National Action Plan on Antimicrobial Resistance (AMR)

2016-2020

April 5, 2016

The Government of Japan

CONTENTS

INTRODUCTION

The challenges of antimicrobial resistance (AMR), including resistance to natural and synthetic antibiotics, have a long history that dates back to the development of penicillin. In Alexander Fleming's speech accepting the 1945 Nobel Prize in Physiology or Medicine for his discovery of penicillin in 1928, he said:

> *"The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."*

In fact, an enzyme which inactivates penicillin named penicillinase had been discovered from penicillin-resistant bacteria in 1940, five years before the speech was given. True to Fleming's prediction, the post-war history of the rapid development of antibiotics can be described as the history of warfare waged against antimicrobial resistance (AMR). In the 1960s, as effective antibiotics against penicillin-resistant bacteria were developed one after another, including methicillin for *Staphylococcus aureus*, and aminopenicillin (ampicillin) and aminoglycosides (gentamicin) for Gram-negative bacteria, people gradually began to believe that bacterial infections could be defeated. With powerful weapons to fight against infectious diseases, such as vaccines and antibiotics, the leading cause of death in developed countries has shifted from infectious diseases to non-communicable diseases (NCDs), and so did the pharmaceutical trends. The development of new antimicrobials has steadily declined since the 1980s. Meanwhile, the threat by new antimicrobial-resistant bacteria began to rise predominantly in hospital settings. It was the emergence of healthcare-associated infections (HAIs) associated with surgery and medical devices developed through the advancement of medical technologies.

These healthcare-associated infections spread also in Japan, caused by antimicrobial-resistant Gram-positive cocci including Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococci* (VRE), followed by antimicrobial-resistant Gram-negative bacilli including multidrug-resistant *Pseudomonas aeruginosa* (MDRP) and multidrug-resistant *Acinetobacter* spp. (MDRA). It remains as a significant problem in medical institutions to the present day. While initially associated with medical institutions, this growing problem is now increasingly found outside the healthcare settings, called community-acquired antimicrobial-resistant infections.

Antimicrobial substances are also used for animals as veterinary antibiotics for animal disease treatment and antibiotic feed additives for effective use of nutrients contained in feeds. The development of antimicrobial-resistant bacteria in animals could reduce the efficacy of medical treatment for animals. In addition, it has been indicated that antimicrobial-resistant bacteria of animal origin have a potential to be transmitted to and cause infectious diseases in humans through livestock products, and consequently reduce the efficacy of antibiotics in humans.

Outside Japan, the rise of antimicrobial resistance is not confined to general bacterial infections. Malaria parasites have become resistant to artesunate, a drug known as a specific medicine against malaria. In addition, multidrug-resistant and extremely drug-resistant tuberculosis (acid-fast bacterium) has spread around the world.

These facts have led to the shared recognition that it is required to adopt a global "One Health" approach, which addresses both human and animal health together. The World Health Organization (WHO) featured antimicrobial resistance on the World Health Day 2011 and called upon the international community to devote global efforts under the One Health approach. In 2013, the G-Science Academies, the national science academies of G8 countries, issued a joint statement regarding the threat of antimicrobial resistance, followed by the first surveillance report by WHO in 2014 on the current, global state of antimicrobial resistance. In May 2015, the World Health Assembly endorsed the Global Action Plan on Antimicrobial Resistance, and urged all Member States to develop relevant national action plans within two years. At the G7 Summit 2015 in Schloss Elmau, Germany, in the following month, antimicrobial resistance was taken up as one of the key issues. The G7 Health Ministers at the G7 Health Ministers Meeting 2015 in Berlin welcomed the formulation of the Global Action Plan by WHO and discussed the necessity of strengthening the One Health approach and of R&D for new drugs. Assuming the G7 presidency for 2016, Japan is determined to intensify its efforts in measures against AMR.

For the purpose of developing a national action plan on antimicrobial resistance (AMR), the Government of Japan established the Antimicrobial Resistance (AMR) Task Force under the Ministry of Health, Labour and Welfare (MHLW) in cooperation with other ministries in November 2015, and has subsequently conducted expert interviews and other efforts of investigation. At the same time, the Steering Committee on National Action Plan on Antimicrobial Resistance (approved by the Director of the Team for Promoting Measures on Emerging Infectious Diseases, December 24, 2015), which was established within the framework of the Ministerial Meeting on

Measures on Emerging Infectious Diseases (approved orally by the Cabinet, September 11, 2015) (hereinafter referred to as the "Ministerial Meeting"), has explored the matter for the purpose of carrying forward antimicrobial resistance control measures through the integrated efforts of the Government of Japan. Furthermore, to promote and enhance the domestic measures and international cooperation to combat antimicrobial resistance, the Ministerial Meeting held on February 9, 2016 partially revised the National Strategy for Strengthening Measures on Emerging Infectious Diseases, and formulated the Action Plan for Strengthening Measures on Emerging Infectious Diseases, which stated the national action plan to be drawn up.

This National Action Plan on Antimicrobial Resistance was developed accordingly by the Ministerial Meeting and presents priorities to be implemented over the next five years to promote antimicrobial resistance measures in Japan.

ABBREVIATIONS

AMED	Japan Agency for Medical Research and Development
AMR	Antimicrobial Resistance
AMS	Antimicrobial Stewardship
AMU	Antimicrobial Use
ARG	Antimicrobial resistance Gene
ARI	Antimicrobial-resistant Infection
ARO	Antimicrobial-resistant Organism
AST	Antimicrobial Stewardship Team
AUD	Antimicrobial Use Density
CAO	Cabinet Office
CAS	Cabinet Secretariat
CAUTI	Catheter-associated Urinary Tract Infection
CCP	Critical Control Point
CDC	Centers for Disease Prevention and Control
CDI	*Clostridium difficile* Infection
CLABSI	Central Line-associated Bloodstream Infection
COI	Conflict of Interest
CRBSI	Catheter-related Bloodstream Infection
CRE	Carbapenem-resistant *Enterobacteriaceae*
DDD	Defined Daily Dose
DOT	Days of Therapy
DPC/PDPS	Diagnosis Procedure Combination / Per-Diem Payment System
ESBL	Extended-spectrum beta-Lactamase
EU	European Union
FAMIC	Food and Agricultural Materials Inspection Center
FAO	Food and Agricultural Organization of the United Nations
FETP-J	Field Epidemiology Training Program Japan
FRA	Fisheries Research Agency
FSC	Food Safety Commission of Japan
G7/G8	Group of Seven/Eight
GAIN Act	Generating Antibiotics Incentives Now Act
GCP	Good Clinical Practice
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
ICD	Infection Control Doctor
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICT	Infection Control Team
ICU	Intensive Care Unit
IDES	Infectious Disease Emergency Specialist (Training Program)
IHR	International Health Regulation
IPC	Infection Prevention and Control
JANIS	Japan Nosocomial Infections Surveillance
JPIAMR	Joint Programming Initiative on Antimicrobial Resistance
JVARM	Japanese Veterinary Antimicrobial Resistance Monitoring System
MAFF	Ministry of Agriculture, Forestry and Fisheries
MALDI-TOF MS	Matrix-assisted Laser Desorption/Ionization Time Of Flight Mass Spectrometry
MBL	Metallo-beta-lactamase
MDRA	Multidrug-resistant *Acinetobacter* spp.
MDRP	Multidrug-resistant *Pseudomonas aeruginosa*
MEXT	Ministry of Education, Culture, Sports, Science and Technology
MHLW	Ministry of Health, Labour and Welfare
MOE	Ministry of the Environment
MOFA	Ministry of Foreign Affairs
MRC	Medical Research Council
MRSA	Methicillin-resistant *Staphylococcus aureus*
NARO	National Agriculture and Food Research Organization
NCDs	Non-Communicable Diseases
NCGM	National Center for Global Health and Medicine
NDB	National Database for Prescription and National Health Check-up
NESID	National Epidemiological Surveillance of Infectious Diseases
NI	Nosocomial Infection
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NIID	National Institute of Infectious Diseases
NTDs	Neglected Tropical Diseases
NVAL	National Veterinary Assay Laboratory
OECD	Organisation for Economic Co-operation and Development
OIE	World Organisation for Animal Health
PCR	Polymerase Chain Reaction
PCU	Population-corrected Unit
PHE	Public Health Emergency
PK/PD	Pharmacokinetics/Pharmacodynamics
PMDA	Pharmaceuticals and Medical Devices Agency
PRSP	Penicillin-resistant *Streptococcus pneumonia*
SSI	Surgical Site Infection
TATFAR	Transatlantic Task Force on Antimicrobial Resistance
UHC	Universal Health Coverage
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WAAW	World Antibiotic Awareness Week
WGS	Whole Genome Sequencing
WHO	World Health Organization
VAP	Ventilator-associated Pneumonia
VRE	Vancomycin-resistant *Enterococci*
VRSA	Vancomycin-resistant *Staphylococcus aureus*

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". Regarding veterinary antimicrobial use, this National Action Plan focuses on antimicrobials against bacteria, which are "veterinary antibiotics" and "antibiotic feed additives", collectively called "antibiotics for animals".

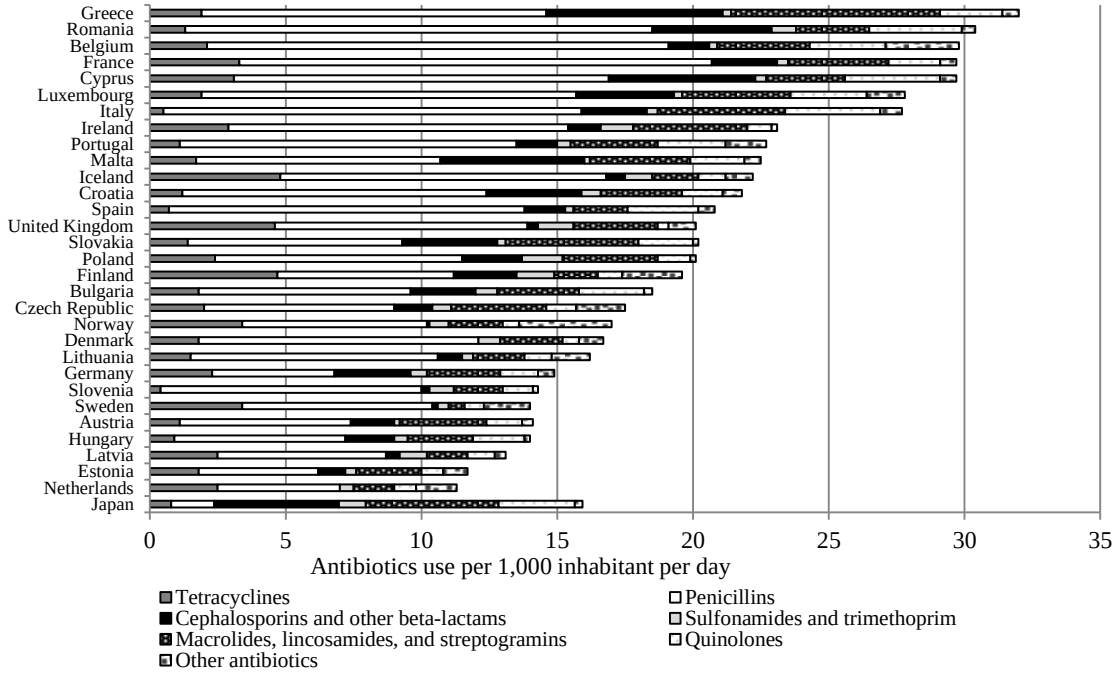
THE CURRENT STATE AND CHALLENGES OF ANTIMICROBIAL RESISTANCE IN JAPAN

THE CURRENT STATE OF ANTIMICROBIAL RESISTANCE IN JAPAN

The inappropriate use of antimicrobials has been indicated as the background to the global spread of antimicrobial resistance (AMR). According to a national research group report[1] in 2010, total antibiotics use in humans in Japan was approximately 15.8 per day per 1,000 inhabitants in 2013, which, compared to developed countries in the European Union (EU), follows Germany in ranking relatively low (see Figure 0.1). However, some specific classes of oral antibiotics which were effective against a wide range of bacteria (broad-spectrum oral antibiotics), namely cephalosporins (more than 60% of them were third-generation), fluoroquinolones, and macrolides, were frequently used in Japan, and penicillins were less frequently used compared to other EU countries.

