to study the effectiveness of such involvement (see Strategy 3.3)
  - Conduct research to evaluate the appropriateness of existing evaluation indicators (disinfectant use and compliance rates) for hand hygiene and to develop evaluation indicators for stratification (each medical institution/region/country)
  - Conduct research toward the development of a comprehensive regional collaboration system to provide benchmarking data on infection prevention and control (IPC) and antimicrobial stewardship (AMS), and surveillance information to the Regional Network for Infectious Diseases Prevention and Control (tentative name) (see Strategy 3.1)
  - Conduct research and development (R&D) for assisting tools to support appropriate diagnosis and treatment of infectious diseases in line with antimicrobial stewardship (AMS) policies
  - Conduct research on the isolation rate and molecular epidemiology of antimicrobial resistance (AMR) in home healthcare[113]
  - Conduct research on antimicrobial use (AMU) with pharmacies as a starting point[114]
  - Conduct research on methods for understanding the actual status of antimicrobial-resistant *H. pylori*

[113] Research on the transmission of antimicrobial-resistant organisms (AROs) among patients under home care is in progress under Health and Labour Sciences Research Grants (Grants-in-aid for Scientific Research) 2015, regional medical platform development and promotion project "Isolation Trend and Molecular Epidemiology of Multidrug-resistant Organisms in Patients under Home Care".

[114] Conduct research on the actual status of antibiotic use and information on the status of unused prescription medicines.

- **Research on antimicrobial stewardship (AMS) of antibiotics for animals and infection prevention and control (IPC) in livestock and aquaculture, and veterinary medicine**
  - Promote research for rearing management that does not rely on antimicrobial agents by livestock species, considering changes in the antimicrobial resistance rates following the discontinuation of use of antibiotics for animals, and secondary risks
  - Conduct research to develop rapid and accurate diagnostic methods to ensure appropriate use of antibiotics for animals

## RELATED MINISTRIES, AGENCIES AND INSTITUTIONS

Ministry of Health, Labour and Welfare (MHLW); Ministry of Agriculture, Forestry and Fisheries (MAFF); National Institute of Infectious Diseases (NIID); National Veterinary Assay Laboratory (NVAL); National Agriculture and Food Research Organization (NARO); Food and Agricultural Materials Inspection Center (FAMIC); National Center for Global Health and Medicine (NCGM)

## EVALUATION INDICES

- Progress in research related to the actions described above

## STRATEGY 5.3 PROMOTE CLINICAL RESEARCH ON THE OPTIMIZATION OF EXISTING METHODS FOR PREVENTION, DIAGNOSIS AND TREATMENT OF INFECTIOUS DISEASES

### BACKGROUND

- The issues of drug lag have been discussed due to limited availability of new vaccines, diagnostics and drugs in Japan, which are available overseas.
- In response to these issues with respect to infectious diseases, the Evaluation Committee on Unapproved or Off-labeled Drugs with High Medical Needs has made requests for development to pharmaceutical companies, which have led to the authorization of benzylpenicillin benzathine in 2021, which is used as a first-line drug for syphilis worldwide and has no reported antimicrobial-resistant bacteria in syphilis, in addition to intravenous metronidazole, colistin and other drugs.[115] There are also challenges with the supply of injectable cephazolin by some manufacturers and distributors, and measures are needed to maintain a stable supply of antimicrobials.
- On the other hand, among antimicrobials that are useful against antimicrobial-resistant organisms (AROs) and are used in Japan but not available overseas due to discontinuation of sales or other reasons, there are agents that are not recommended in international guidelines due to insufficient clinical evidence.[116]
- For some antimicrobials, administration and dosage have not been adjusted based on the latest Pharmacokinetics/Pharmacodynamics (PK/PD) to enable appropriate antimicrobial use. There are also drugs that include indications covered by health insurance, which are not globally recommended for specific infectious diseases. For example, guidelines in the U.S. and Europe don't recommend to use third-generation oral cephalosporin antibiotics for patients with *streptococcal pharyngitis*.[117,118]
- Japan's antimicrobial use (AMU) is not high compared to other developed countries. In the AWaRe classification [119] recommended by World Health Organization (WHO), an indicator for antimicrobial stewardship (AMS), World Health Organization (WHO) aims for the ratio of "Access" antibiotics to all antibiotics to be at least 60%. In Japan, however, the percentage tends to be lower than in other countries, and was 21.1% in 2020.[120] Clinical and epidemiologic research toward the optimization of existing methods for prevention, diagnosis and treatment should be promoted to further promote appropriate use.

[115] List of drugs for which companies were invited, or for which requests for development were made, based on the results of evaluation at the Evaluation Committee on Unapproved or Off-labeled Drugs with High Medical Needs, Ministry of Health, Labour and Welfare (MHLW): http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/kaihatsuyousei/; Accessed on 7July 2022.

[116] Nafcillin, ertapenem, nitrofurantoin, cefiderocol, etc.

[117] Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guideline for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America [published correction appears in Clin Infect Dis. 2014 May;58(10):1496. Dosage error in article text]. Clin Infect Dis. 2012;55(10):e86-e102. doi:10.1093/cid/cis629

[118] ESCMID Sore Throat Guideline Group, Pelucchi C, Grigoryan L, et al. Guideline for the management of acute sore throat. Clin Microbiol Infect. 2012;18 Suppl 1:1-28. doi:10.1111/j.1469-0691.2012.03766.x

[119] The AWaRe classification is based on the World Health Organization's (WHO) Model Lists of Essential Medicines, 20th edition, as an indicator of appropriate use of antibiotics. It classifies antibiotics into four categories: "Access" (Antibiotics that should be of high quality, affordable, and widely available in all countries, with low concern for antimicrobial resistance, used as first or second-line drugs for common infections, e.g., ampicillin, cephalexin, etc.), "Watch" (Antibiotics that should only be used for limited diseases or indications due to concerns about antimicrobial resistance, e.g., vancomycin, meropenem, levofloxacin, ceftriaxone, etc.), "Reserve" (Antibiotics that should be used as a last resort when other measures are no longer available, e.g., tigecycline, colistin, daptomycin, etc.), and Unclassified. This classification was revised in 2019 and the new category "non-recommended" (antibiotics that are not recommended for clinical use by the World Health Organization (WHO), e.g., cefoperazone/sulbactam) was added.

[120] Muraki Y, Kitamura M, Maeda Y, et al. Nationwide surveillance of antimicrobial consumption and resistance to Pseudomonas aeruginosa isolates at 203 Japanese hospitals in 2010. Infection. 2013;41(2):415-423. doi:10.1007/s15010-013-0440-0

## POLICIES

○ Implement reviews on existing methods of prevention, diagnosis and treatment of infectious diseases which are available overseas and contribute to containment of antimicrobial resistance (AMR), and promote research on optimizing the indications and usage of antimicrobials to be used in Japan, based on the latest scientific evidence

○ Promote research to accumulate the scientific evidence and apply them to antimicrobial resistance (AMR) control measures

## ACTIONS

■ **Research on the optimization of existing methods for prevention, diagnosis and treatment**

- Conduct research to introduce or re-introduce useful methods for prevention, diagnosis and treatment of infectious diseases for antimicrobial resistance (AMR) control measures, which are available in other countries but not in Japan (either unapproved or withdrawn from the market)
- Promote research on usage regulation to preserve the effectiveness of antimicrobials, which is useful measures for antimicrobial resistance (AMR)
- Conduct research on the treatment of antimicrobial-resistant infections (ARIs) by modification of therapeutics including combination therapy and high-dose therapy
- Conduct research on the development of the Antimicrobial Stewardship System (tentative name) and the utilization of pharmacists (same as Strategy 4.1)
- Implement research on the evaluation of Japan based on the AWaRe classification recommended by the World Health Organization (WHO) as an indicator of antimicrobial stewardship (AMS) and research on actions in antimicrobial stewardship team (AST) and outpatient prescriptions using the AWaRe classification

## RELATED MINISTRIES, AGENCIES AND INSTITUTIONS

Ministry of Health, Labour and Welfare (MHLW); National Institute of Infectious Diseases (NIID); National Center for Global Health and Medicine (NCGM)

## EVALUATION INDICES

- Progress in research related to the actions described above

## STRATEGY 5.4 PROMOTE RESEARCH AND DEVELOPMENT OF NOVEL METHODS FOR PREVENTION, DIAGNOSIS AND TREATMENT AND PROMOTE THE COOPERATION OF INDUSTRY, ACADEMIA AND GOVERNMENT

### BACKGROUND

- Japan has developed many antimicrobials which are used as standard drugs globally. Drugs developed in Japan include meropenem and doripenem, which are carbapenem antibiotics that have been used as the last resort against antimicrobial-resistant organisms (AROs), colistin, one of the few antibiotics that are effective on carbapenem-resistant *Enterobacteriaceae* (CRE), and delamanid, an anti-tuberculous agent that is effective on multidrug-resistant tuberculosis.
- Since 2016, 13 new antimicrobials have been launched in Japan, including 7 antibiotics ,[121] 2 antifungal agents,[122] 2 antiparasitic agents[123], 1 antituberculosis agents,[124] and 1 anti non-tuberculous mycobacterium agents[125]. Of these, lascufloxacin, fosravuconazole, and ceftolozane in ceftolozane/tazobactam were originated in Japan.
- Although it is necessary to further promote the development of new antibiotics, the development of new antimicrobials is subject to antimicrobial stewardship (AMS) regulation to prevent further antimicrobial resistance (AMR), which undermines economic incentives for drug discovery at pharmaceutical companies.
- As detective method, the SMA disc method for detecting metallo-β-lactamase-producing bacteria and the PCR-based ORF Typing (POT) method for molecular epidemiological analysis by polymerase chain reaction (PCR) have been developed in Japan, but they are still few in number.
- In Japan, research and development (R&D) on infectious diseases has been specifically promoted under the Japan Agency for Medical Research and Development (AMED), which was established in April 2015 as per the Act on Promotion of Healthcare Policy (Act No. 48 of May 2014) and the Act on the Independent Administrative Agency of Japan Agency for Medical Research and Development (Act No. 49 of 2014). In Africa and Asia, tuberculosis control is still one of the most important policy issues due to the increase of multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) caused by inadequate tuberculosis treatment and other factors. Under these circumstances, Japan is actively working on the development of drugs for developing countries against malaria, tuberculosis and neglected tropical diseases (NTDs), etc., by utilizing the Global Health Technology Fund (GHIT Fund), which also contributes to the promotion of international cooperation in health and medical care.
- In the field of livestock production, surveillance and research are implemented by universities and private organizations under national projects, concerning determination methods for antimicrobial susceptibility required for the prudent use of veterinary antibiotics.

[121] Lascufloxacin, a new quinolone; relebactam/imipenem/cilastatin, a combination of carbapenem and beta-lactamase inhibitor; ceftolozane/tazobactam, a combination of cephalosporin and beta-lactamase inhibitor; tedizolid, an anti methicillin-resistant *Staphylococcus aureus* ( MRSA) drug; fidaxomicin, an anti-*clostridium difficile* infection (CDI) drug; bezlotoxumab (Monoclonal antibody), which inhibits recurrent *clostridium difficile* infection (CDI); and benzylpenicillin benzathine, a long-acting drug used to treat syphilis.
[122] Fosravuconazole, a novel triazole for the treatment of tinea unguium; Posaconazole, a novel azole for the treatment of deep mycosis
[123] Artemether/lumefantrine, an antimalarial drug; spiramycin, an anti-toxoplasma drug
[124] Bedaquiline for treatment of multidrug-resistant tuberculosis
[125] Inhaled amikacin for non-tuberculous mycobacterium infection

## POLICIES

- ○ Promote research to contribute to the development of novel methods for prevention, diagnosis and treatment against human and veterinarian infectious diseases, including the development of new vaccines and other infection disease preventive methods, rapid diagnostics that contributes to the promotion of antimicrobial stewardship (AMS), antimicrobials with novel mechanisms, and other non-traditional therapeutics
- ○ Enhance the measures taken by the council to promote public private partnership on antimicrobial resistance (AMR) to set R&D priorities and create incentives for R&D, taking into account the frequency of emergence of antimicrobial-resistant organisms(AROs) and needs to obtain medical countermeasures in the shortest period possible

## ACTIONS

### ■ Promote research and development of novel methods for prevention

- Promote the R&D of new vaccines to reduce incidence of zoonosis
- Promote R&D on novel preventive approaches that do not induce the emergence of antimicrobial-resistant organisms (AROs)[126]

### ■ Promote research and development of novel diagnostics

- Promote R&D on rapid and simplified diagnostic tools (including POC) and equipment [127] for identification of causal organisms and antimicrobial resistance (AMR), which contribute to antimicrobial stewardship (AMS) and antimicrobial-resistant organisms (AROs) containment measures
- Develop simplified test methods that contribute to the prudent use of veterinary antibiotics on production sites

### ■ Promote research and development of novel therapeutics

- Further promote R&D of antimicrobials with novel mechanisms that contributes to the treatment of human antimicrobial-resistant infections (ARIs) (see Strategy 5.6)
- Promote R&D of non-conventional therapeutics[128] for infectious diseases that differ from antimicrobials

### ■ Promote cooperation among industry, academia and government

- Strengthen the measures by the 7 Academic Society and the Drug Discovery Promotion Review Committee and the AMED Public and Private Partnerships for Infectious Diseases R&D, and promote drug discovery in the infectious disease field through industry-academia-government collaboration, aimed at the R&D of methods for prevention, diagnosis and treatment of antimicrobial-resistant infections (ARIs), and at promoting research and other activities to elucidate mechanisms of emergence and transmission of antimicrobial resistance (AMR)

### ■ Create incentives for research and development

- Promote harmonization of clinical evaluation methods for the development of antimicrobials among international regulatory authorities, including Japan, the U.S., and the EU (see Strategy 5.5 and Strategy 6.1)
- Promote R&D for methods for prevention, diagnosis and treatment of antimicrobial-resistant tuberculosis, malaria, etc. through Global Health Innovation Technology (GHIT) Fund
- Continue the mechanism for the priority review of drugs for antimicrobial-resistant infections (ARIs) in regulatory approval process (see Strategy 5.6)

[126] E.g. preventive approach in specific clinical conditions, such as the prevention of human infectious diseases related to surgery or chemotherapy
[127] E.g. expedited antimicrobial susceptibility testing, multiplex nucleic acid amplification tests for antimicrobial-resistance genes (ARGs), immune chromatography for antimicrobial resistance gene (ARG) products
[128] E.g. phage therapy, immunotherapy including antibodies, synthesized microbial flora (e.g. synthesized intestinal bacterial flora that simulates the normal intestinal bacterial flora, which is expected as a therapy for *Clostridium difficile* infection), gene therapy

- Continue consultation service for pharmaceutical strategies specialized in drugs for antimicrobial-resistant infections (ARIs) in regulatory approval process
- Support for the development of vaccines, immunostimulants, which contribute to reduce the use of antimicrobials
- Introduce a market incentive mechanism for new antimicrobials under the "Antimicrobial Securement Support Program" (see Strategy 5.6)

## RELATED MINISTRIES, AGENCIES AND INSTITUTIONS

Office for Healthcare Policy, Cabinet Office (CAO); Ministry of Foreign Affairs (MOFA); Ministry of Education, Culture, Sports, Science and Technology (MEXT); Ministry of Health, Labour and Welfare (MHLW); Ministry of Agriculture, Forestry and Fisheries (MAFF); National Institute of Infectious Diseases (NIID); National Veterinary Assay Laboratory (NVAL); National Agriculture and Food Research Organization (NARO), National Center for Global Health and Medicine (NCGM); Japan Agency for Medical Research and Development (AMED)

## EVALUATION INDICES

- Progress in research related to the actions described above

# STRATEGY 5.5 PROMOTE GLOBAL RESEARCH COLLABORATION ON AMR AND RESEARCH AND DEVELOPMENT OF NOVEL METHODS FOR PREVENTION, DIAGNOSIS AND TREATMENT OF ANTIMICROBIAL-RESISTANT INFECTIONS