Figure 0.2 shows that the proportions of AMR in Gram-positive bacteria, represented by methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumonia* (PRSP), are higher in Japan than in other countries. In contrast, for Gram-negative bacteria, the proportion of AMR in Japan, represented by carbapenem-resistant *Pseudomonas aeruginosa* and third-generation cephalosporin-resistant *Escherichia coli*, maintain levels equal to or lower than those in other countries. The prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE), which is of particular concern around the world, remains low with a percentage of 0.1-0.2% in Japan.[2]

Figure 0.1. Comparison of antibiotic use for humans in EU countries and Japan[3]

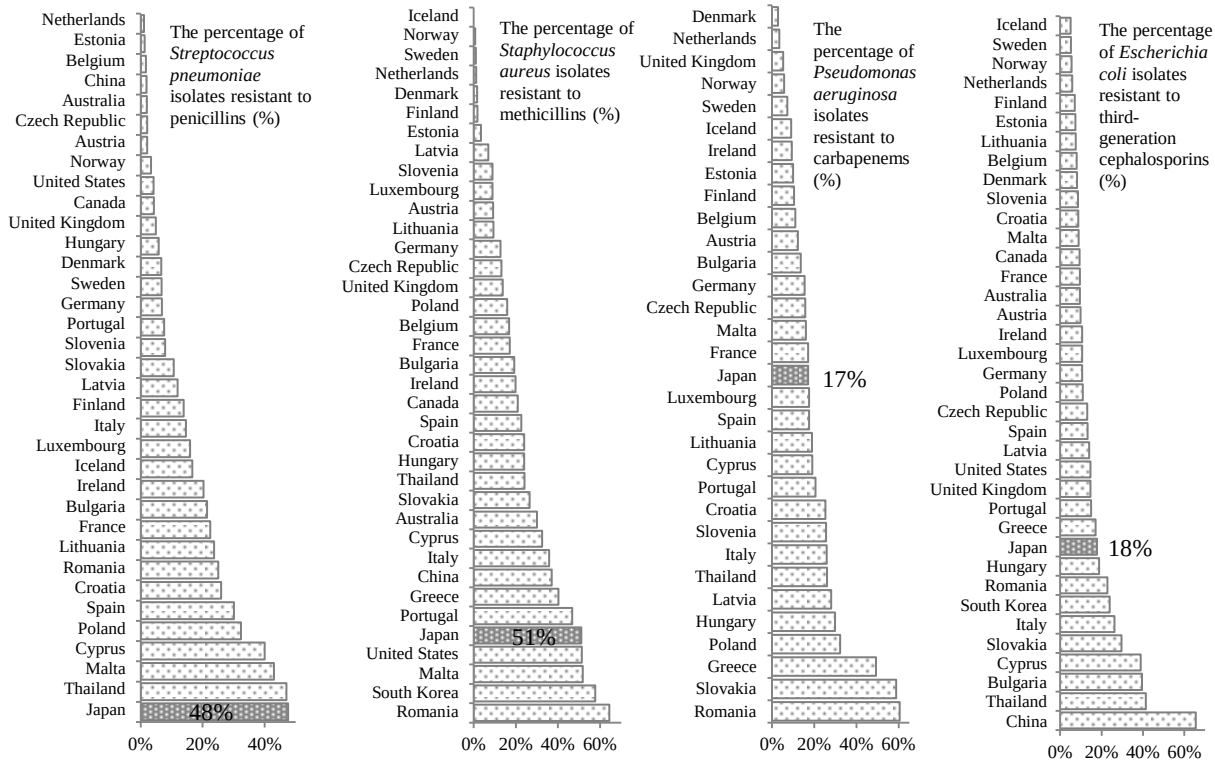


[1] Muraki Y, et al., Nationwide surveillance of antimicrobial consumption and resistance to *Pseudomonas aeruginosa* isolates at 203 Japanese hospitals in 2010. *Infection*. 2013; 41:415-23.

[2] Annual Open Report, Clinical Laboratory Division, Japan Nosocomial Infections Surveillance (JANIS)

[3] ECDC AMR Surveillance Report 2012; Muraki Y, et al. *Infection*. 2013; 41: 415-23. (EU data from 2010; Japan data from 2013)

Figure 0.2. International comparison of antimicrobial resistance proportions in major microorganisms in humans causing problems due to antimicrobial resistance[4]

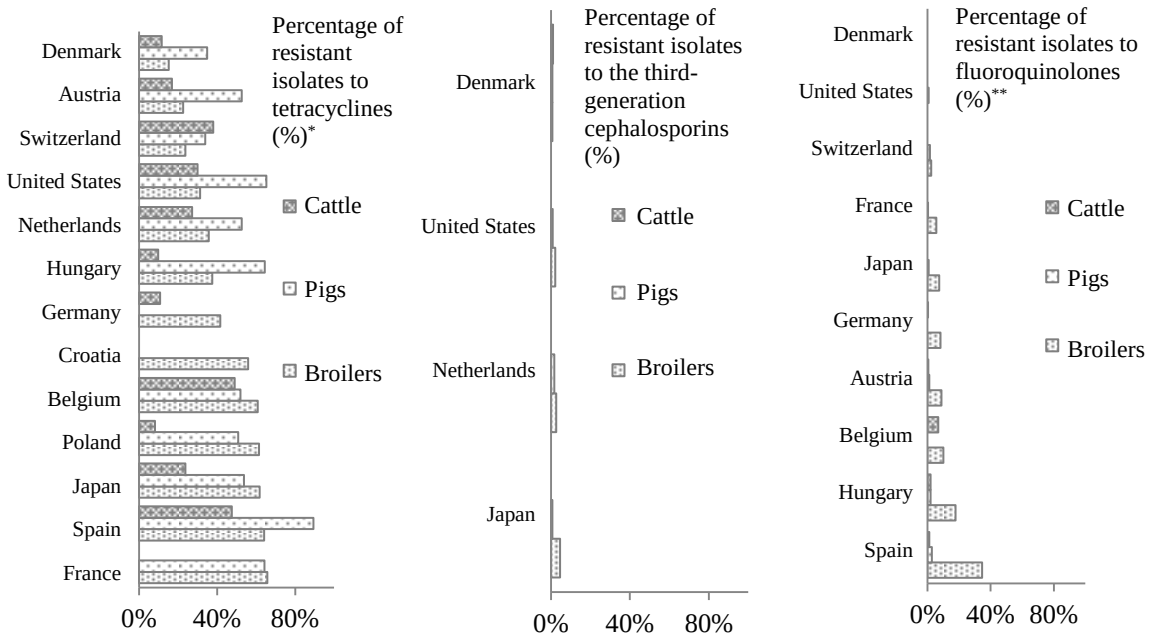


The current state of AMR in livestock in different countries is not simply comparable because of the differences in target animals and survey methods. Concerning *Escherichia coli*, an indicator bacterium for monitoring AMR, the international comparison of the prevalence of AMR (Figure 0.3) shows that the percentages of isolates resistant to tetracyclines, the third-generation cephalosporins, and fluoroquinolones in Japan are at comparable levels to those in Western countries. Tetracyclines are largely used in livestock, and the third-generation cephalosporins and fluoroquinolones 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.[5] The percentages of isolates resistant to tetracyclines, third-generation cephalosporins, and fluoroquinolones in *Escherichia coli* of animal origin are 45.2%, 1.5%, and 4.7%, respectively, in Japan in 2014 (Figure 0.4).

[4] Antimicrobial Resistance: Global report on Surveillance 2014, World Health Organization (WHO), 2014

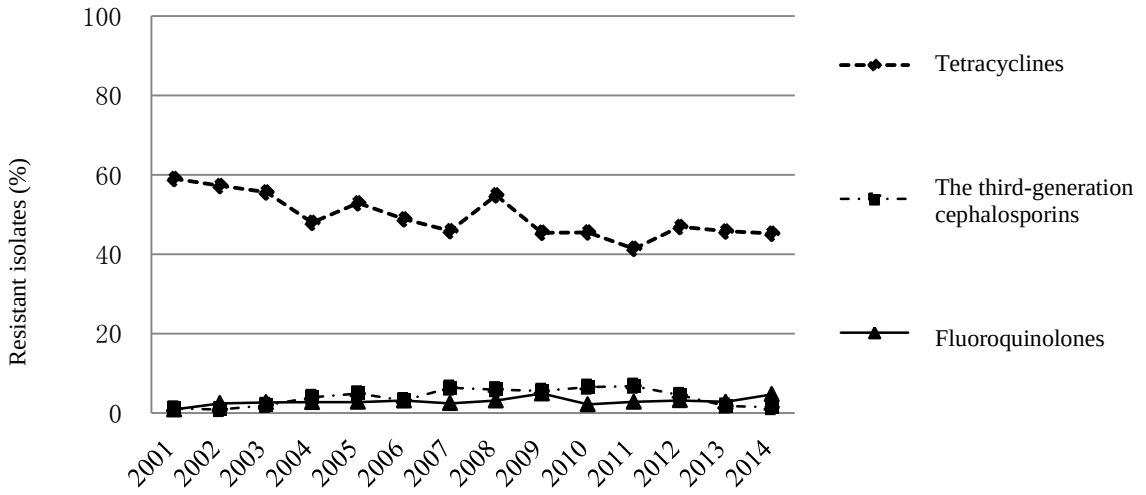
[5] Ranking of human antibiotics according to their importance in human medical practice for the assessment of the effect of food commodities contaminated by antimicrobial-resistant bacteria on human health

Figure 0.3. International comparison of antimicrobial resistance in *Escherichia coli* of livestock animal origin (2013)[6]



* No data on pigs in Germany, cattle and pigs in Croatia, and cattle in France
** No data on cattle in Denmark, Switzerland and France, and pigs in Germany and Denmark

Figure 0.4. Trends in antimicrobial resistance in *Escherichia coli* of livestock animal origin in Japan (2001-2014)[7]



[6] National Surveillance of Antimicrobial Resistance in Bacteria Isolated from Farm Animals in Japan, FY2013(JVARM), Animal Antimicrobial Resistance Annual Report 2013 (NARMS), Scientific Report of EFSA and ECDC EU Summary Report on Antimicrobial Resistance in Zoonotic and Indicator Bacteria from Humans, Animals and Food in 2013, DANMAP2013 - Use of Antimicrobials and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark

[7] Calculated from the data presented in Report of the Japanese Veterinary Antimicrobial Resistance Monitoring System -2000 to 2007, and Report of the Japanese Veterinary Antimicrobial Resistance Monitoring System -2008 to 2011

EFFORTS TO TACKLE ANTIMICROBIAL RESISTANCE IN JAPAN

Efforts against AMR in Japan have started with antibiotic R&D, and focused subsequently on infection control mainly in healthcare facilities, and ensuring the appropriate antibiotic use in animals.

RESEARCH AND DEVELOPMENT

Japan has produced many novel antibiotics since the 1950s.They have been used as antibiotics of a global standard.[8] Colistin, amikacin, and meropenem, among others, are the few antibiotics that remain effective against highly resistant bacteria called multidrug-resistant bacteria. Because infectious diseases were no longer the leading cause of death, antibiotic development has steadily declined since the 1990s. The global pharmaceutical trends shifted to drug development for non-communicable diseases (NCDs), which are perceived to produce more continuous returns.

Under such circumstances, the Japan Agency for Medical Research and Development (AMED) was established in April 2015, based on the Act on Promotion of Healthcare Policy (Act No. 48 of 2014, May) and the Act on the Independent Administrative Agency of Japan Agency for Medical Research and Development (Act No. 49 of 2014, May). AMED promotes integrated medical R&D activities from basic R&D to R&D focused on practical application under the Headquarters for Healthcare Policy and based on the Plan for Promotion of Medical Research and Development (approved by the Headquarters for Healthcare Policy, July 2014). To protect both Japanese citizens and people worldwide from infectious disease, the Agency focuses on the promotion of measures against infectious diseases and will strengthen measures to combat infectious diseases by promoting research at home and overseas into infectious diseases and will ensure more efficient, effective linkage of these results into the development of therapeutic drugs, diagnostic drugs, and vaccines.

CONTROL OF NOSOCOMIAL INFECTIONS

Nosocomial infections by antimicrobial-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) emerged in Japan in the 1980s. MRSA was not isolated in the 1970s. However, studies demonstrated a rapid rise in the isolation rate of MRSA (the percentage of MRSA among *Staphylococcus aureus* isolates obtained in a hospital) from 6.2% in 1984 to 58% in 1987 in an academic hospital.[9]

In response to this problem, the Ministry of Health, Labour and Welfare (MHLW) newly incorporated the Premiums for Nosocomial Infection Prevention in medical fee at the revision in April 1996, and has constantly reviewed the requirements for the premiums to support nosocomial infection control by medical institutions. MHLW established the Advisory Committee on Nosocomial Infections under the Ministry in 2002 to discuss how to tackle nosocomial infections. In the following year, the Committee complied a report, entitled "Future Nosocomial Infection Control". This led to the creation of a standing advisory council of experts, the Central Council on Control of Nosocomial Infection in 2004.

The 2006 revision of the Medical Care Act (the Act to Amend the Medical Care Act in Establishing a System that Provides High Quality Medical Care (Act No. 84 of 2006)) required all medical institutions to formulate nosocomial infection control guidelines, to establish a nosocomial infection control committee (clinics without hospitalization function and dental clinics may assign a manager instead), and to conduct seminars on nosocomial infections for all employees.

In 2000, MHLW launched the Japan Nosocomial Infections Surveillance (JANIS) program to promote rapid detection and appropriate response to nosocomial infections, and has constantly analyzed and assessed the prevalence of AMR and other related matters at the Central Council on Control of Nosocomial Infections in MHLW. Participation of medical institutions to JANIS has been increasing year by year, currently reaching 1,859 organizations as of January 2016.

[8] Colistin (1951), cefazolin (1971), amikacin (1977), clarithromycin (1991), levofloxacin (1991), meropenem (1995), piperacillin/tazobactam (2001), and doripenem (2005) are examples of antibiotics developed in Japan as global standard.

[9] Kobayashi H, The current state of Methicillin resistant *Staphylococcus aureus* (MRSA), *Infection and Disinfection*. 2006; 13: 71-73.

Such enhancement of nosocomial infection control has enabled the isolation rate of MRSA to drop from 58.7% (2009) to 49.1% (2014) in medical institutions.[10]

ENSURING THE APPROPRIATE AND PRUDENT USE OF ANTIBIOTICS FOR ANIMALS IN LIVESTOCK PRODUCTION AND AQUACULTURE

Control of AMR in livestock production and aquaculture in Japan is implemented according to the risk analysis principles defined in the international standards stipulated by the World Organisation for Animal Health (OIE) and the Codex Alimentarius Commission. Based on the scientific risk assessment results and taking the on-farm feasibility into consideration, risk management measures are developed and implemented according to the risk level.