## BACKGROUND

- Research on antimicrobials as countermeasure to combat against antimicrobial resistance (AMR), antimicrobial resistance (AMR) diagnostic techniques and vaccines to reduce humans and animals that become infected, have been stagnated for many years. Recently, the U.S. and Europe have re-accelerated research and development (R&D) concerning novel methods for prevention, diagnosis and treatment. The "Group of Seven (G7) Finance Ministers' Statement on Actions to Support Antibiotic Development" agreed at the 2021 Group of Seven (G7) Finance Ministers' Meeting commits to take specific and appropriate additional measures to enhance antibiotic research and development with respect to antimicrobial resistance (AMR) and to create appropriate economic conditions to bring new drugs to market.[129] The 2022 Group of Seven (G7) Leaders' Statement also called for enhanced research and innovation in new anti-microbials in international partnerships.
- As is represented by the U.S. Generating Antibiotics Incentives Now (GAIN) Act, R&D of new antimicrobials is in progress around the world. Harmonized R&D activities under international joint research initiatives[130] are important to avoid overlapping or uncoordinated competition.
- The U.S. and Europe have promoted cooperation for new drug development through the Transatlantic Task Force on Antimicrobial Resistance (TATFAR) since 2009, [131] and the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) and the Global Research Collaboration for Infectious Diseases Preparedness (GloPID-R) are promoting international collaboration in antimicrobial resistance (AMR) research. In 2015, Japan Agency for Medical Research and Development (AMED) joined the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) and the Global Research Collaboration for Infectious Diseases Preparedness (GloPID-R),[132 ,133] and is working to promote international collaboration.
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has established common guidelines for Good Clinical Practice (GCP) concerning pharmaceuticals for human use, including antimicrobials. [134] The use of common clinical evaluation requirements in the clinical development process has been desired to promote R&D on a global scale and to expedite the commercialization of the products. As a result of technical discussions between the regulatory authorities in Japan, the U.S., and the EU, no agreement was finally reached on the standardization of the guidelines themselves, taking into account the local characteristics of infectious diseases. Since the outbreak of coronavirus infectious disease, emerged in 2019 (COVID-19), each country has been working to promote collaboration and regulatory harmonization among international regulatory authorities, not only in clinical evaluation methods for antimicrobials, but also in response to infectious disease in general.
- Regarding documents required for application for approval of veterinary medicinal products, such as antibiotic agents, including antimicrobial resistance (AMR)-related documents, the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) has established common tripartite guidelines in Japan, U.S., and the EU.[135 ,136]

[129] Group of Seven (G7) Finance Ministers' Statement on Actions to Support Antibiotic Development
[130] Joint Programming Initiative on Antimicrobial Resistance (JPIAMR); Global Research Collaboration for Infectious Disease Preparedness (GloPID-R)
[131] Transatlantic Task Force on Antimicrobial Resistance, Centers for Disease Prevention and Control, http://www.cdc.gov/drugresistance/tatfar/, accessed on 24 December 2015.
[132] JPIAMR Press Release, Japan joins as newest JPIAMR member, 19 October 2015. http://www.jpiamr.eu/japan-joins-as-newest-jpiamr-member/,accessed on 24 December 2015.
[133] GloPID-R Press Release, New member joins the fight against global epidemics, 4 August 2015. http://www.glopid-r.org/new-member-joins-the-fight-against-global-epidemics/, acceded on December 24, 2015.
[134] Guidelines for Good Clinical Practice E6 (R1), ICH harmonized tripartite guideline – Implemented in June 1996.
[135] Pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance, VICH GL27 (Antimicrobial resistance: pre-approval) - Implemented in December 2004.
[136] Studies to evaluate the safety of residues of veterinary drugs in human food: General approach to establish a microbiological ADI, VICH GL36 (R) (Safety) May 2004 – Implemented in June 2013

## POLICIES

- ○ Contribute to promote R&D on a global scale through contribution to the international research collaboration through participating in the international activities related to antimicrobial resistance (AMR) by AMED and other related institutions and exchanging information
- ○ Work with regulatory authorities in Japan, U.S., the EU and other countries to accelerate the development of new drugs, including harmonization of clinical evaluation methods to promote the development of antimicrobials in cooperation on a global scale

## ACTIONS

### ■ Promote international harmonization of clinical evaluation methods

- Promote harmonization of clinical evaluation methods for development of antimicrobials among international regulatory authorities, including Japan, the U.S., and the EU (see Strategy 5.4 and Strategy 6.1)
- Promote harmonization of documents required for application for approval of veterinary medicinal products, such as antibiotic agents, in the framework of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) including Japan, the U.S. and the EU (see Strategy 6.1)

### ■ Promote international research collaboration

- Continue participation in international activities related to antimicrobial resistance (AMR), including international personnel exchanges of researchers, and utilize the Japan-led ARO Alliance for ASEAN and East Asia (ARISE) platform to contribute to the promotion of research and development related to antimicrobial resistance (AMR)[137]
- Establish a system of collaboration with overseas Public Private Partnership (PPP) scheme, bring promising seeds related to antimicrobial resistance (AMR) to the early clinical stage, and bank therapeutic drug candidates ,to accelerate drug development in the event of outbreaks caused by pathogenic bacteria, etc.,
- Promote bridging between research and policies through international dialogue, including cooperation with foreign national funding organizations such as the U.S. National Institutes of Health (NIH) and the U.K. Medical Research Council (MRC) (see Strategy 6.1)
- Promote four R&D areas 1) surveillance system and laboratory network, 2) health-care management, 3) antimicrobial access and regulation, and 4) research and development, on Asia-Pacific One Health Initiative on AMR (ASPIRE) with Asian countries

## RELATED MINISTRIES, AGENCIES AND INSTITUTIONS

Office for Healthcare Policy, Cabinet Office (CAO); Ministry of Foreign Affairs (MOFA); Ministry of Education, Culture, Sports, Science and Technology (MEXT); Ministry of Health, Labour and Welfare (MHLW); Ministry of Agriculture, Forestry and Fisheries (MAFF); National Institute of Infectious Diseases (NIID); National Veterinary Assay Laboratory (NVAL); Pharmaceuticals and Medical Devices Agency (PMDA); National Center for Global Health and Medicine (NCGM); Japan Agency for Medical Research and Development (AMED)

[137] Research Project on Clinical Research and Clinical Trial Promotion, Enhancement of the involvement of International ARO Alliance with Asian and Japanese academic institutions and establishment of a network of cooperation with relevant organizations to respond to infectious disease emergencies. Haruhito SUGIYAMA, Hospital Director, Center Hospital of the National Center for Global Health and Medicine

## EVALUATION INDICES

- Creation of joint documents among international regulatory authorities including Japan, the U.S., and the EU that outlines regulatory measures that contribute to the development of antimicrobials
- Creation of internationally harmonized guidelines on the studies required for application for the approval of veterinary pharmaceuticals, such as antibiotic agents

## STRATEGY 5.6 SUSTAINABLE RESEARCH AND DEVELOPMENT OF ANTIMICROBIALS AND ENHANCEMENT OF STABLE SUPPLY

### BACKGROUND

- Japan has developed many antimicrobials which are used as standard drugs globally. Drugs developed in Japan include meropenem and doripenem, which are carbapenem antibiotics that have been used as the last resort against antimicrobial-resistant organisms (AROs), colistin, one of the few antibiotics that are effective on carbapenem-resistant Enterobacteriaceae (CRE), and delamanid, an anti-tuberculous agent that is effective on multidrug-resistant tuberculosis.
- Research on antimicrobials, a weapon in the combat against antimicrobial resistance (AMR), has been stagnant for many years, and in recent years, international efforts have been made to re-accelerate research and development on novel methods for prevention, diagnosis and treatment.
- In 2020, the "AMR Action Fund" was established to launch four new antimicrobials by 2030, funded by more than 20 pharmaceutical companies worldwide, with support and backing from outside the pharmaceutical industry, including the World Health Organization (WHO) and the European Investment Bank.[138]
- In the research project for the development promotion of novel antimicrobials for emerging and re-emerging infectious diseases, epidemiological surveys, basic research and development of basic technologies on antimicrobial-resistant bacteria are promoted to strengthen measures against infectious diseases, while promoting integrated research and development of drugs, including diagnostic drugs, therapeutic drugs and vaccines. In addition, research and development of antimicrobial agents are also supported in the Cyclic Innovation for Clinical Empowerment (CiCLE).
- For the continuous development of new antimicrobials, it is important to create an attractive investment environment and build an environment in which new antimicrobials are continuously launched, in addition to public research fund support for R&D (so-called "push incentives"), and market incentives (so-called "pull incentives")[139] are required to motivate companies to pursue R&D by increasing the predictability of profits after launch. The international community also discussed antimicrobial incentives at the Group of Seven (G7) Finance Ministers' Meeting in 2021, including consideration of a wide range of options with particular emphasis on supporting relevant market incentives, and the Group of Seven (G7) Leaders' Statement in 2022 also called for the encouragement of the development of new antimicrobials with particular emphasis on market incentives. Market incentives are being introduced or considered in the United States,[140] United Kingdom,[141] Sweden,[142] and other countries. In the Group of Seven (G7) process, the Group of Seven (G7) countries are expected to promote research and development of new antibiotics and international cooperation, and to play a leading role in international actions.
- In addition, supply shortages of antibiotics are occurring around the world, and Japan is also experiencing large-scale supply shortages of antibiotic, including challenges with the supply of injectable cephazolin in 2019. Stable supply of antibiotics is an important issue to promote antimicrobial stewardship (AMS) and to control further spread of antimicrobial resistance (AMR), and measures to maintain stable supply of antimicrobials are required in addition to promote research and development of new antibiotics.

[138] AMR Action Fund https://www.amractionfund.com/ja/ ,accessed on 4 July 2022.
[139] In contrast to push incentives, which are incentives directly related to R&D, such as research support subsidies and tax benefits for R&D expenditures, pull incentives are incentives that motivate the promotion of R&D, such as preferential post-market drug prices, pre-screening of drug prices, guaranteed purchase of new drugs, market entry incentives, preferential exclusivity period and permission for transfer of exclusivity period to other products.
[140] The U.S. Generating Antibiotic Incentives Now Act (GAIN Act) includes the priority review process for new antimicrobial candidates, patent term extension, etc. In June 2021, the PASTEUR Act was resubmitted in Congress as a bill.
[141] Mark Perkins, David Glover, "Mark Perkins and David Glover Medicine," https://www.england.nhs.uk/blog/how-the-nhs-model-to-tackle-antimicrobial-resistance-amr-can-set-a-global-standard/,accessed on 4 July 2022.
[142] Public Health Agency of Sweden, "Availability of antibiotics," 1 December 2020, https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/communicable-disease-control/antibiotics-and-antimicrobial-resistance/availability-of-antibiotics/,accessed on 4 July 2022.

## POLICIES

- ○ Explore concrete methodologies to secure therapeutic drugs for antimicrobial-resistant bacteria, such as market incentives, and introduce them
- ○ Promote maintenance of a stable supply of antimicrobials

## ACTIONS

- ■ **Promote research and development of new antimicrobials**
  - Promote R&D of antimicrobials with novel mechanisms that contribute to the treatment of human antimicrobial-resistant infections (ARIs) (see Strategy 5.4)
- ■ **Pilot introduction of a market incentive mechanism in the antimicrobial market**
  - Introduce a market incentive mechanism for new antimicrobials under the "Antimicrobial Securement Support Program" (see Strategy 5.4)
  - Continue the mechanism for the priority review system of drugs for antimicrobial-resistant infections (ARIs) in regulatory approval process (see Strategy 5.4)
- ■ **Strengthen stable supply of antimicrobials by promoting domestic production of raw materials, etc.**
  - Implement "Pharmaceutical Stable Supply Support Program" to strengthen the supply chain of antimicrobials and other pharmaceuticals that are highly dependent on overseas suppliers of active pharmaceutical ingredients, etc., and to develop a stable supply system in Japan

## RELATED MINISTRIES, AGENCIES AND INSTITUTIONS

Ministry of Health, Labour and Welfare (MHLW); Pharmaceuticals and Medical Devices Agency (PMDA); National Center for Global Health and Medicine (NCGM); Japan Agency for Medical Research and Development (AMED)

## EVALUATION INDICES

- The number of new antimicrobials developed, and the number of those approved

# GOAL 6
# ENHANCE GLOBAL MULTIDISCIPLINARY COUNTERMEASURES AGAINST ANTIMICROBIAL RESISTANCE

## Strategies

(6.1) Strengthen Japan's Leadership for Global Policies on Antimicrobial Resistance

(6.2) Promote International Cooperation to Achieve the Global Action Plan on Antimicrobial Resistance

# STRATEGY 6.1 STRENGTHEN JAPAN'S LEADERSHIP FOR GLOBAL POLICIES ON ANTIMICROBIAL RESISTANCE

## BACKGROUND

- Antimicrobial resistance (AMR) is considered as a global health security threat and has been discussed at the World Health Organization (WHO) and the Group of Seven (G7) process. It remains one of the most important health issues.[143]
- In Japan, antimicrobial resistance (AMR) control measures have been promoted in the fields of medicine, livestock and aquaculture for many years, and antimicrobial resistance (AMR) surveillance systems have been established. Antimicrobial use has also been at a lower level than the average of Organisation for Economic Co-operation and Development (OECD).[144] Thus, Japan should play a leading role in AMR control measures in the world, particularly in the Asia-Pacific region. The "Asia-Pacific One Health Initiative on AMR (ASPIRE)" was established in 2016 to promote the One Health approach in Asia-Pacific countries.
- Japan should also make international contribution as a Leading Country of Antimicrobial Resistance (AMR) Action Package of the Global Health Security Agenda (GHSA), a multilateral initiative aimed at strengthening the implementation of World Health Organization's (WHO) International Health Regulation (IHR), for the purpose of enhancing capacities on infectious diseases in each country. The AMR Clinical Reference Center (AMRCRC) and the Antimicrobial Resistance (AMR) Research Center are both designated as World Health Organization (WHO) collaborating centers and conduct international activities for antimicrobial stewardship (AMS) and countermeasures against antimicrobial resistance (AMR).
- In the fields of livestock and aquaculture, the Ministry of Agriculture, Forestry and Fisheries (MAFF) has made contribution by participating in related meetings and proactively providing inputs in the process of formulating international standards of the World Organisation for Animal Health (WOAH), the Code of Practice and Guidelines of the Codex Alimentarius Commission, and Food and Agricultural Organization of the United Nations.
- In the ongoing initiative by the World Organisation for Animal Health (WOAH) to establish a database of antibiotics for animals, Japanese experts have participated in the relevant meetings to provide data and advice.
- In the environmental area, antimicrobial resistance (AMR) was identified as one of the six areas of concern in the United Nations Environment Programme's Frontiers Report released at the third session of the United Nations Environment Assembly, and the United Nations Environment Programme (UNEP), in cooperation with the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), and the World Organisation for Animal Health (WOAH), has been working on a "Quadripartite"[145] initiative. Japan closely monitors the United Nations Environment Programme's (UNEP) activities.

## POLICIES

- Support global antimicrobial resistance (AMR) control measures by World Health Organization (WHO) both at a high level and at a grass root level, particularly in the Asia-Pacific region, and take actions to support implementation of the Global Action Plan on Antimicrobial Resistance (AMR) through the Antimicrobial Resistance (AMR) Action Package of the Global Health Security Agenda (GHSA)
- Promote research, development, and international cooperation and play a leading role in international actions with the aim of strengthening commitment to antimicrobial resistance (AMR) in the Group of Seven (G7) process, including the 2023 Group of Seven (G7) Hiroshima Summit, the Group of Seven (G7) Nagasaki Health Ministers' Meeting, and the Group of Seven (G7) Miyazaki Agriculture Ministers' Meeting.