Measures have been in place to ensure the appropriate use of antibiotics in animals, including setting standards for their use in accordance with relevant legislation. In addition, the Government of Japan developed guidelines for prudent use of veterinary antibiotics to ensure the concept of "prudent use", which is to carefully consider the necessity of using veterinary antibiotics, and use them in a manner maximizing the therapeutic effect and minimizing the selection of antimicrobial-resistant bacteria".

Furthermore, the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) was put in place in 1999 and has continuously conducted nation-wide monitoring. The results of the monitoring provide the basis for understanding the trends of antimicrobial-resistant bacteria, and developing and implementing risk assessment and risk management measures. The System started to collaborate with the human healthcare sector to exchange and mutually use monitoring data for the purpose of establishing a comprehensive antimicrobial resistance monitoring system across humans and livestock.

DIRECTION OF FUTURE MEASURES AGAINST ANTIMICROBIAL RESISTANCE (AMR)

This National Action Plan outlines the measures to minimize the emergence of AMR and prevent the spread of infectious diseases caused by antimicrobial-resistant organisms towards a world free of the burden of infectious diseases caused by AMR. To date, the related ministries and agencies have individually implemented measures against AMR in their relevant areas. From hereon, however, all organizations under the Government of Japan will collaborate under necessary coordination by the Cabinet Secretariat (CAS), thereby promoting collaborative efforts, integrating perspectives from every area.

[10] Annual Open Report, Clinical Laboratory Division, Japan Nosocomial Infections Surveillance (JANIS)

NATIONAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE (AMR) (2016-2020)

OBJECTIVES

To slow the emergence of antimicrobial resistance (AMR) and prevent its spread, it is important to: (1) increase public knowledge and understanding of AMR and use of antimicrobials, particularly in those involved in healthcare, nursing care, food, and livestock production and aquaculture, (2) understand the state of AMR emergence and prevalence, and use of antimicrobials (including surveillance and monitoring), and to assess the risk based on the understanding, (3) enhance proper infection prevention and control (IPC), (4) ensure antimicrobial stewardship (AMS) in order to reduce antimicrobial- resistant organisms (AROs), and (5) accelerate research on the mechanism of AMR emergence and transmission, and its impact on social economy, and promote R&D for new preventive, diagnostic, and therapeutic technologies in order to ensure the continued availability of effective preventive, diagnostic, and therapeutic treatments for antimicrobial-resistant infections (ARIs).

Japan has been tackling AMR issues since the 1990s and this experience puts Japan in the position to take leadership for the world, especially for Asian-Pacific countries. The following priority measures over the next five years (2016 - 2020) were developed in this perspective. Relevant ministries, agencies, and organizations should engage in a common effort to undertake these measures under One Health approach.

FRAMEWORK

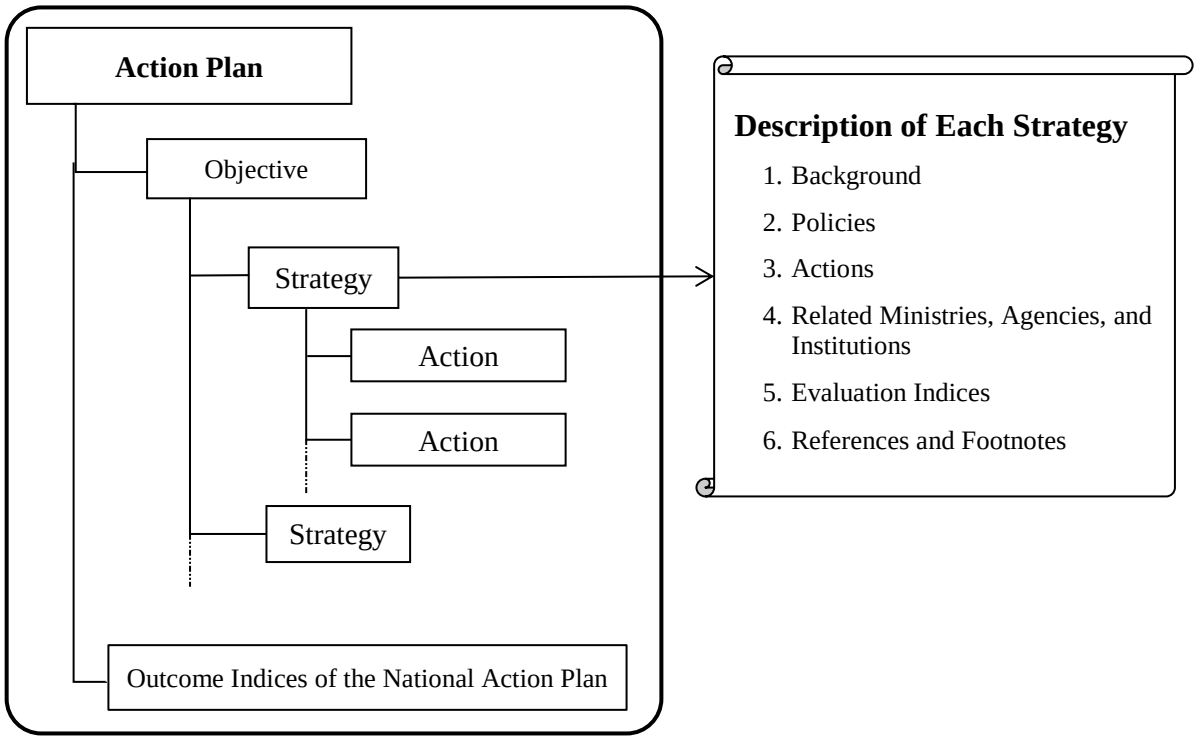
In its aim of promoting countermeasures on antimicrobial resistance (AMR), this National Action Plan is structured around goals (top tiers) in the following six areas: (1) Public Awareness and Education, (2) Surveillance and Monitoring, (3) Infection Prevention and Control, (4) Appropriate Use of Antimicrobials, (5) Research and Development, and (6) International Cooperation. Fields (1) - (5) were defined in line with the five strategic objectives set out by the Global Action Plan on AMR, which the World Health Assembly endorsed in May 2015. Field (6) was added to fulfill Japan's responsibilities for the international community as the host country for 2016 G7 Ise-Shima Summit. Strategies (middle tiers) to achieve goals and specific actions (bottom tiers) to implement the strategies are presented for each goal. The goals in the fields are set out in Table 1.1.

Table 1.1. Six Areas and Goals for Countermeasures on AMR

Fields		Goals
1	Public Awareness and Education	Improve Public Awareness and Understanding, and Promote Education and Training of Professionals
2	Surveillance and Monitoring	Continuously Monitor Antimicrobial Resistance and Use of Antimicrobials, and Appropriately Understand the Signs of Change and Spread of Antimicrobial Resistance
3	Infection Prevention and Control	Prevent the Spread of Antimicrobial-resistant Organisms by Implementing Appropriate Infection Prevention and Control
4	Appropriate Use of Antimicrobials	Promote Appropriate Use of Antimicrobials in the Fields of Healthcare, Livestock Production and Aquaculture
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
6	International Cooperation	Enhance Global Multidisciplinary Countermeasures against Antimicrobial Resistance

The strategies to achieve the above goals are described with their purposes, background, specific actions, related ministries, agencies, and institutions for the actions, and indices to evaluate the actions (Figure 1.1). The numerical targets for the overall National Action Plan are defined as outcome indices.

Figure 1.1. The Framework of the National Action Plan on AMR and the Description of Each Strategy



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 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 AMR and antimicrobials. However, the current level of public awareness is still limited.
- For example, an awareness survey conducted in the U.K. in 2010 suggested that about half of citizens in the U.K. believed antibiotics are effective for viral diseases. In addition, the survey indicated that about half of citizens in the U.K. believed that antibiotics can weaken the immune system.[11]
- A survey in Japan in 2014 found that one in three parents have adjusted the dosage of a prescribed medicine from a medical institution on their own judgment for their children to take. The survey also revealed that two in three parents have given left-overs of a prescribed medicine of their own judgment for their children to take.[12] Such use of antimicrobials at inappropriate dose or for inappropriate duration contributes to the emergence of AMR.
- Junior high school and high school students learn about infectious disease control and the importance of using medicines appropriately, as part of their health education at schools.[13]
- Therefore, in addition to conducting awareness-raising activities for the general public, targeted outreach for specific audience, including young children and their guardians, and elderly people, is important.[14] 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 the One Health approach, for the purpose of raising the public awareness of AMR
- Establish the National Council on Countermeasures against AMR (tentative name) to develop and implement public awareness campaigns on the threat of AMR in partnership with related organizations, groups, and media
- 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 AMR and academic groups in healthcare, animal health, and food hygiene

Key Messages to Raise Public Awareness on

- **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.
- **Infection Prevention and Control**: Practicing the etiquette of covering coughs, handwashing, and receiving vaccination (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and influenza) are key to preventing infections.

[11] Behaviour change and antibiotic prescribing in healthcare settings: Literature review and behavioural analysis. Public Health England and Department of Health, UK 2015 (PHE gateway number: 014719)
[12] Survey on the awareness and knowledge of appropriate use of medicine (online survey, January 2014), Risk/Benefit Assessment of Drugs-Analysis and Response (RAD-AR) Council of Japan (http://www.rad-ar.or.jp/information/pdf/nr13-140218(data).pdf)
[13] "For Healthy Life (FY2015)" (for high school students), School Health Education Division, Ministry of Education, Culture, Sports, Science and Technology (MEXT)
[14] Plan national d'alerte sur les antibiotiques 2011-2016, Ministère du Travail, de L'emploi et de la Santé, France, 2011

- **One Health approach**: Integrated efforts across the areas, including human healthcare, veterinary medicine, livestock production and aquaculture, and food hygiene, are important to combat antimicrobial resistance.

ACTIONS

■ For General Population

- Establish the National Council for Countermeasures on AMR (tentative name)
- Develop and provide awareness-raising tools
- Launch and run a platform to communicate information on AMR (website)
- Implement awareness-raising events in collaboration with the World Antibiotic Awareness Week (WAAW)
- Make thorough risk communication[15] in the areas of veterinary medicine, livestock production and aquaculture, and food hygiene
- Implement regular surveys on the knowledge, attitude, and practice regarding 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

- Continue to promote education regarding infectious disease control and the importance of using medicine appropriately

Scope: Travelers to overseas destinations

- Provide information regarding AMR through websites for travelers to overseas destinations[16]

Scope: Companies with business related to 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)
- Request a statement of cooperation for countermeasures against AMR

RELATED MINISTRIES, AGENCIES, AND INSTITUTIONS

Coordination Office of Measures on Emerging Infectious Diseases under Cabinet Secretariat (CAS); Ministry of Foreign Affairs (MOFA); Ministry of Education, Culture, Sports, Science and Technology (MEXT); Ministry of Health, Labour and Welfare (MHLW); and Ministry of Agriculture, Forestry and Fisheries (MAFF)

[15] Risk communication means exchanging and sharing information and opinions among risk management organizations, risk assessment organizations, consumers, producers, and other stakeholders from their respective viewpoints throughout the risk analysis process. Risk communication improves the knowledge and understanding of the nature and impact of the risk in question and enables risk management and assessment to function effectively.

[16] 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), MHLW (http://www.forth.go.jp)

EVALUATION INDICES

- Level of antimicrobial resistance (AMR) awareness
- Number of AMR awareness-raising tools distributed
- Number of access to the AMR information platform (website)

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 AMS and IPC among professionals dealing with antimicrobials and infectious diseases, their behavioral change based on increased knowledge and understanding of AMR is critical in addition to the strengthening regulations.
- Studies on educational effect on healthcare professionals have been conducted mainly in the developed countries. An example of such studies is a multicenter clinical study in Wales in the U.K. in 2007 - 2008. The study reported that AMS training for general practitioners resulted in 4.5% reduction of the dose of antibiotic prescribed for outpatients, without negative effect on the prognosis.[17]
- Japan, however, has only a small number of experts of infectious disease control. For example, there are 1,049 Board-Certified Infectious Disease Physicians working in medical institutions, which are approximately 1/20th of board-certified surgeons and 1/3rd of acute care surgeons, as of December 2014. Moreover, there are only 443 physicians working in infectious disease departments, which is 0.2% of total working physicians in hospitals and clinics.[18] Number of other certified healthcare professions in infectious disease control is significantly limited; there are 2,053 Certified Nurses in Infection Control, 32 Certified Nurse Specialists in Infection Control Nursing, 882 Certified Pharmacists in Infection Control, and 528 Infection Control Microbiological Technologists, as of February 2015.
- The roles of veterinarians and those engaged in livestock production and aquaculture who use veterinary antibiotics or antibiotic feed additives are especially significant in reducing risk in livestock production and aquaculture. They need to use antibiotics with correct understanding of AMR and appropriate and prudent use of antibiotics.
- Regulatory systems based on relevant laws and regulations[19] are in place to ensure the appropriate use of veterinary antibiotics, and prefectural veterinary pharmaceutical inspectors monitor and supervise the compliance with the systems. Additionally, guidelines on prudent use of veterinary antibiotics in livestock were formulated in December 2013. The guidelines have been since provided to veterinarians and producers through national and prefectural training and seminars.
- In aquaculture, a brochure, entitled "Use of Aquaculture Drugs", has been distributed annually to aquaculture farmers nationwide. Prefectural training and seminars are conducted to raise awareness on appropriate use of veterinary antibiotics in aquaculture.
- Regarding antibiotic feed additives, standards are stipulated for animal species, breeding stages and amounts to be added in feed for each additive, ensuring appropriate use of antibiotic feed additives.[20] Substances that adversely affect human health are not designated as antibiotic feed additives.
- Veterinarians learn about the bacterial mechanisms of resistance development and AMR control in their professional education curriculum, which includes subjects on use of veterinary antibiotics and antimicrobial-resistant bacteria. In addition, training for new veterinarians includes the subject on AMR.
- These efforts in the education and dissemination of the knowledge regarding antimicrobial resistance need to be further enhanced.