[143] Abe S. Japan's vision for a peaceful and healthier world. Lancet. 2015;386(10011):2367-2369. doi:10.1016/S0140-6736(15)01172-1

[144] Muraki Y, Kitamura M, Maeda Y, et al. Nationwide surveillance of antimicrobial consumption and resistance to Pseudomonas aeruginosa isolates at 203 Japanese hospitals in 2010. Infection. 2013;41(2):415-423. doi:10.1007/s15010-013-0440-0

[145] Partnership between the following four organizations: World Health Organization(WHO), Food and Agriculture Organization (FAO), World Organisation for Animal Health (WOAH) and United Nations Environment Programme (UNEP)

○ Support to strengthen international initiatives on antimicrobial resistance (AMR), including the formulation and revision of international standards and the establishment of a database by the World Organisation for Animal Health (WOAH), and contribute to international measures related to antimicrobial resistance (AMR) under the Codex Alimentarius Commission, by participating in the process for revising the relevant standards

## ACTIONS

### ■ Promote global policies on antimicrobial resistance (AMR)

- Support efforts of World Health Organization (WHO) against antimicrobial resistance (AMR)
  - ✓ Share information among stakeholders in Asian countries and international organizations, promote antimicrobial resistance (AMR) control measures in each country by holding the annual Tokyo AMR One-Health Conference continuously
- Further promote efforts in antimicrobial resistance (AMR) measures in Group of Seven (G7) process
  - ✓ In the Group of Seven (G7) process, and promote research and development that contributes to combating antimicrobial resistance (AMR), and play a leading role in international actions including strengthening efforts related to antimicrobial resistance (AMR) and the introduction of new market incentives for the development of antimicrobials
- Support efforts against antimicrobial resistance (AMR) by FAO and World Organisation for Animal Health (WOAH)
  - ✓ Continue to support efforts to create and revise the FAO guideline and international standards of the World Organisation for Animal Health (WOAH) on antimicrobial resistance (AMR), and to create a database for monitoring the use of antibiotics for animals
- Contribute to efforts of the Codex Alimentarius Commission on antimicrobial resistance (AMR)
  - ✓ Contribute by participating in the efforts to revise the Code of Practice and Guidelines of the Codex Alimentarius Commission on antimicrobial resistance (AMR)
- Promote efforts as a Leading Country of the Antimicrobial Resistance (AMR) Action Package of Global Health Security Agenda (GHSA)
- Promote international cooperation through multilateral dialogue, including cooperation with foreign national funding organizations such as the U.S. National Institutes of Health (NIH) and the U.K. Medical Research Council (MRC) (see Strategy 5.5)
- Promote harmonization of clinical evaluation methods for the development of anti-microbial agents among international regulatory authorities, including Japan, the U.S., and the EU. (see Strategy 5.5)
- Contribute through participation in the work to develop and revise the global common study guidelines required for the approval of veterinary antibiotics in the framework of the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), including Japan, the U.S., and the EU (see Strategy 5.5)
- Contribute to the efforts to combat antimicrobial resistance (AMR) by monitoring closely the moves of the United Nations Environment Programme (UNEP)

## RELATED MINISTRIES, AGENCIES AND INSTITUTIONS

Office for COVID-19 and Other Emerging Infectious Disease Control, Cabinet Secretariat; National Healthcare Policy Secretariat, Cabinet Office; Ministry of Foreign Affairs (MOFA); Ministry of Agriculture, Forestry and Fisheries (MAFF); Ministry of the Environment; National Institute of Infectious Diseases (NIID); National Veterinary Assay Laboratory (NVAL); Pharmaceuticals and Medical Devices Agency (PMDA); Food and Agricultural Materials Inspection Center (FAMIC); National Center for Global Health and Medicine (NCGM); Japan Agency for Medical Research and Development (AMED)

## EVALUATION INDICES

- Progress in each action
- Countries participating in the relevant meetings
- Group of Seven (G7) Progress Report, Commitment 13 (AMR) Indicators
- Progress in the attainment of the Global Health Security Agenda (GHSA) Antimicrobial Resistance (AMR) Action Package targets

# STRATEGY 6.2 PROMOTE INTERNATIONAL COOPERATION TO ACHIEVE THE GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE

## BACKGROUND

- The Global Action Plan on Antimicrobial Resistance (AMR) by the World Health Organization (WHO) calls for donor countries to support to achieve the Global Action Plan, particularly with regard to surveillance, ensuring the availability of antimicrobials with measures to ensure their efficacy, and new methods for prevention, diagnosis and treatment.[146]
- At the 2016 Tokyo Meeting of Health Ministers on Antimicrobial Resistance in Asia, the Asia-Pacific One Health Initiative on AMR (ASPIRE) was adopted to collaboratively confront the issue of antimicrobial resistance (AMR) in the Asia-Pacific region and draw a roadmap to achieve regional antimicrobial resistance (AMR) control measures. Asia-Pacific One Health Initiative on AMR (ASPIRE) identified four priority areas: 1) surveillance system and laboratory network, 2) health-care management, 3) antimicrobial access and regulation, and 4) research and development. This was followed by the Kobe Communiqué of the Group of Seven (G7) Health Ministers and the Political Declaration on Antimicrobial Resistance (AMR) at the High-Level Meeting of the 71st session of the United Nations General Assembly. In response to these developments, the Tokyo Antimicrobial Resistance (AMR) One Health Conference was held in 2017, where the promotion of the Global Action Plan to combat antimicrobial resistance (AMR) in Asia was discussed and a summary of the results was presented. The 2019 Tokyo Antimicrobial Resistance (AMR) One Health Conference was co-hosted by the Ministry of Health, Labour and Welfare (MHLW) and the World Health Organization Western Pacific Regional Office (WPRO), and the Asia-Pacific One Health Initiative on AMR (ASPIRE) Coordinating Committee was formed to advance the four priority issues (pillars). At the 2021 Tokyo Antimicrobial Resistance (AMR) One Health Conference, led by the chair, the current status of the four priority issues (pillars) and future activities were discussed under the Asia-Pacific One Health Initiative on AMR (ASPIRE) Coordinating Committee.
- 2021 World Health Organization (WHO) accredited the National Center for Global Health and Medicine AMR Clinical Reference Center (AMRCRC) as a "World Health Organization (WHO) Collaborating Center for prevention, preparedness and response to Antimicrobial Resistance" and the Antimicrobial Resistance Research Center at the National Institute of Infectious Diseases as a "World Health Organization (WHO) Collaborating Center for Antimicrobial Resistance (AMR) surveillance and research".
- Japan has a long history of R&D on antimicrobials and control of infectious diseases, as well as a history of promoting pharmaceutical quality control, high-quality surveillance, and clinical infection prevention and control (IPC). Through Japan International Cooperation Agency (JICA), Japan has undertaken cooperation in infection prevention and control (IPC) and the capacity building with a particular focus on countermeasures against healthcare-associated infections (HAIs). From these viewpoints, Japan is able to provide support for antimicrobial resistance (AMR) measures in a broad range.
- Japan has also undertaken international cooperation concerning antimicrobial resistance (AMR) in the framework of the Research on Emerging and Re-emerging Infectious Diseases and Immunization handled by the Ministry of Health, Labour and Welfare (MHLW).
- In the fields of livestock and aquaculture, Japan has cooperated in training held by the World Organisation for Animal Health (WOAH) and Food and Agricultural Organization of the United Nations (FAO), and dispatched experts in antimicrobial-resistant organisms to seminars requested by individual countries, among other cooperative efforts.

## POLICIES

- Promote international cooperation in antimicrobial resistance (AMR) with a focus on the Asia-Pacific region, through further collaboration among related agencies and institutions, research institutes, business enterprises and other entities

[146] Global Action Plan on Antimicrobial Resistance, World Health Organization 2015, ISBN 978 92 4 150976 3.

## ACTIONS

### ■ International cooperation in public health

- Promote international cooperation for AMR measures in the Japan Agency for Medical Research and Development (AMED) and the National Institute of Infectious Diseases (NIID) by:
  - ✓ Strengthening the surveillance function by utilizing a Japan's online surveillance platform[147]
  - ✓ Implementing the capacity-building of laboratories for AMR examinations, coupled with the strengthening surveillance
  - ✓ Developing new pharmaceutical seeds for prevention, diagnosis and treatment through AMR genome database
  - ✓ Contributing to surveillance activities for antimicrobial-resistant (AMR) *Mycobacterium leprae* in the Asia-Pacific region
- Promote the efforts of the Antimicrobial Resistance (AMR) Research Center at the National Institute of Infectious Diseases and the National Center for Global Health and Medicine (NCGM) AMR Clinical Reference Center (AMRCRC) as a World Health Organization (WHO) Collaborating Center
  - ✓ Supporting the World Health Organization (WHO) actions in the Western Pacific region by raising awareness of antimicrobial stewardship (AST), infection prevention, surveillance, and antimicrobial resistance (AMR) in each country, as well as responding to outbreaks of antimicrobial-resistant organisms (AROs)
  - ✓ Strengthen implementation of the following measures in the Western Pacific region
- Strengthen the AMR surveillance in each country by utilizing WHONET[148] and the overseas version of the "Japan Nosocomial Infections Surveillance (JANIS)" (ASIARS-Net)
- Enhance capacity for testing for antimicrobial-resistant organisms (AROs)
- Technical assistance for countries participating in the One Health Antimicrobial Resistance (AMR) Surveillance (tricycle surveillance) using *E. coli* in collaboration with the World Health Organization (WHO)
- Support pathogen analysis of antimicrobial resistance (AMR) outbreaks by utilizing Whole genome sequencing (WGS)
- Develop guidance document for Antimicrobial resistance (AMR) surveillance and outbreak response
- Support for revision of the Global AMR Surveillance System (GLASS)
- Promote infection prevention and control (IPC) activities, promote access to antimicrobials and their appropriate use to preserve their effectiveness, and enhance laboratory functions through the JICA technical cooperation
- Promote international cooperation for elimination of antimicrobial resistant tuberculosis utilizing new methods for diagnosis and treatment for antimicrobial resistant tuberculosis developed in Japan and approved by World Health Organization (WHO)

### ■ International cooperation in animal health

- Support the promotion of international cooperation by international organisations such as Food and Agricultural Organisation (FAO) and the World Organisation for Animal Health (WOAH) concerning AMR control measures, particularly in the Asian region

[147] E.g. Japan Nosocomial Infections Surveillance (JANIS), Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM), antimicrobial resistance (AMR) genome database (GenEpid-J)

[148] Microbiology laboratory database software that was developed by World Health Organization (WHO) Collaborating Center for Antimicrobial Resistance Surveillance in Brigham and Women's Hospital, Boston, U.S., and has been used in 130 countries worldwide

- In collaboration with the World Organisation for Animal Health (WOAH), promote international cooperation concerning surveillance and monitoring, utilizing the World Organisation for Animal Health (WOAH) collaborating center function in the National Veterinary Assay Laboratory (NVAL), as well as the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) Outreach Forum

## RELATED MINISTRIES, AGENCIES AND INSTITUTIONS

National Healthcare Policy Secretariat, Cabinet Office; Ministry of Foreign Affairs (MOFA); Ministry of Health, Labour and Welfare (MHLW); Ministry of Agriculture, Forestry and Fisheries (MAFF); NIID; NVAL; JICA; National Agriculture and Food Research Organization (NARO); National Center for Global Health and Medicine (NCGM); AMED

## EVALUATION INDICES

- The number of seminars held and the number of participating countries
- The number of countries with which Japan has cooperated in the development and implementation of national action plans on antimicrobial resistance (AMR)

# OUTCOME INDICES FOR THE ACTION PLAN

The following outcome indices are specified for National Action Plan on AMR (2023-2027).

## HUMAN-RELATED INDICES

1. Maintain the number[149] of patients with vancomycin-resistant *Enterococci* (VRE) infections in 2027 at 80 or less (the level as of 2019)
2. Lower the methicillin resistance[150] of *Staphylococcus aureus* to 20% or less by 2027
3. Maintain the fluoroquinolone resistance[151] of *E. coli* at 30% or less in 2027.
4. Lower the carbapenem (MEPM=R) resistance[152] of *Pseudomonas aeruginosa* to 3% or less by 2027.
5. Maintain a carbapenem resistance[153] of *E. coli* and *Klebsiella pneumoniae* at 0.2% or less in 2027

* The antimicrobial resistance rate projection chart is based on Japan Nosocomial Infections Surveillance (JANIS) data from 2011 to 2021, and the numbers of future detections were predicted by Poisson regression for antimicrobial-susceptible and resistant bacteria, respectively, based on the data of target bacteria detected in the samples (blood, urine, and respiratory tract) for the antimicrobial-resistant bacteria subject to this outcome measure. The antimicrobial resistance rates were calculated using the total number of bacteria detected in each year as the denominator and the number of antimicrobial-resistant bacteria as the numerator. The impact of seasonality, antimicrobial consumption, and Corona virus infectious disease, emerged in 2019 (COVID-19) from 2011 were included as variables in the projection, and the figures were calculated up to 2027. Note that the results should be considered as reference values with uncertainty, since the projection is for a long period of time, from 2022 to 2027. The antimicrobial resistance rates were calculated individually from published Japan Nosocomial Infections Surveillance (JANIS) data quarterly.

[149] Vancomycin-resistant *Enterococci* infections are one of the most serious antimicrobial resistance threats, currently expanding worldwide due to the paucity of therapeutic options available. It is a antimicrobial resistant organism for which horizontal transmission in hospitals and elderly care facilities should be controlled, and the actual number of infections is a new additional indicator of infection control during normal times (notifiable disease surveillance). It can spread across hospitals and within a community and can also serve as an indicator for evaluating local infection control collaboration. The goal is to prevent the spread of the disease in the community and maintain the current low number of infections

[150] The methicillin resistance rate of *Staphylococcus aureus* is about 50% in 2020, which is high compared to other developed countries. Since bloodstream infections contribute significantly to the disease burden and with the intention of excluding the effects of bacterial carriage, blood specimens shall be used as indicators. Based on data from 2011 to 2021, the estimated rate in 2027 is 32%, considering the impact of seasonality, antimicrobial consumption, and Corona virus infectious disease, emerged in 2019 (COVID-19) and the measured rate of 35.9% in 2020. The target is set at 20%, considering that the promotion of infection prevention and control (IPC) to be implemented in this national action plan will accelerate the rate by 1.4% annually.

[151] The fluoroquinolone resistance rate of *E. coli* is highly correlated with fluoroquinolone usage. Since it is more difficult to treat than non-resistant bacteria and accounts for a large proportion of deaths in Japan, we will continue to use it as an indicator. The indicator is based on urinary specimens, as it targets urinary tract infections in the outpatient setting, in which antimicrobial-resistant bacteria are directly linked to the treatment. Based on data from 2011 to 2021, the estimated rate in 2027 is 42%, considering the impact of seasonality, antimicrobial consumption, and Corona virus infectious disease, emerged in 2019 (COVID-19), and the measured rate of 35.0% in 2020. The target is set at 30%, considering that the promotion of antimicrobial stewardship (AMS) and thorough infection prevention and control (IPC) for urinary catheter infections to be implemented in this national action plan will accelerate the rate by 2.4% annually.

[152] The carbapenem resistance rate of *Pseudomonas aeruginosa* is 11.0% as of 2020, a figure that is not high as compared to other countries. Bloodstream infections are used as an index using blood samples with the intention of excluding the effects of bloodstream infections that contribute significantly to the disease burden and the effects of bacterial carriage. Based on data from 2011 to 2021, the estimated rate in 2027 is 6%, considering the impact of seasonality, antimicrobial consumption, and Corona virus infectious disease, emerged in 2019 (COVID-19), and the measured rate of 7.1% in 2020. The target is set at 3%, considering that the promotion of infection prevention and control (IPC) to be implemented in this national action plan will accelerate the rate by 0.6% annually.

[153] Carbapenem-resistant *Enterobacteriaceae* (CRE) infections are a growing and serious antimicrobial resistance threat worldwide due to the paucity of therapeutic options. Fortunately, the carbapenem resistance rates of *Escherichia coli* and *Klebsiella pneumoniae* in Japan are extremely low at 0.1% and 0.2%, respectively, as of 2020. Therefore, appropriate antimicrobial resistance measures should be taken to maintain the antimicrobial resistance rates at the same level.

6. Reduce antimicrobial use[154] per day per 1,000 inhabitants by 15% from 2020 levels by 2027
7. Reduce the use[155] of oral third generation cephalosporins, oral fluoroquinolones, and oral macrolides per day per 1,000 inhabitants by 40%, 30%, and 25%, respectively, from 2020 levels by 2027.
8. Reduce the use[156] of intravenous carbapenems per day per 1,000 inhabitants by 20% from 2020 levels by 2027.

**Supplemental** Antimicrobial use targets will improve patient outcomes through appropriate antimicrobial use and minimize the impact of antimicrobial resistance by reducing unnecessary antimicrobial use.