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[17] Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. BMJ. 2012; 344: d8173.

[18] 2014 Survey Summary on Physicians, Dentists, and Pharmacists, the Ministry of Health, Labour and Welfare, (MHLW), http://www.mhlw.go.jp/toukei/list/33-20.html

[19] Measures have been taken to ensure appropriate and restricted use of veterinary antibacterial agents. For example, use of veterinary antibacterial agents requires medical advice from a veterinarian (Veterinarian Act (Act No. 186 of 1949)). Veterinary antibacterial agents are not allowed to be sold to clients who are not instructed by a veterinarian, and their standard of use has been defined (Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (Act No. 145 of 1960)).

[20] Measures have been taken to ensure appropriate and restricted use of antibiotic feed additives, based on the Act on Safety Assurance and Quality Improvement of Feeds (Act No. 35 of 1953).

POLICIES

- ○ Accumulate the necessary knowledge, develop practical education programs, and promote their use in relevant organizations in order to improve knowledge on AMR, and promote education on IPC and AMS among professionals and workers in various areas, including healthcare, nursing care, food, veterinary medicine, livestock production, aquaculture, and agriculture
- ○ Establish and promote a continuous 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[21], veterinary medicine[22], nursing care and public welfare[23], agriculture, livestock production, aquaculture and food hygiene

- Increase or enhance of contents on AMR, IPC, and AMS in school curricula and training guidelines, and promote educational activities in relevant organizations, as appropriate

■ National Qualification

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

- Increase or enhance the subjects on AMR, IPC, and AMS in standard questions for qualifying examinations, as appropriate

■ Post-Graduate Education and Training in Early Stage

Scope: Physicians and dentists

- Incorporate AMS education in residency systems for physicians and dentists, as appropriate (linked to Strategy 4.1)

Scope: Pharmacists

- Develop and introduce standard training programs on AMR, IPC, and AMS in post-graduate introductory training

Scope: Veterinarians

- Develop and introduce training programs related to AMR in post-graduate clinical training
- Improve and implement seminars and training for animal health inspectors and clinical veterinarians

Scope: Healthcare professionals other than physicians, dentists, and pharmacists, and other workers in medical institutions[24]

- Develop and introduce training programs related to IPC in post-graduate introductory training

[21] 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.
[22] Veterinarians, animal care technicians, etc.
[23] Social workers, certified care workers, psychiatric social workers, care managers, home care workers, etc.
[24] 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, linen keepers, janitors, and guards.

■ Continuing Education

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

- Develop training programs related to AMR in continuing education
- Encourage relevant groups to use the training programs and enhance relevant training
- Support education and training through the Infectious Disease Education Consortium (tentative name)
- Improve and implement seminars and training for livestock producers, aquaculture farmers, and feed manufacturers
- Ensure prefectures to instruct on-site practices in veterinary medicine and livestock production, and to raise thorough awareness thereon

Scope: Responsible local government officers

- Develop training programs related to outbreaks of antimicrobial-resistant infections (ARIs) as a part of professional education and training (linked to 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[25] and examinees for qualification by health care groups, academic associations, and certification authorities regarding infectious diseases

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

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

- Provide support to promote AMR-related requirements to be included in existing relevant qualifications

Scope: Veterinarians

- Instituting a new certification system for the appropriate management of infectious diseases in animals, as appropriate

■ Ensuring Capacity for Awareness Raising and Education

Scope: People involved in human healthcare, veterinary medicine, nursing care, public welfare, livestock production, aquaculture, agriculture, and food

- Establish the Infectious Disease Education Consortium (tentative name), which dispatches experts (instructors) in related areas to conduct education and training, as appropriate

[25] 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)

Infectious Disease Education Consortium (tentative name): The Consortium is an interdisciplinary network for education, consisting of experts from relevant technical areas (including healthcare, animal, food, infection prevention and control, and antimicrobial stewardship). To address the shortage of experts who can provide AMR education and training, this Consortium functions as a pool of experts to be dispatched for educational tool development and awareness-raising and educational activities.

Scope: Local government officers, and workers engaged in healthcare, nursing care, and public welfare

- Establish a clinical reference center on AMR (Clinical Reference Office for Antimicrobial Resistance (tentative name)), as appropriate. The Office develops education contents to be used for providing information and education, and raising awareness about AMR concerning healthcare, nursing care, and public welfare

Clinical Reference Office for Antimicrobial Resistance (tentative name): The Office gathers information on antimicrobial resistance related to healthcare and welfare. In addition, the Office provides the information and training online for healthcare professionals and welfare workers. The Office will be established in the National Center for Global Health and Medicine (NCGM).

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

- Improve the functions and systems of core AMR laboratory in agriculture, and aquaculture. Establish and maintain a platform to provide information regarding AMR

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 training and seminars 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 Surveillance and Monitoring in the Fields of Veterinary Medicine, Livestock Production and Aquaculture

(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 two systems dedicated to the surveillance in healthcare: the Japan Nosocomial Infections Surveillance (JANIS) which monitors the trends of AMR and the National Epidemiological Surveillance of Infectious Diseases (NESID) based on the Act on Prevention of Infectious Diseases and Medical Care for Patients Suffering Infectious Diseases (Act No. 114 of 1998, October).
- However, the prevalence of certain antimicrobial-resistant organisms (AROs) is not monitored because neither of the two systems is applied for these AROs.[26] JANIS targets medical institutions with inpatient facilities. Therefore, the situation of AMR has not been systematically monitored in clinics or nursing care facilities.
- Healthcare-associated Infections (HAIs)[27] occur in association with medical interventions (see Table 2.1). There were an estimated 720,000 HAIs per year in U.S. acute care hospitals, resulted in 75,000 deaths.[28] The medical costs attributable to HAIs are estimated to be 9.8 billion U.S. dollars (approximately 1.2 trillion yen).[29] Accurate monitoring of the state of HAIs directly contributes to the assessment of disease burden in hospitals caused by AMR. Results of such monitoring can be used as outcome indices to evaluate the success and quality of infection prevention and control (IPC) and antimicrobial stewardship (AMS). It can also help estimating the effects of infection control in hospitals, including reduced medical costs and shortened length of hospital stay.
- JANIS monitors HAIs in intensive care units (ICUs) and neonatal Intensive care units (NICUs). JANIS also monitors data on post-operative patients[30] collected from some hospitals. Though some medical institutions are implementing their own surveillance system by an infection control team (ICT), the number of such hospitals is limited. The whole picture of AMR disease burden in medical institutions is yet to be understood. The Survey on Assessment of the FY2012 Revision of Medical Fees[31] found that HAI surveillance is conducted in 37% of medical institutions pricing premium for infection control for catheter-related bloodstream infections (CRBSIs), 36% for surgical site infections (SSIs), 25% for catheter-associated urinary tract infections (CAUTIs), and 17% for ventilator-associated Pneumonia (VAP), revealing less than half of these medical institutions are conducting HAI surveillance.

POLICIES

- Strengthen AMR surveillance in healthcare through reviewing and expanding target organizations and subjects to be targeted by the surveillance, and aim for establishing robust surveillance system particularly for drug-resistant tuberculosis and drug-resistant *Neisseria gonorrhoeae* infections, which are spreading around the world
- Endeavor to monitor the trends of AMR in residents in nursing care facilities and outpatients through reviewing target organizations and subjects of JANIS

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[26] The national systems do not collect data on certain AROs, including multidrug-resistant *Neisseria gonorrhoeae*, drug-resistant Tuberculosis, and fluoroquinolone-resistant species in *Salmonella* and *Shigella*. Multidrug-resistant *Neisseria gonorrhoeae* and drug-resistant Tuberculosis have been monitored by individual research groups.

[27] Friedman ND, et al. Health Care–Associated Bloodstream Infections in Adults: A Reason To Change the Accepted Definition of Community-Acquired Infections. Ann Intern Med. 2002; 137: 791-797.

[28] Magill SS, et al. Multistate Point-Prevalence Survey of Health Care–Associated Infections. N Engl J Med. 2014; 370: 1198-208.

[29] Zimlichman E, et al. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med. 2013; 173: 2039-46.

[30] Among the total of 1,859 medical institutions participating in JANIS, 193 organizations submitted their data on ICUs, 114 organizations on NICUs, and 771 organizations on surgical site infections (SSIs), as of January 2016.

[31] Survey on Assessment of the FY2012 Revision of Medical Fees (Survey in FY2012) (on Patient Safety, etc.), General Assembly of the Central Social Insurance Medical Council (the 242nd), May 2013 <General Assembly - 5 - 2>
http://www.mhlw.go.jp/stf/shingi/2r98520000032e8y.html

- ○ Develop efficient HAI surveillance methods, which are based on physicians' consultations, and link HAI surveillance data with JANIS data to facilitate assessment and management of HAI risk caused by AROs in hospitals
- ○ Strengthen comprehensive think-tank function regarding AMR, including collection of various information on 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 (NESID)

- Promote monitoring of drug-resistant Tuberculosis and multidrug-resistant *Neisseria gonorrhoeae* infections
  - ✓ Standardize the methods and subjects of antimicrobial susceptibility tests
  - ✓ Conduct molecular epidemiological research on multidrug-resistant *Neisseria gonorrhoeae*
- 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 full digitalization of reporting of medical institutions to public health centers
- Proceed with data link of antimicrobial-resistant infections (ARIs), which are included in Category V infectious diseases, and infectious diseases facing the problem of AMR, with the data collected by JANIS and review reporting standards, as appropriate

■ Strengthening the Japan Nosocomial Infections Surveillance (JANIS)

- Conduct research to aid the review of target organizations and subjects of JANIS (see Strategy 3.1)
- Support implementation of AMR surveillance in medical institutions without an in-house clinical microbiological laboratory, in partnership with off-site contract laboratories for testing
- Expand targets of surveillance to include bacteria covered by the WHO Global Antimicrobial Resistance Surveillance System (GLASS)[32]
- Accelerate data collection and analysis on key antimicrobial resistance genes (ARGs)[33]
- Introduce a system to analyze JANIS data at the regional level. Promote the application of JANIS data to surveillance activities through the Regional Network for Infectious Diseases Prevention and Control (tentative name)[34] (linked to Strategy 3.1)

■ Promote Research on Healthcare-associated Infection (HAI) Surveillance

- Conduct research on HAI surveillance system capable of evaluation at both the local and nation-wide levels

[32] *Salmonella*, and *Shigella* including dysentery bacillus.
[33] ARGs include genes coding enzymes accountable for third-generation cephalosporin resistance, such as extended-spectrum beta-lactamases (ESBL), AmpC enzymes. ARGs also include other key antimicrobial resistant-genes, including MCR-1 gene and genes coding carbapenemases, such as metallo-beta-lactamases (MBL), KPC, and OXA enzymes.
[34] A system to analyze 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).

- ✓ Explore the possibilities of developing a HAI surveillance system using the Regional Infection Control Support System[35]
- ✓ Conduct preliminary collection of HAI data as part of the work of the Antimicrobial Stewardship Team (AST) in some medical institutions and regions

- Coordinate efforts with the development of an automated system to detect suspected HAI carriers symptoms from electronic medical records (see Strategy 4.1)
- Link HAI data with JANIS, as appropriate[36]
- Provide training to provide necessary knowledge and techniques to implement HAI surveillance (linked to Strategies 1.2 and 3.3)

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

- Establish the Antimicrobial Resistance Research Center (tentative name) in the National Institute of Infectious Diseases (NIID)

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 drug-resistant tuberculosis and multidrug-resistant *Neisseria gonorrhoeae* infections.
- Number of medical institutions participating in AMR surveillance and its research.

Table 2.1. 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)	Bacteremia 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* (CDIs may be facilitated by selective proliferation of the strain by antibiotic use.)

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

[35] Development of the Regional Infection Control Support System is conducted under a program, Research on Infection Control in Medical Institutions, supported by FY2014 Health and Labour Sciences Research Grants (Grants-in-Aid for Scientific Research), Establishment of National Surveillance System on Antibiotic Use and Evaluation of the Effect of Premium for Infection Control, supported by FY2013 Grants-in-Aid for Scientific Research. Data on specific HAIs (including catheter-related bloodstream infections (CRBSIs) and clostridium difficile infections (CDIs)) have been collected.

[36] The Regional Infection Control Support System is designed to enable the collaboration with JANIS. By interchanging its data with HAI surveillance data, the System can identify the AROs that contribute to cause HAIs and analyze the degree thereof.

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).[37] It is demonstrated that reduction of AMU represses the emergence of antimicrobial-resistant organisms (AROs).[38]
- National research on AMU surveillance in medical institutions and the application of AMU indicators[39]to quantitative and qualitative evaluation of antimicrobial stewardship (AMS) between medical institutions by linking AMR surveillance data collected by JANIS has been conducted.[40]
- Furthermore, using the AMU indicators, which are of international standards, enables comparison of AMU state in Japan with the world.
- However AMU surveillance has been implemented among inpatients as a national research project, the state of AMU is mostly unknown among outpatients, which counts 90% of the prescription, and among residents in nursing care facilities, except the sales of antimicrobials.