* The antimicrobial use projection chart calculates daily use per 1,000 population based on National Database for Prescription and National Health Check-up (NDB) data from 2013 to 2019 and used Poisson regression to project future antimicrobial use. Only the impact of the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020) was entered as a variable when forecasting, and figures were calculated up to 2027. Since this is a long-term forecast from 2021 to 2027, the results should be considered as a reference value with uncertainty.

[154] The daily antimicrobial use in Japan in 2020 is estimated to be 10.4 per 1,000 people, which is relatively low compared to Europe (Figure 1). The daily antimicrobial use per 1,000 population is 13.1 DID in 2019 and 10.4 DID in 2020.Based on data from 2013 to 2019 and considering the impact of the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020), the projected value for 2027 is 9.0 DID. The target is set at a 15% decrease (8.85 DID), considering that the promotion of antimicrobial stewardship (AMS) for upper respiratory tract infection in this National Action Plan will further accelerate the rate by 0.3% annually starting in 2020.

[155] The daily use of oral third-generation cephalosporins per 1,000 population is 2.72 DID in 2019 and 1.93 DID in 2020. The projected value for 2027 is 1.24 DID based on data from 2013 to 2019, considering the impact of the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020). The target is set at 40% reduction (1.16 DID) considering that the promotion of antimicrobial stewardship (AMS) for upper respiratory tract infection in this National Action Plan will further accelerate the rate by 0.8% annually starting in 2020.

The daily use of oral fluoroquinolones per 1,000 population is 2.46 DID in 2019 and 1.76 DID in 2020. The projected value for 2027 is 1.32 DID based on data from 2013 to 2019 and considering the impact of implementation of the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020). The target is set at 30% reduction (1.23 DID), considering that the promotion of antimicrobial stewardship (AMS) for upper respiratory tract infection in this National Action Plan will accelerate the rate by 1% annually from 2020.

The daily use of oral macrolides per 1,000 population is 4.37 DID in 2019 and 3.30 DID in 2020. The projected value for 2027 is 2.49 DID based on data from 2013 to 2019, considering the impact of implementation of the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020). The target is set at 2.48 DID (25% reduction), considering that the promotion of antimicrobial stewardship (AMS) for upper respiratory tract infection in this National Action Plan will further accelerate the rate by 0.1% annually starting in 2020.

[156] The daily use of intravenous carbapenem antibiotics per 1,000 population is 0.063 DID in 2019 and 0.058 DID in 2020. The projected value for 2027 is 0.05 DID based on data from 2013 to 2019, considering the impact of implementation of the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020). The target is set at 20% reduction (0.046 DID), considering that the promotion of antimicrobial stewardship (AMS) for upper respiratory tract infection in this National Action Plan will further accelerate the rate by 1.5% annually starting in 2020.

## ANIMAL-RELATED INDICES

1. Lower the tetracycline resistance[157] of *E. coli* to 20% or less in cattle, 50% or less in swine, and 45% or less in chickens by 2027
2. Lower the third-generation cephalosporin resistance[158] of *E. coli* to 1% or less in cattle, 1% or less in swine, and 5% or less in chickens by 2027.
3. Lower the fluoroquinolone resistance[159] of *E. coli* to 1% or less in cattle, 2% or less in swine, and 15% or less in chickens by 2027.
4. Reduce the total use[160] of veterinary antibiotics in the livestock field by 15% from 2020 levels by 2027.
5. Reduce total use [161] of second-line drugs (third-generation cephalosporins, 15-membered macrolides (tulathromycin and gamithromycin), fluoroquinolones, and colistin) in the livestock field to 27 t or less in 2027.

[157] Since tetracycline is the most commonly used antimicrobial in livestock, it has been established since the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020) was formulated as it reflects the use of antimicrobial agents in livestock. In this National Action Plan, it will continue to be set from the perspective of continuity. In addition, the antimicrobial resistance status and sanitary management differ by livestock species, and this National Action Plan sets targets by livestock species in order to use them as indicators of the results of addressing the issues. The target values are calculated by using a single regression line to calculate trend values from 2021 to 2027 based on the values from 2012, when timber harvesting at slaughterhouses and poultry slaughterhouses began, to 2020. In the case of an upward trend toward 2027, the minimum value obtained between 2016 and 2020 is used as a reference (if the value is 0%, the average of the values from 2016 to 2020 is used), and in the case of a downward trend, the trend value in 2027 is used as a reference.

[158] 3rd-generation cephalosporins are important antimicrobial agents in human medicine and are used as second-line agents in livestock. For this reason, it has been established as one that needs to be monitored in livestock since the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020) was formulated. Although the target set in the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020) (to maintain the same level as the Group of Seven (G7) countries) has been achieved, it will continue to be set from the perspective of continuity. In addition, the antimicrobial resistance status and sanitary management differ by livestock species, and this National Action Plan sets targets by livestock species in order to use them as indicators of the success in addressing the issues. The target values are calculated by using a single regression line for the trend values from 2012, when timber harvesting at slaughterhouses and poultry slaughterhouses began, to 2027. In the case of an upward trend toward 2027, the minimum value obtained between 2016 and 2020 is used as a reference (if the value is 0%, the average of the values from 2016 to 2020 is used), and in the case of a downward trend, half of the trend value in 2027 is used as a reference.

[159] Fluoroquinolones are important antimicrobial agents in human medicine and are used as second-line drugs in livestock. For this reason, it has been established as one that needs to be monitored in livestock since the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020) was formulated. Although the target set in the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020) (to maintain the same level as the Group of Seven (G7) countries) has been achieved, it will continue to be set from the perspective of continuity. In addition, the antimicrobial resistance status and sanitary management differ by livestock species, and this National Action Plan sets targets by livestock species in order to use them as indicators of the success in addressing the issues. The target values are calculated by a single regression line for the trend values from 2012, when timber harvesting at slaughterhouses and poultry slaughterhouses started, to 2027. In the case of an upward trend toward 2027, the minimum value obtained between 2016 and 2020 is used as a reference (if the value is 0%, the average of the values from 2016 to 2020 is used), and in the case of a downward or flat trend, half of the trend value in 2027 is used as a reference.

[160] Antimicrobial agents are not set in the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020) from the perspective that antimicrobial agents are used in response to disease outbreaks and that indicators indicate the results of appropriate use of antimicrobial agents. Antimicrobial agents are important materials in the treatment of bacterial infections in livestock, and it is necessary to develop a situation in which they can be used when necessary and obtain the desired effect in the future, and in recent years, as the EU and other countries have been promoting measures to reduce the amount of antimicrobial agents used (sold), there is concern that the high amount of antimicrobial agents used (sold) for veterinary use in Japan compared to other countries will damage the image of the entire agricultural field and lower consumer confidence in Japan. From this perspective, the amount of veterinary antimicrobials used (sold) in the livestock field has been newly set as a performance indicator. The target value is set with reference to the sum of the value calculated as the amount that can be reduced by promoting appropriate use in cattle and poultry and the value calculated based on the reduction achieved in swine as specified in the National Action Plan on Antimicrobial Resistance (AMR) (2016-2020).

[161] Among antimicrobial agents for veterinary use, antimicrobial agents important for human medicine are designated as second-line drugs. Second-line drugs are used only when treatment with first-line drugs is ineffective and are currently considered the minimum necessary dosage. In order to avoid overuse of second-line drugs by reducing the overall usage (sales volume), the current volume should not be increased and a new target will be set.

# MONITORING AND EVALUATION OF PROGRESS

Progress in each strategy and action, as well as process indices, should be evaluated annually in the framework of the International Cooperation Ministerial Meeting for Strengthening Measures on Emerging Infectious Diseases. The outcome indices should be evaluated by issuing the annual Nippon AMR One Health Report (NOAR).

# REFERENCE

## GLOSSARY

- **Antimicrobial Resistance (AMR)**
  Refers to the phenomenon where antimicrobials (see below) become ineffective, or pharmaceutical effects decline, against infectious diseases caused by organisms (bacteria, fungi, viruses and parasites).
- **Antimicrobial-resistant organisms (AROs)**
  Refers to organisms (bacteria, fungi, viruses and parasites) that exert AMR; bacteria that indicate AMR are particularly referred to as antimicrobial-resistant bacteria.
- **Antimicrobial-resistant genes (ARGs)**
  Refers to genes and gene groups in a chromosome or plasmid (extranuclear DNA) that cause AMR in antimicrobial-resistant organisms.
- **Plasmid-mediated antimicrobial-resistant genes (Plasmid-mediated ARGs)**
  Refers to antimicrobial-resistant genes that are located in extranuclear DNA outside the bacterial nucleus; these genes may be transferred AMR to other antimicrobial susceptible bacteria through conjugation. Most antimicrobial-resistant Gram-negative bacilli that have recently become an issue have these kinds of genes.
- **Horizontal transfer**
  Refers to the transfer of plasmid through bacterial conjugation, and to the transfer of antimicrobial resistance genes (ARGs) to originally antimicrobial susceptible bacteria, through mechanisms such as transformation (antimicrobial resistant gene is transferred when DNA isolated from the bacterial cell enters another bacteria) and transduction (a bacteria is infected by a virus (phage)); Horizontal transfer occurs not only in the same bacterial species but also across different species.
- **Antimicrobials**
  Collectively refers to agents that have antimicrobial activity against pathogenic organisms and are used for humans, animals and agriculture, for the purpose of treating or preventing infectious diseases, or for effectively utilizing nutrients in animal feeds; Antimicrobials include antimicrobials used for humans, as well as antimicrobials used for animals and in agriculture. Antimicrobials for humans include antibacterial agents (agents with antimicrobial activity against bacteria; includes antibiotics and synthetic antibacterials), antifungal agents, antiviral agents and antiparasitic agents. Veterinary antimicrobials include antibiotics for animals (agents with antimicrobial activity against bacteria; includes antibiotics and synthetic antibacterials), antifungal agents, antiviral agents and antiparasitic agents used for animals. Antibiotics for animals include both veterinary antibiotics used for treating veterinary infectious diseases and antibiotic feed additives used for the effective utilization of nutrients in feeds.
- **Selection pressure**
  Refers to pressure applied toward the survival of selected antimicrobial-resistant organisms, resulting from the elimination of organisms that are susceptible to a certain agent by using that agent; Among various mechanisms of AMR, selection pressure is one of the largest inducing factors.
- **One Health approach**
  Refers to a concept where the public health sector, the animal health sector, the environmental health sector, and other related sectors pursue collaborative and integrated response to infectious diseases that are caused through complicated interaction among humans, animals, the environment and other factors; With respect to AMR countermeasures, it has been pointed out that, when antibiotics and other antimicrobials are used in the practice of medicine, long-term care, veterinary medicine, livestock and aquaculture, agriculture, etc., AROs that are selected through the use of such agents, as well as genes that cause AMR (ARGs), may be transferred to humans via food chain and the environment. This indicates the necessity of collaborative efforts by these sectors.
- **Surveillance**
  To conduct periodic surveys for grasping the actual status of an issue, thereby identifying trends and detecting changes.
- **Monitoring**

  To conduct periodic surveys to determine whether any corrective actions are required.

- **Japan Nosocomial Infections Surveillance (JANIS)**
  A surveillance project for identifying trends in the AMR of organisms detected in medical institutions that have beds under the control of the Ministry of Health, Labour and Welfare (MHLW); Participation in this project is voluntary. A surveillance report on the analysis of trends in AMR in each institution is provided to the participating medical institutions. Open Reports that indicate national trends in AMR are disclosed to the public.

- **Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)**
  A system of the Ministry of Agriculture, Forestry and Fisheries (MAFF) for monitoring AMR in livestock and aquaculture and the amounts of sales of veterinary antibiotics; The system is implemented by the National Veterinary Assay Laboratory (NVAL) as the core laboratory, in collaboration with the prefectural governments, the Food and Agricultural Materials Inspection Center (FAMIC), fisheries research and laboratory facilities and other related institutions. The results of surveillance and monitoring are published every year in Japanese, and every few years in English.

- **Healthcare-associated Infection (HAI)**
  Collectively refers to infectious diseases associated to medical intervention; Major healthcare-associated infections (HAIs) include catheter-related blood stream infections(CRBSIs), catheter-associated urinary tract infections (CAUTIs),
  surgical site infections(SSIs), ventilator-associated pneumonia (VAP), and *Clostridium difficile* infections (CDIs). By conducting hospital-based surveillance for these infections, disease burden of AMR in a hospital can be measured.

- **Antimicrobial Susceptibility Test**
  A test for determining whether or not specific pathogenic organisms (bacteria or fungi) are susceptible to an antibacterial or antifungal agent (i.e. whether or not an agent is effective on specific organisms); when a pathogenic organism is able to develop in an environment that exceeds the pre-determined agent concentration ("breakpoint"), the organism is classified as "resistant". A list that indicates the rates of susceptibility to each antimicrobial agent, classified by the type of organism, is called "antibiogram".

- **Antimicrobial Use (AMU)**
  Indicator for the amount of use of an antimicrobials; because it is impossible to directly compare the amounts of use, the number of persons, the days of administration, the Antimicrobial Use Density (AUD), and the Days of Therapy (DOT) are used. For the animal field, it indicates the amount of antibiotics intended to be used, and figures given by correcting the amount administered, the amount of sales of agents, feeding volume by the number of animals and average body weight.

- **Antimicrobial Use Density (AUD)**
  One of the standard indicators for measuring AMU for humans; AUD indicates daily AMU per day per 1,000 or 100 population. Because the Defined Daily Dose (DDD) varies by agent, the total pure powder consumed is divided by DDD, and is further divided by the total days of administration in the target population.

- **Days of Therapy (DOT)**
  One of the indices for measuring AMU for humans that was developed by the U.S. Centers for Disease Control and Prevention (CDC), and is mainly used in developed countries; Unlike AUD, DOT only evaluates the days of administration of antimicrobials, regardless of the amount of use per day.

- **AMR diagnostics**
  The diagnosis of AMR is mainly performed through phenotypic testing (antimicrobial susceptibility testing) or genotypic testing (typing of (the products of) antimicrobial resistance genes (ARGs)). While phenotypic testing evaluates the reactivity of organisms to actual agents, genotypic testing evaluates specific antimicrobial resistance genes (ARGs) and their products (proteins).
  Genotypic testing contributes to determination whether certain AMR has been vertically or horizontally transferred.

- **Codex Alimentarius Commission**
  The Codex Alimentarius Commission is a global intergovernmental organization established by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) in 1963, for the purpose of protecting the health of consumers and guaranteeing the fair trade of food. The Commission develops international food standards (Codex standards), etc. Japan joined the Commission in 1966.

- **Livestock Health Inspector**
  Those appointed by prefectural governors pursuant to Article 53, Paragraph (3) of the Act on the Prevention of Infectious Diseases in Livestock from among prefectural officials who are veterinarians in order to have them engage in the affairs provided for in the Livestock Infectious Disease Prevention Act. However, when particularly necessary, the prefectural governor shall appoint a veterinarian other than a veterinarian who is an official of said prefecture and who has knowledge and experience in the prevention of infectious diseases of domestic animals.

- **Fish Epidemic Prevention Officer**
  Those appointed by prefectural governors from among prefectural employees to engage in the affairs of prevention of infectious diseases of aquaculture aquatic animals and plants in accordance with paragraph 1 of Article 13 of the Sustainable Aquaculture Production Assurance Act (Act No. 51 of 1999).

- **Biosecurity Standards**
  The standards to be observed by livestock owners with respect to sanitary management methods pertaining to the keeping of livestock, in accordance with Article 12-3 of the Act on the Prevention of Infectious Diseases in Livestock.

- **World Organisation for Animal Health (WOAH) Collaborating Centres**
  Inspection and research laboratories accredited by the World Organisation for Animal Health (WOAH) for scientific knowledge and technical assistance related to animal health.

- **Second-line drugs in the livestock field**
  Antimicrobial agents to be used in livestock used only when first-line drugs are ineffective. Second-line drugs are designated based on the results of the risk assessment of antimicrobial resistant bacteria by the Food Safety Commission (FSC) (assessment of the likelihood and extent to which antimicrobial resistant bacteria selected through the use of antimicrobial agents in livestock and other food animals can spread to humans via food and affect their health).