POLICIES

- Develop surveillance methods to monitor AMU in medical institutions (inpatient and outpatient departments)
- Monitor AMU indicators of individual medical institutions. Explore how to use the data for quantitative and qualitative benchmarking of AMS by linking them with AMR surveillance data from JANIS. Investigate how to use the data for developing relevant measures, as needed
- Monitor the state of antimicrobials prescribed in nursing care facilities

ACTIONS

■ **Antimicrobial Use Surveillance in Medical Institutions**

- Continue the research on the AMU surveillance system for outpatient departments in hospitals and explore its application by collaborating with JANIS
- Conduct research aimed at the development of an AMU surveillance system in hospital outpatient departments and clinics
- Explore the application of big data collected in the National Database for Prescription and National Health Check-up (NDB)
- Encourage participation of medical institutions in the AMU surveillance system
- Conduct research on the integration of AMU surveillance systems in inpatient and outpatient departments

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[37] Bell et al. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis.* 2014; 14: 13.

[38] Dancer SJ et al. Approaching zero: temporal effects of a restrictive antibiotic policy on hospital-acquired *Clostridium difficile*, extended-spectrum β-lactamase-producing coliforms and methicillin-resistant *Staphylococcus aureus*. *Int J Antimicrob Agents*. 2013; 41: 137-42.

[39] The AMU indicator is antimicrobial use density (AUD) and days of therapy (DOT), and their combination.[40] Establishment of National Survey System on Trends of Antibiotic Use and Evaluation of the Effect of Premium for Infection Control, supported by the FY 2013 Health and Labour Sciences Research Grants (Grants-in-Aid for Scientific Research)

[40] Establishment of National Survey System on Trends of Antibiotic Use and Evaluation of the Effect of Premium for Infection Control, supported by the FY 2013 Health and Labour Sciences Research Grants (Grants-in-Aid for Scientific Research)

- Explore collaboration possibilities between JANIS and the AMU surveillance systems for inpatient and outpatient departments

■ **Apply Antimicrobial Use Surveillance to Risk Assessment and Risk Management**

- Link AMU indicators of some medical institutions with JANIS data utilizing research products
- Implement preliminary quantitative and qualitative evaluation of AMS in individual medical institutions (see Strategy 4.1)
- Develop guidelines to evaluate the quality of AMS using AMU indicators
- Prepare a system capable of quantitative and qualitative evaluation using AMU indicators in the Regional Network for Infectious Diseases Prevention and Control (tentative name) (see Strategy 3.1)

■ **Monitor the State 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

- AMU in medical institutions
- Number of organizations participating in AMU surveillance for inpatient and outpatient departments
- Number of local governments conducting systematic evaluation of local AMU indicators.

STRATEGY 2.3 STRENGTHEN SURVEILLANCE AND MONITORING IN THE FIELDS OF VETERINARY MEDICINE, LIVESTOCK PRODUCTION AND AQUACULTURE

BACKGROUND

- Since 1999, the Government of Japan has had in place a system to monitor nation-wide trends of antimicrobial resistance (AMR) in livestock, called the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM). Its core laboratory, the National Veterinary Assay Laboratory (NVAL), conducts surveillance and monitoring of antimicrobial-resistant organisms (AROs) in partnership with prefectures, the Food and Agricultural Materials Inspection Center (FAMIC), and other organizations, and publishes an annual report on the outcomes. Data on antimicrobial use (AMU) is also collected as part of JVARM, and the results are published annually.
- JVARM has been promoting collaboration with the Japan Nosocomial Infections Surveillance (JANIS) for the mutual use of each other's data. Its collaboration with relative areas needs to be expanded and enhanced toward the establishment of a One Health Surveillance system.
- JVARM conducts survey and research including characterization of various AROs and uses the results as the basis for risk assessment. However, JVARM has not yet conducted further advanced research such as whole genome analysis.
- The Food and Agricultural Organization of the United Nations (FAO) considers that antimicrobial-resistant bacteria of aquacultural origin has a minor impact on human health.[41] Organized surveillance and monitoring systems are not seen overseas in this sector. Surveillance and monitoring in Japan have been also limited to study antibiotic susceptibility of certain pathogens which can be affected by veterinary antibiotics used in aquaculture.
- As the World Organisation for Animal Health (OIE) has not been considering pets as a subject of surveillance and monitoring, surveillance and monitoring of pets are not currently conducted in Japan. Some countries, however, conduct surveillance and monitoring on antibiotic susceptibility in pets.
- Organized surveillance and monitoring systems in the agricultural sector are not seen in and out of Japan.

POLICIES

- Strengthen the capacity and system of the core AMR laboratory in livestock production and aquaculture. Establish an integrated surveillance and monitoring system with collaborating testing agencies
- Strengthen surveillance and monitoring by establishing a survey system to study antimicrobial resistance genes (ARGs) in livestock production and aquaculture
- Establish a surveillance and monitoring system for pets to enable monitoring of AMR trends in pets.
- 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 and implement risk management measures and to ensure prudent use of antibiotics

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

ACTIONS

■ Establish and Strengthen Surveillance and Monitoring Systems in Livestock Production, Aquaculture, and Veterinary Medicine

- Strengthen surveillance and monitoring in livestock production and aquaculture
  - ✓ Expand the AMR surveillance and monitoring for livestock and farm-raised aquatic animals through strengthening JVARM
  - ✓ Develop an antibiotic susceptibility test manual to uniform comparison and evaluation in livestock production and aquaculture (Strategy 2.4). Strengthen the capacity and system of NVAL, which serves as the core laboratory to integrate such efforts
  - ✓ Collect data based on a uniformed methods and controlled quality ensured by collaborating testing agencies
  - ✓ Establish survey systems for targets including ARGs
  - ✓ Engage in integrated surveillance and monitoring through enhanced collaboration with JANIS
  - ✓ Establish AMU surveillance and monitoring systems of antibiotic feed additives for each animal species
- Establish a surveillance and monitoring system for pets
- Implement surveillance and monitoring on antimicrobial use in agriculture

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

- Surveillance and monitoring report
- 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, drug susceptibility tests, nucleic acid amplification tests, antimicrobial resistance gene (ARG) tests, and AMR rapid diagnosis kits. Epidemiological genome analysis (molecular epidemiology) is used to study antimicrobial-resistant organism (ARO) outbreaks. However, quality control measures have not uniformly been applied nationwide to these tests, posing obstacles to the implementation and evaluation of AMR surveillance and monitoring. The number of laboratories capable of conducting detailed analysis on AMR including ARG is still limited, and examination standards, targets, and methods used among them are not standardized.
- In-house clinical microbiological laboratories play significant roles in AMR and healthcare-associated infections (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 quality control systems for AMR tests
- Conduct research on microbial examination systems, which aims to enhance AMS in medical institutions
- Explore the possibilities of introducing new technologies and equipment in public and animal health laboratories[42] to enhance their reference capacity for AMR

ACTIONS

■ **Standardize Testing Methods and Strengthen Quality Control**

- Develop a drug susceptibility test manual in line with the international standards, which enables uniformed comparison and evaluation in each sector and implement training using the manual
- Support the establishment of external quality control systems and promote the introduction of the system in medical institutions and outsourced laboratory services
- Develop manuals and guidelines for testing ARGs and comparative analysis of AROs
- Develop manuals and guidelines for each medical institution to create an antimicrobial susceptibility table (e.g. antibiogram) of major causative microorganisms
- Standardize the methods used in testing agencies for livestock, farm-raised aquatic animals and pets. Provide training and conduct quality control for tests. These measures will be implemented under the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM)

[42] 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

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

- Strengthen and expand AMR reference capacity in public and animal health laboratories
- Promote clinical research on the use of clinical laboratory examinations related to AMR[43] basic microbial testing[44], which may contribute enhancing AMS (see Strategy 5.2)

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

- Develop new technologies for surveillance and monitoring based on molecular epidemiology[45] And promote their application in public and animal health laboratories
- Strengthen surveillance and monitoring based on molecular epidemiology[46] by expanding the 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

[43] 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).
[44] Basic microbial tests include: Gram staining, fluorescent labeling, bacterial culture and identification, anaerobic culture test, bacterial drug susceptibility test, acid-fast bacilli culture test, acid-fast bacilli drug susceptibility test, yeast-like fungus antifungal susceptibility test, rapid diagnosis of various bacteria and viruses.
[45] New technologies for surveillance and monitoring based on molecular epidemiology include: Microarray, whole genome sequencing (WGS), and metagenomic analysis.
[46] Elucidate the transmission pathways of ARGs and AROs by interchanging data from 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 AMR.
- Japan currently has two 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. Their collaboration has been promoted. On food, research has been conducted on multidrug-resistant *Enterobacteriaceae* and Vancomycin-resistant *Enterococci*. Data on AMR in bacteria of food origin has been collected by prefectural and municipal public health institutes. Research for linking these data from JANIS and JVARM is in progress.
- Surveillance and monitoring have not been conducted for other areas (e.g. aquatic environment, pets, and wild animals).

POLICIES

- Create a network to gather and share data, consisting of 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 a One Health Surveillance system, which links data from multiple surveillance and monitoring systems including the JANIS and JVARM
- Establish a national council, which integrates information from different surveillance and monitoring and makes international comparison for the analysis and evaluation to regularly analyze and evaluate AMR trends and control measures, and use the outcomes during the review process of this National Action Plan in 2020
- Build and strengthen surveillance and monitoring systems for livestock, aquaculture, and pets. Also, conduct surveillance and monitoring of antimicrobial use in agriculture
- Conduct research to prepare for establishing surveillance and monitoring systems of antimicrobial-resistant organisms (AROs) in food
- Conduct research also on surveillance and monitoring of AROs and residual antimicrobials in aquatic and terrestrial environment, as well as in wild animals

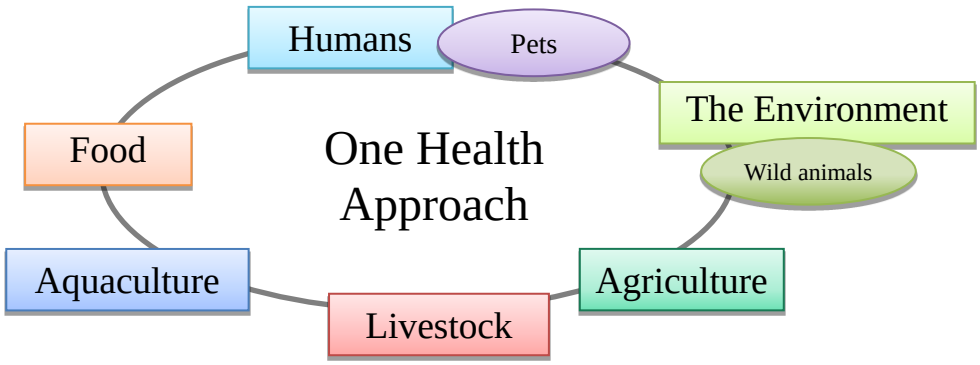

Figure 2.1. Collaboration under One Health approach

ACTIONS

■ Establish a Comprehensive One Health Surveillance System

- Launch the One Health Surveillance Council on Antimicrobial Resistance (tentative name)[47] for AMR and AMU, and subsequently implement the following;
  - ✓ Create the One Health Surveillance Network on AMR (tentative name), which includes NIID, NVAL, NCGM to gather and share data
  - ✓ Analyze and evaluate AMR and AMU based on the integrated data from surveillance and monitoring, other scientific studies, and tests conducted by local governments
  - ✓ Create and publish a comprehensive surveillance and monitoring report annually
  - ✓ Develop guidelines for surveillance and monitoring
- Conduct research to prepare for establishing an AMR surveillance and monitoring system for food[48,49]
- Analyze transmitting factors of AMR in humans, animals, and food. Conduct research to elucidate linkage between their transmission processes
- Conduct research to monitor AMR and residual antimicrobials in aquatic and terrestrial environment
- Enhance the AMR surveillance and monitoring of livestock and farm-raised aquatic animals through strengthening JVARM and establish AMR surveillance and monitoring system for pets
- Link data related to AMR surveillance and monitoring across humans, animals, and food
- Implement surveillance and monitoring on agricultural AMU
- Modify the national surveillance and monitoring projects to align with the Global Antimicrobial Resistance Surveillance System (GLASS)

RELATED MINISTRIES, AGENCIES, AND INSTITUTIONS

Food Safety Commission of Japan (FSC), Cabinet Office (CAS); Ministry of Health, Labour and Welfare (MHLW); Ministry of Agriculture, Forestry and Fisheries (MAFF); Ministry of the Environment (MOE); NIID; 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

- Report on surveillance under One Health approach
- Number of samples obtained by AMR surveillance and research in each sector

[47] Targets: Healthcare, livestock production, aquaculture, agriculture, environment, food, and others
[48] This includes imported food products.
[49] The research is in progress under the project, the Research on the Prevalence Trends of Antimicrobial-resistant Bacteria of Food Origin and Hygiene Control, supported by the FY2015 Health and Labour Sciences Research Grants.

GOAL 3
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

(3.2) Promote Infection Prevention and Control in Livestock Production, 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 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 among medical institutions are being established to support infection control of small and medium-sized medical institutions.[50]
- 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 infections (ARIs) have become a hot issue in nursing care facilities, efforts to control healthcare-associated infections (HAIs)[51] are being promoted as a broader concept.[52] However, current nosocomial infection control is mainly intended for inpatient departments of medical institutions, and it is not clearly stated to cover outpatient departments and nursing care facilities.

POLICIES

- Promote a cooperation system in which 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 AMR control, linking the efforts of the existing infection control team (ICT) at the field level with those of antimicrobial stewardship (AMS)
- Regarding 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 IPC (automatic analytical system of clinical data, etc.)
- Enhance IPC through promoting vaccination and utilizing the relevant framework of medical care quality evaluation

ACTIONS

■ Promote Infection Prevention and Control and Strengthen Regional Cooperation

- Promote measures for promoting IPC at outpatient departments and for home care by the Technical Advisory Board on Antimicrobial Resistance (tentative name) (see Stratety 4.1), as appropriate
- Implement research to review target facilities and subjects to the Japan Nosocomial Infections Surveillance (JANIS) (see Strategy 2.1).
- Implement research to develop a concrete activity model of regional infection control measures, i.e. Regional Network for Infectious Diseases Prevention and Control (tentative name)

[50] 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.
[51] L. J. Strausbaugh. Emerging health care-associated infections in the geriatric population. *Emerg Infect Dis*. 2001 Mar-Apr; 7(2): 268–271.
[52] Cohen CC et al., State focus on health care-associated infection prevention in nursing homes. *Am J Infect Control*. 2014; 42: 360-5.

- Disseminate concrete application models of premium for regional cooperation in infection control, and promote more effective operation
- Introduce AMS and AMR screening components into the IPC guidelines and manuals, based on current situation surveys of antimicrobials at nursing care facilities, as appropriate (linked to Strategy 5.2)

■ **Foster Local 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
- Conduct research to develop a manual for risk assessment and management on AMR in cooperation with local stakeholders
- Conduct benchmarking for IPC at the level of medical institutions, regions and nation, and implement research for promoting IPC measures based on the results

■ **Promote Infection Prevention**

- Promote vaccinations (pneumococcal vaccines, *Heamophilus influenzae* Type b vaccines, influenza vaccines, etc.) contributing to the prevention of ARIs
- Promote evaluations related to IPC, 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 HAIs caused by AROs
- Number of municipalities that have established Regional Network for Infectious Diseases Prevention and Control (tentative name) that meets the requirements
- Immunization rates of pneumococcal vaccine, *Haemophilus influenzae* Type b (Hib), and Influenza vaccine

STRATEGY 3.2 PROMOTE INFECTION PREVENTION AND CONTROL IN LIVESTOCK PRODUCTION, 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 veterinary antibiotics. 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 Standards of Rearing Hygiene Management were established based on the provisions of the Act on Domestic Animal Infectious Diseases Control (Act No. 166 of 1951). Hygienic control status of the rearing of domestic animals (cattle, pig, poultry, etc.), the implementation status of instructions, advice, recommendations and orders submitted by the Prefectural Governor, and the status of securing animal health inspectors are announced to the public every year by each prefecture, to promote the improvement in the conditions of hygienic control.
- Prepare and distribute a Handbook for Hygienic Management during Production, that describes comprehensive measures to produce safer animal products as well as to prevent the occurrence of food poisoning, in addition to measures to prevent infectious diseases in domestic animals provided in the Standards of Rearing Hygiene Management (FY2011: for beef cattle, for broilers; FY2012: for layers; not prepared for pork).
- During food processing and distribution processes, promote countermeasures to reduce contamination with AROs and other microorganisms as well as to prevent food poisoning from occurring by promoting HACCP (Hazard Analysis and Critical Control Point).[53]
- 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

- Try to raise and promote awareness of infection prevention and control at facilities related to livestock production and aquaculture as well as veterinary medicine through further stringent compliance with the Standards of Rearing Hygiene Management, appropriate vaccinations, and preparation and distribution of the Handbook for Hygienic Management during Production
- Raise awareness that the prevention of infectious diseases will result in antimicrobial resistance control, reducing the opportunities to use veterinary antibiotics
- Promote HACCP for food processing and the distribution process

[53] A food hygiene control procedure that controls especially important process to prevent contamination with food poisoning bacteria and foreign substances that may occur from receipt to release of raw materials.

ACTIONS

- **Promote Infection Prevention and Control of Livestock, Farm-raised Aquatic Animals and Pets**
  - Promote development and usage of vaccines for livestock, farm-raised aquatic animals and pets
  - Ensure full compliance with the Standards of Rearing Hygiene Management based on the provisions of the Act on Domestic Animal Infectious Disease Control, and wider use of the Handbook for Hygienic Management during Production
- **Promote Infection Prevention and Control of Food processing and Distribution Process**
  - Promote HACCP (Hazard Analysis and Critical Control Point)

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 put to practical use
- Status of compliance with the Standards of Rearing Hygiene Management
- Number of distributed copies of the Handbook for Hygienic Management during 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 ARIs by establishing guidelines and providing training seminars.
- Moreover, outbreaks of 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 ARI outbreaks. The outbreak of enterohemorrhagic *Escherichia coli* O104 in Germany in 2011 was also associated with ARO.[54] Strengthening the ability to respond to mass food poisoning with antimicrobial-resistant foodborne bacteria is also an important issue to be addressed.[55]
- At present, as a support to respond to outbreaks, there is only epidemiological support by the National Institute of Infectious Diseases (NIID), and a system that provides the necessary support for infection prevention and control, clinical management, and administrative responses has not been established.

POLICIES

- Develop manuals and guidelines to respond to both nosocomial and community outbreaks of ARIs at a local level , and establish a system whereby local professionals provide support to respond to an outbreak
- Strengthen response capacities and establish a network through increasing education and training opportunities for those involved in the ARI outbreak
- Establish a rapid 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

ACTIONS

- **Support Local Responses to Outbreaks of Antimicrobial-Resistant Infections**
  - Support local response to ARI outbreaks by the Regional Network for Infectious Diseases Prevention and Control (tentative name) (see Strategy 3.1)
    - ✓ Prepare manuals and guidelines to respond to nosocomial outbreaks at a local level
    - ✓ Establish criteria for early reporting to prevent the spread of a local outbreak
  - Conduct training seminars for members of the Regional Network for Infectious Diseases Prevention and Control (linked to Strategy 2.1)
  - Implement training seminars for the responsible persons in local governments (linked to Strategy 2.1)

[54] Muniesa M, et al. Shiga Toxin-Producing Escherichia coli O104:H4: a New Challenge for Microbiology. *Appl Environ Microbiol*. 2012; 78: 4065-73.
[55] Antibiotic resistance in foodborne germs is an ongoing threat, CDC 2012 http://www.cdc.gov/media/releases/2014/p0701-antibiotic-resistance.html ,accessed on Dec 16, 2015

- **Strengthen the Capacity to Respond to Large Scale Outbreaks**
  - Consider a system to create a talent pool of AMR professionals[56] who can respond in case of an extreme shortage of human resources associated with an outbreak

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 ARIs
- Number of training seminars implemented for relevant parties

[56] Graduates of the Field Epidemiology Training Program Japan (FETP-J), 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, IPC and public health who belong to other medical institutions and research institutes

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

Strategy

(4.1) Promote Antimicrobial Stewardship at Medical Institutions

(4.2) Ensure Prudent Use of Antibiotics for Animals in the Field of Livestock Production, 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), IPC cannot prevent the emergence of antimicrobial-resistant organisms (AROs) and the resultant occurrence of antimicrobial-resistant infections (ARIs) by itself.
- To minimize the occurrence of ARIs and to reduce the resultant disease burden, it is extremely important to ensure appropriate use of antimicrobials, i.e. antimicrobial stewardship (AMS) for inpatient and outpatient.[57] For example, in the U.S., antibiotics are administered to 40 million people every year for respiratory problems, among which 27,000 persons are reportedly administered with unnecessary antibiotics.[58]
- AMS has effects to reduce unnecessary prescriptions and suppress the emergence of AROs, while controlling medical expenses. In Japan, there is research that, after a simple test to distinguish between bacterial infections and viral infections (gram stain) was introduced for outpatient at clinics, the use of broad-spectrum oral antibiotics was reduced to less than one-third, the monetary amount of antibiotics consumed per outpatient was cut down to one-fifth, and patients with pediatric sinusitis not using antibiotics were increased nine-fold.[59] There is also a report that a university hospital that introduced an AMS program succeeded to reduce its annual expenditure by approximately 300 million yen.[60]
- However, many medical institutions in Japan have promoted antimicrobial stewardship measures, including the mandatory pre-authorization or reporting for specified antibiotics use, which is a requirement for the IPC premium.[61] On the other hand, no comprehensive national AMS program has been established.
- AMS is an area that essentially requires consideration concerning conflict of interest (COI) with the pharmaceutical industry. In the U.S.,[62] Europe,[63,64] Hong Kong,[65] and other regions, public agencies have issued official guidelines or manuals pertaining to the appropriate treatment of infectious diseases.

Policies

- Establish a national council focusing on promotion of AMS, and develop comprehensive AMS guidelines and official clinical management manuals for infectious diseases
- Develop guidance to enable each medical institution to formulate its AMS guidelines and management manuals for infectious diseases based on the institution-specific antimicrobial susceptibility
- Promote AMS and appropriate clinical management of infectious diseases through operation of antimicrobial stewardship teams (ASTs) and the quality evaluation of AMS

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[57] Society for Healthcare Epidemiology of America, Infectious Diseases Society of America and 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: 322-7.

[58] Shapiro DJ, et al. Antibiotic prescribing for adults in ambulatory care in the USA, 2007-09. *J Antimicrob Chemother*. 2014; 69: 234-40.

[59] Maeda, et al. Changes in the Selection and Use of Antibiotics following the Introduction of Gram Staining at Otorhinolaryngologic Clinics: A Preliminary Study. Japan Primary Care Association Journal 2015; 38: 335-9.

[60] Niwa T, et al. Outcome measurement of extensive implementation of antimicrobial stewardship in patients receiving intravenous antibiotics in a Japanese university hospital. *Int J Clin Pract*. 2012; 66: 999–1008.

[61] Broad-spectrum antibiotics including anti-MRSA drugs and carbapenem antibiotics

[62] Harris AM, et al. Appropriate Antibiotic Use for Acute Respiratory Tract Infection in Adults: Advice for High-Value Care From the American College of Physicians and the Centers for Disease Control and Prevention. *Ann Intern Med.* 2016; doi:10.7326/M15-1840. [Published online 19 January 2016]

[63] Swedish Institute for Communicable Disease Control, Behandlingsrekommendationer för vanliga infektioner i öppenvård. http://www.folkhalsomyndigheten.se/publicerat-material/publikationer/Behandlingsrekommendationer-for-vanliga-infektioner-i-oppenvard

[64] Belgian Antibiotic Policy Coordination Committee. Guide belge des traitements anti-infectieux en pratique ambulatoire - édition 2012.

[65] Centre for Health Protection. Reducing bacterial resistance with IMPACT-Interhospital Multi-disciplinary Programme on Antimicrobial Chemotherapy, Fourth Edition.

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

ACTIONS

■ Publish guidelines/manuals for Antimicrobial Stewardship

- Establish a Technical Advisory Board on Antimicrobial Resistance (tentative name) within Ministry of Health, Labour and Welfare (MHLW) to promote IPC and AMS (linked to Strategy 3.1)
- Formulate national AMS guidelines and clinical management manuals for infectious diseases

■ Review regulations regarding diagnosis and treatment to promote Antimicrobial Stewardship

- 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 official clinical management guidelines for infectious diseases and other documents

➢ Review regulations regarding the prescription of antimicrobials for outpatients with acute upper respiratory tract infection based on related research results[66] (linked to Strategy 5.2)

■ Support establishment of a system to promote Antimicrobial Stewardship at medical institutions

- Add the specific AMS components to professional education and training for physicians, pharmacists, nurses, clinical technologists and particular professionals (see Strategy 1.2)
- Support medical institutions in the formulation of AMS guidelines, including proper management of COI and clinical management manuals for infectious diseases based on the institution-specific antimicrobial susceptibility at each medical institution (linked to Strategy 2.4)
- Establish ASTs at medical institutions and implement research on the policy performance of securing AMS-dedicated personnel
- Add an AMS governance role into the institutional nosocomial infection control committee, as needed, based on the research results
- Establish local mechanisms that introduce experts to conduct training and provide consultation services based on requests (linked to Strategy 1.2) through the Regional Network for Infectious Diseases Prevention and Control (tentative name) (see Strategy 3.1) in addition to promotion of institutional peer-review based on the premium for regional cooperation in infection control
- Conduct research on the development of the Antimicrobial Chemotherapy Registration System (tentative name) and the utilization of pharmacists (see Strategy 5.3)

> **Antimicrobial Chemotherapy Registration System (tentative name):** A system for registering antibiotic regimens in medical records and/or ordering systems to standardize the quality of antibiotic chemical treatment regimens, while clarifying the purpose of use of antibiotics, thereby supporting AMS core elements, including the promotion of culture sampling before antimicrobial administration, the selection of standard therapy, the optimization of dosage and administration route and duration including de-escalation.

[66] 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 AMS strategies.
Spurling GKP et al. Delayed antibiotics for symptoms and complications of acute respiratory tract infections. *Cochrane Database Syst Rev*. 2013; 4: CD004417.
Dar OA at al. Exploring the evidence base for national and regional policy interventions to combat resistance. *Lancet*. 2015 Nov 17. pii: S0140-6736(15)00520-6.

Related Ministries, Agencies and Institutions

MHLW; National Center for Global Health and Medicine (NCGM)

Evaluation Indices

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

STRATEGY 4.2 ENSURE PRUDENT USE OF ANTIBIOTICS FOR ANIMALS IN THE FIELD OF LIVESTOCK PRODUCTION, 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, measures are taken in Japan based on the principles of risk analysis established by the international standards of the World Organisation for Animal Health (OIE) and the Codex Alimentarius Commission. Based on the results of risk assessment concerning the impact of antimicrobial- resistant bacteria on human health through food, conducted by the Food Safety Commission of Japan (FSC), the Ministry of Agriculture, Forestry and Fisheries (MAFF) formulates and implements risk management measures in accordance with the extent of risks, taking into account the on-farm feasibility of such measures.
- Appropriate use of veterinary antibiotics is ensured through various regulatory systems based on applicable laws.[67] Pharmaceutical inspectors in each prefecture are taking measures to raise awareness concerning compliance with those regulations, while supervising and guiding actual use.
- Guidelines concerning the use of veterinary antibiotics have been formulated by the OIE, the Codex Alimentarius Commission, other international organizations, and many national governments. The Japanese government has also established guidelines concerning the prudent use of veterinary antibiotics in livestock farming, and is seeking to raise awareness toward prudent use, through the implementation of guidance and seminars held by national and prefectural governments aimed at veterinarians and producers.
- 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.[68] Products that may negatively affect human medicine are not to be designated as feed additives.
- Risk assessment by FSC remains to be conducted for certain antibiotic feed additives, but has been completed for additives which account for the majority of the total antibiotic feed additive use. The results of risk assessments of most ingredients have been determined as “negligible” or that “the absence of adverse effects on human health is clear (and therefore the risk assessment is not required)”.

POLICIES

- Formulate continued 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

[67] To ensure the proper and limited use of veterinary antibiotics, measures are taken with regard to the use and sales of veterinary drugs 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 (Pharmaceutical and Medical Device Act, Law No. 145 of 1960).

[68] Measures are taken to promote the proper and limited use of antibiotic feed additives, based on the Act on Safety Assurance and Quality Improvement of Feeds (Law No. 35 of 1953).

bacteria on human health through food, conducted by FSC, in accordance with the principles of risk analysis established by the international standards of OIE and the Codex Alimentarius Commission

- ○ Establish and enhance methodology 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 AMR due to antibiotic use in animals:**
  - Formulate and appropriately implement risk management measures approval in accordance with the results of risk assessment conducted by FSC, taking into account the on-farm feasibility and the guidelines for developing risk management measures (such measures may include the revocation of designation, temporary prohibition of use, narrowed scope of applicable animal species and breeding stages, and strengthened surveillance and monitoring.)
  - 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 criteria considered necessary to assess the effect of antimicrobial-resistant bacteria on human health through food, and the "Ranking of the Importance of Antimicrobials against Bacteria which Affect Human Health through Food", which is basic material to assess the effect of food commodities contaminated by antimicrobial-resistant bacteria on human health
  - Review, as needed, the guidelines for developing risk management measures concerning veterinary antibiotics and antibiotic feed additives

- **Strengthen the system for ensuring the prudent use of veterinary antibiotics**
  - 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 Veterinary Antibiotics in Livestock Production" and "Guidance concerning the Appropriate Use of Aquaculture Drugs"; and review, as needed, brochures targeted at veterinarians and leaflets targeted at producers
  - Prepare leaflets concerning the appropriate use of antibiotic feed additives, targeted at producers and feed manufacturers
  - Establish determination methods for antibiotic susceptibility as the basis for the prudent use of veterinary antibiotics, and indices concerning the effectiveness of treatment
  - Examine and implement a status survey concerning the consumption of veterinary antibiotics on production sites
  - Strengthen the leadership of specialists (e.g. veterinarians, pharmaceutical inspectors, aquatic animal health inspectors) in the use of veterinary antibiotics for farm-raised aquatic animals

- **Identify the appropriate amounts of consumption of antibiotics for animals**
  - Estimate and monitor the total amounts of consumption of antibiotics for humans and of veterinary antibiotics in Japan, through collaboration between the surveillance and monitoring by the Japanese Veterinary Resistance Monitoring System (JVARM) in animal health and the surveillance and monitoring in human medicine
  - Calculate the amounts of consumption of veterinary antibiotics for each animal species, based on appropriate units of consumption of veterinary antibiotics, and internationally compare the calculated amounts

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 TO SECURE THE MEANS TO PREVENT, DIAGNOSE AND TREAT THE ANTIMICROBIAL-RESISTANT INFECTIONS

Strategies

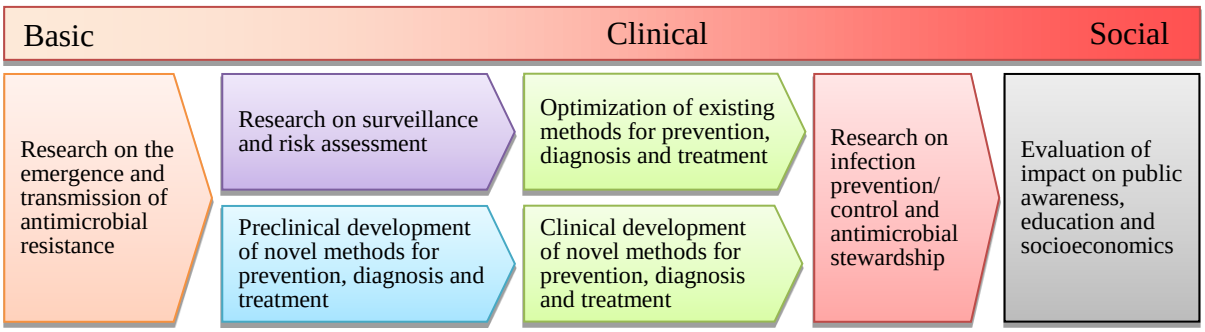
(5.1) Promote Research to Elucidate the Mechanism of the Emergence and Transmission of Antimicrobial Resistance and its Socioeconomic Impact

(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



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 AMR, specifying the types of organisms that acquire resistance, the mechanism of acquisition, and the channels and extent of the spread. Activities have been enhanced globally to figure out this entire ecosystem of AMR.[69]
- It is important to preserve strains isolated from antimicrobial-resistant organisms (AROs) and to accumulate genome data including antimicrobial-resistant genes (ARGs) to promote AMR-related research and development (R&D), including the research on AMR mechanisms and the development of new methods for prevention, diagnosis and treatment. In the U.S., the Centers for Disease Prevention and Control (CDC) and the Food and Drug Administration (FDA) established an FDA-CDC Antimicrobial Resistance Isolate Bank in July 2015, and R&D has been promoted using this bank.[70]
- Estimation of the impact of 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 U.K. Review on Antimicrobial Resistance has estimated that deaths due to 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.[71]
- According to provisional estimation by a research supported by the Health and Labour Sciences Research Grants (Grants-in-Aid for Scientific Research),[72] additional medical expense for the treatment of Methicillin-resistant *Staphylococcus aureus* (MRSA), including pre-emptive therapy, at 1,133 cooperating medical institutions that have introduced the Per Diem Payment System based on Diagnosis Procedure Combination (DPC/PDPS) in 2014 would reach 170 billion yen (approximately 3.5% of all inpatient medical expenses), with additional hospitalization days at 3.73 million days (3.1% of all hospitalization days), and additional deaths of 10,340 (3.1% of all deaths).

POLICIES

- Promote research to elucidate the emergence and transmission of AMR based on the genome analysis
- Promote AMR genome surveillance to figure out AMR mechanisms and drug discovery by promoting the preservation of ARO strains, and utilizing the pathogen genomics database that contains antimicrobial resistance data provided by the National Institute of Infectious Diseases (NIID)
- Establish a genome database of resistant bacteria in the fields of agriculture and aquaculture in the National Veterinary Assay Laboratory (NVAL), to contribute to AMR measures in collaboration with the AMR genome database (GenEpid-J) of the NIID
- 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

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[69] Strategic Research Agenda, Joint Programming Initiative on Antimicrobial Resistance, http://www.jpiamr.eu/activities/strategicresearchagenda/, accessed on 21 December 2015.

[70] FDA-CDC Antimicrobial Resistance Isolate Bank, http://www.cdc.gov/drugresistance/resistance-bank/ , accessed on 21 December 2015.

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

[72] Health and Labour Sciences Research Grants (Grants-in-aid for Scientific Research) 2015, "Research concerning the Evaluation of Risks in Health and Economics Caused by the Prevalence of Drug-resistant Organisms".

ACTIONS

■ Promote research on the emergence and transmission of antimicrobial resistance

- Promote research to elucidate the AMR mechanisms, the transmission process of AROs/ARGs, and the ecosystem of AROs/ARGs including their spread and interaction in general society and the environment (linked to Strategy 2.1)
- Promote the preservation of isolates and the creation of an isolates bank that is accessible to industry, academia and government (linked to Strategy 2.4 and Strategy5.4)
- Promote AMR genome surveillance, research on mechanisms of AMR emergence and transmission, and R&D for drug discovery, including through utilizing the isolates bank and AMR genome database (GenEpid-J)
- Expand AMR genome database, including through data collection of isolates at home and overseas
- Establish a genome database in the fields of agriculture and aquaculture, as part of the Japanese Veterinary Resistance Monitoring System (JVARM)
- Conduct research to elucidate the mechanisms on AMR emergence and transmission, and Critical Control Points (CCP) in livestock production, aquaculture and veterinary medicine

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

- Promote research on the disease burden[73] and economic burden[74] of ARIs at healthcare institutions (linked to Strategy 2.1)
- Promote research concerning the effect of AMR measures on the reduction of medical expenses
- Promote research on systematic risk assessment based on surveillance results
- Utilize the prescription big data in the National Database for Prescription and National Health Check-up (NDB) to figure out antimicrobial use

RELATED MINISTRIES, AGENCIES AND INSTITUTIONS

Office of Healthcare Policy, Cabinet Secretariat (CAS); Ministry of Education, Culture, Sports, Science and Technology (MEXT); Ministry of Health, Labour and Welfare (MHLW); Ministry of Agriculture, Forestry and Fisheries (MAFF); 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

[73] Incidence rate, mortality, rate of sequelae, hospitalization days, disease burden indices (e.g. DALYs, YLD), etc.
[74] Research is in progress under Health and Labour Sciences Research Grants (Grants-in-aid for Scientific Research) 2015, "Research concerning the Evaluation of Risks in Health and Economics Caused by the Prevalence of Drug-resistant Organisms".

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-raising and education activities, research on identifying people's knowledge, attitudes and practices concerning antimicrobial use and AMR, and messages leading to behavior modification is crucial. In the U.S. and Europe, research has been undertaken regarding effective campaign methods targeted at people and at healthcare professionals.[75,76] On the other hand, there are only a few surveys on public awareness that exist in Japan and we face a lack of basic data on public knowledge, attitudes and practices on antimicrobial use and AMR.
- Japan has economic incentive mechanisms of regional cooperation in infection prevention and control (IPC), and research is in progress concerning its effectiveness.[77]
- 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 (Figure 0.1). At the same time, a comprehensive national system for supporting AMS in medical institutions has yet to be introduced, and the relevant research activities are still small in scale.
- In the field of livestock production, surveillance and research have been conducted concerning indices and scientific evidence required for the prudent use of veterinary antibiotics.
- For the effective implementation of antimicrobial resistance-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.

POLICIES

- Conduct research on effective intervention methods and benchmarking methods to measure the effectiveness of promoting public awareness and education, IPC, and AMS

ACTIONS

- **Research on behavior change**
  - Implement 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 and infection prevention and control in human medicine**

[75] Perz JF et al., Changes in Antibiotic Prescribing for Children After a Community-wide Campaign. *JAMA*. 2002; 287: 3103-3109.
[76] Goossens H et al., National campaigns to improve antibiotic use. *Eur J Clin Pharmacol*. 2006; 62: 373-9.
[77] 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".

- Conduct research to evaluate progress in AMS and its effectiveness and cost-effectiveness at medical institutions (linked to Strategy 4.1)
- Conduct clinical research on the utilization of basic microbiological tests that contributes to AMS (linked to Strategy 2.4)
- Conduct research on the effectiveness and safety of prescription regulation for outpatients with acute upper respiratory tract infection (linked to Strategy 4.1)
- Conduct research on the risk of colonization by antimicrobial-resistant organisms (ARO) and the relevant screening methods at medical institutions
- Conduct research on the status of antimicrobial use at nursing care facilities (linked to Strategy 3.1)
- Conduct research toward the development of a comprehensive regional collaboration system to provide benchmarking data on IPC and AMS, and surveillance information to the Regional Network for Infectious Diseases Prevention and Control (tentative name) (linked to Strategy 3.1)
- Conduct research and development (R&D) for assisting tools to support appropriate diagnosis and treatment of infectious diseases in line with AMS policies
- Conduct research on the isolation trend and molecular epidemiology of AMR in home healthcare[78]

■ **Research in livestock production, aquaculture and veterinary medicine**

- Promote research for preparing manuals for the use of veterinary antibiotics for in each disease in the fields of livestock production and aquaculture, as well as research concerning changes in the resistance following the discontinuation of use of antibiotics for animals, and secondary risks

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

[78] 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".

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 medicines in Japan due to strict pharmaceutical licensing regulation.
- 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 colistin and other drugs.[79] On the other hand, there are drugs that have yet to be approved and those that have been withdrawn from the market, despite their importance in antimicrobial stewardship (AMS).[80]
- For some antimicrobials, administration and dosage have not been adjusted based on the latest Pharmacokinetics/Pharmacodynamics (PK/PD) to enable optimal antimicrobial use. There are also drugs that include indications covered by health insurance, which are not global recommended for specific infectious diseases. For example, guidelines in the U.S. and Europe recommend not to use third-generation oral cephalosporin antibiotics for patients with streptococcal pharyngitis.[81,82]
- The total amount of consumption of antibiotics is relatively smaller in Japan than in other developed European countries; however, it has been pointed out that the proportion of broad-spectrum oral antibiotics including cephalosporins, fluoroquinolones, macrolides that promote antimicrobial resistance (AMR) is higher in Japan[83] and only limited measures have been taken to promote clinical and epidemiologic research toward the optimization of existing methods for prevention, diagnosis and treatment.

POLICIES

- Implement reviews on existing methods of prevention, diagnosis and treatment of infectious diseases which contribute to containment of AMR and have not become available in Japan, and promote research on optimizing drugs to be used in Japan, based on the latest scientific evidence
- Promote research to accumulate the scientific evidence and apply them to AMR measures

[79] 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, MHLW: http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iyakuhin/kaihatsuyousei/; Accessed on 7 January 2016.

[80] Nafcillin, benzathine penicillin, ertapenem, nitrofurantoin, etc.

[81] Shulman ST, et al., Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012; 55: e86-e102.

[82] Pelucci C, et al., ESCMID Guideline for the Management of Acute Sore Throat. *Clin Microbiol Infect*. 2012; 18 (Suppl. 1): 1–27.

ACTIONS

- **Research on the optimization of existing methods for prevention, diagnosis and treatment**
  - Conduct research to introduce or re-introduce useful methods to prevent, diagnose and treat infectious diseases for AMR countermeasures, which are available in other countries but not in Japan (either unapproved or withdrawn from the market)
  - Conduct research on regulation to preserve the existing effectiveness of antimicrobials
  - Conduct research on the treatment of antimicrobial-resistant infections (ARIs) by modification of existing therapeutics including combination therapy and high-dose therapy
  - Conduct research on the development of the Antimicrobial Chemotherapy Registration System (tentative name) and the utilization of pharmacists (same as Strategy 4.1)

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.
- ○ However, the number of antimicrobials developed in Japan has been declining after peaking out in the 1980s. 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.
- ○ 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 May 2014). The development of new drugs for developing countries is also in progress aimed at the promotion of international cooperation in health and medicine, including new drugs for drug-resistant malaria, tuberculosis and neglected tropical diseases (NTDs) through the Global Health Innovation Technology Fund (GHIT Fund).
- ○ In the field of livestock production, surveillance and research are implemented by universities and private organizations under national projects, concerning determination methods for antibiotic susceptibility required for the prudent use of veterinary antibiotics.

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 AMS, antimicrobials with novel mechanisms, and other non-traditional therapeutics
- ○ Establish a council to promote public private partnership on AMR to set R&D priorities and create incentives for R&D, taking into account the frequency of emergence of 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 infectious diseases in humans and animals

- Promote R&D on novel preventive approaches that do not induce the emergence of AROs[84]

■ **Promote research and development of novel diagnostics**

- Promote R&D on rapid diagnostic tools and equipment for identification of causal organisms and AMR, which contribute to AMS and ARO containment measures[85]
- Develop simplified test methods that contribute to the prudent use of veterinary antibiotics on production sites

■ **Promote research and development of novel therapeutics**

- Promote R&D of antimicrobials with novel mechanisms that contributes to the treatment of human antimicrobial-resistant infections (ARIs)
- Promote R&D of non-traditional therapeutics for infectious diseases that differ from traditional antimicrobials[86]

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

- Establish a council for cooperation among industry, academia and government, comprising representatives from medical institutions, administrative agencies, public research institutions, universities, business enterprises, etc., aimed at the R&D of methods for prevention, diagnosis and treatment of ARIs, and at promoting research and other activities to elucidate mechanisms of emergence and transmission of AMR

■ **Create incentives for research and development**

- Formulate guidelines for internationally harmonized clinical evaluation for the development of human antimicrobials (see Strategy 5.5)
- Promote R&D for novel methods for prevention, diagnosis and treatment of resistant tuberculosis, malaria, etc. through GHIT Fund
- Establish a mechanism for the priority review of new antimicrobials for ARIs in regulatory approval process
- Establish consultation service for pharmaceutical strategies specialized in antimicrobials for ARIs in regulatory approval process
- Consider preferable incentives and novel possible arrangements to promote the development of new drugs for ARIs with low market value, in the framework of the Public-Private Partnership Platform for Combating Infectious Diseases in Developing Countries, taking into account policies and conditions in other countries[87]

RELATED MINISTRIES, AGENCIES AND INSTITUTIONS

Office of Healthcare Policy, Cabinet Secretariat (CAS); 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)

[84] E.g. preventive approach in specific clinical conditions, such as the prevention of human infectious diseases related to surgery or chemotherapy

[85] E.g. expedited drug susceptibility tests, multiplex nucleic acid amplification tests for -antimicrobial resistance genes (ARG), immune chromatography for ARG products

[86] 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

[87] The U.S. Generating Antibiotics Incentives Now (GAIN) Act includes the specification of new prospective antibiotics as prioritized review items, and the extension of patent period.

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 fight against antimicrobial resistance (AMR), 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. At the G7 Health Ministers Meeting 2015 in Berlin, the need for promoting R&D against AMR was discussed, and the Berlin Declaration on Antimicrobial Resistance was adopted.[88]
- As is represented by the U.S. Generating Antibiotics Incentives Now (GAIN) Act, R&D activities, including the development of new antimicrobials, is in progress around the world. Harmonized R&D activities under international joint research initiatives[89] are important to avoid overlapping or uncoordinated competition.
- The U.S. and Europe have promoted cooperation for the R&D of new drugs since 2009, under the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR).[90] The international research collaboration initiatives, the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) and the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) have been established to accelerate international research collaborations including AMR. The Japan Agency for Medical Research and Development (AMED) joined JPIAMR and GloPID-R in 2015,[91,92] and explores the possibility of collaboration in AMR-related research,
- 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.[93] 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. However, such common requirements have yet to be established, forming a barrier in the promotion of international research collaboration.
- The International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) has established common tripartite guidelines concerning AMR-related materials that are required for the authorization of veterinary antibiotics used for livestock.[94,95]

[88] Berlin Declaration on Antimicrobial Resistance – Global Union for Antibiotics Research and Development (GUARD) agreed by G7 Health Ministers in Berlin 2015. 8-9 October 2015 in Berlin.
[89] Joint Programming Initiative on Antimicrobial Resistance (JPIAMR); Global Research Collaboration for Infectious Disease Preparedness (GloPID-R)
[90] Transatlantic Task Force on Antimicrobial Resistance, Centers for Disease Prevention and Control, http://www.cdc.gov/drugresistance/tatfar/, accessed on 24 December 2015.
[91] 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.
[92] 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 24 December, 2015.
[93] Guidelines for Good Clinical Practice E6 (R1), ICH harmonized tripartite guideline – Implemented in June 1996.
[94] 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.
[95] 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

○ Promote R&D on a global scale through contribution to the international research collaboration through participating in the international research collaboration initiatives related to AMR by AMED and other related institutions

○ Accelerate R&D of new drugs through global cooperation, including development of common clinical evaluation guidelines for new antimicrobials for humans by harmonization of the regulatory authorities including Europe, the U.S. and Japan

ACTIONS

■ Formulate/revise a common clinical trial/evaluation guidelines

- Develop common tripartite clinical evaluation guidelines for the development of new antimicrobials for human use by Europe, the U.S. and Japan (see Strategy 5.4 and Strategy 6.1)
- Develop and revise internationally harmonized guidelines on the trials required for the authorization of veterinary antibiotics in the framework of VICH

■ Promote international research collaboration

- Contribute to the promotion of R&D on AMR through continuous participation in the international research collaboration initiatives, including the international exchange of researchers
- 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) (linked to Strategy 6.1)

RELATED MINISTRIES, AGENCIES AND INSTITUTIONS

Office of Healthcare Policy, Cabinet Secretariat (CAS); 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)

EVALUATION INDICES

- Creation of a global common clinical evaluation guidelines for the development of antimicrobials for human use
- Creation of internationally harmonized guidelines on the studies required for the authorization of veterinary antibiotics

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 a threat on global health security, and has been discussed in the World Health Organization (WHO) and at the Group of Seven (G7) Summit. It is deemed as one of the most important health issues in the new global health architecture, together with measures related to the Universal Health Coverage (UHC), aging population, and Public Health Emergencies (PHEs).[96]
- In Japan, AMR control measures have been promoted in the fields of medicine, livestock production and aquaculture for many years, and AMR surveillance systems both for humans and animals have been established. Antimicrobial use for humans has also been at a lower level than the average of Organisation for Economic Co-operation and Development (OECD).[97] Thus, Japan should play a leading role in AMR control measures in the world, particularly in the Asia-Pacific region.
- Japan should also make international contribution as a Leading Country of AMR Action Package of the Global Health Security Agenda (GHSA), a multilateral initiative aimed at strengthening the implementation of WHO's International Health Regulation (IHR), for the purpose of enhancing capacities on infectious diseases in each country.
- In the fields of livestock production 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 the Terrestrial Animal Health Code of the World Organisation for Animal Health (OIE) and the Code of Practice and Guidelines of the Codex Alimentarius Commission.
- In Japan, the Food Safety Commission (FSC) conducts risk assessment in accordance with these international standards. Based on the assessment results, the MAFF formulates and implements risk management measures for reducing the risk of antimicrobial-resistant bacteria as well as ensure the prudent use of veterinary antibiotics, and the monitoring of antibiotic use and resistance in animals.
- In the ongoing initiative by the OIE to establish a database of antibiotic use in animals, Japanese experts have participated in the relevant meetings to provide data and advice.

POLICIES

- Support global AMR control measures by 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 AMR through the AMR Action Package of the Global Health Security Agenda (GHSA)
- Promote R&D and international cooperation by strengthening commitment for combating AMR as urged at the G7 Summit 2015 in Schloss Elmau, through the G7 Japan 2016 Ise-Shima Summit, the G7 Kobe Health Ministers' Meeting and the G7 Niigata Agriculture Ministers' Meeting
- Support to strengthen international initiatives on AMR, including the formulation and revision of international standards and the establishment of a database by the OIE, and contribute to international measures related to AMR under the Codex Alimentarius Commission, by participating in the process for revising the relevant standards

[96] S Abe, Japan's vision for a peaceful and healthier world. *Lancet*. 2015; 386: 2367-9.
[97] Muraki Y, et al., Nationwide surveillance of antimicrobial consumption and resistance to Pseudomonas aeruginosa isolates at 203 Japanese hospitals in 2010. *Infection*. 2013; 41:415-23.

ACTIONS

■ Promote global policies on antimicrobial resistance

- Support efforts of WHO against AMR
  - ✓ Organize a Tokyo Meeting of Health Ministers in the Asia on Antimicrobial Resistance in April 2016 in cooperation with WHO, and promote countermeasures on AMR, particularly in the Asia-Pacific region
- Continue to promote efforts in AMR measures in G7
  - ✓ Strengthen efforts on combating AMR as the Chair of the G7 Summit,, promote international cooperation on the development and implementation of national action plans in developing countries, and promote R&D that contributes to combat AMR
- Support efforts against AMR by OIE
  - ✓ Continue to support efforts to create and revise the OIE Code and manuals on AMR, and to create a database for monitoring the use of antimicrobial agents in animals
- Contribute to efforts of the Codex Alimentarius Commission on AMR
  - ✓ Contribute by participating in the efforts to create and revise the Code of Practice and Guidelines of the Codex Alimentarius Commission on AMR
- Promote efforts as a Leading Country of the AMR Action Package of 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) (linked to Strategy 5.5)
- Develop common tripartite clinical evaluation guidelines for the development of new antimicrobials for human use by Europe, the U.S. and Japan (see Strategy 5.5)

RELATED MINISTRIES, AGENCIES AND INSTITUTIONS

Coordination Office of Measures on Emerging Infectious Diseases, Cabinet Secretariat (CAS); Office of Healthcare Policy, CAS; Ministry of Foreign Affairs (MOFA); Ministry of Agriculture, Forestry and Fisheries (MAFF); 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
- G7 Progress Report, Commitment 14 (AMR) Indicators
- Progress in the attainment of the GHSA AMR Action Package targets

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

BACKGROUND

- The World Health Organization (WHO) Global Action Plan on Antimicrobial Resistance (AMR) requested the donor countries to commit international cooperation for developing countries to develop and implement their action plans, particularly in surveillance and laboratory capacity development, promoting access to antimicrobials coupled with measures to preserve the effectiveness thereof, and research and development (R&D) new methods for prevention, diagnosis and treatment.[98]
- 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 IPC and the supply of essential medicines. From these viewpoints, Japan is able to provide support for AMR measures in a broad range.
- Japan has also undertaken international cooperation concerning AMR in the framework of the Emerging and Re-emerging Infectious Diseases Research Projects handled by the Ministry of Health, Labour and Welfare (MHLW).
- In the fields of livestock production and aquaculture, Japan has cooperated in training held by the World Organisation for Animal Health (OIE), and dispatched experts in antimicrobial-resistant organisms to seminars requested by individual countries, among other cooperative efforts.

POLICIES

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

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[99]
  - ✓ Implementing the capacity-building of laboratories for AMR examinations, coupled with the strengthened surveillance
  - ✓ Developing new pharmaceutical seeds for prevention, diagnosis and treatment through AMR genome database
  - ✓ Contributing to surveillance activities for antimicrobial-resistant *Mycobacterium leprae* in the Asia-Pacific region
- Promote IPC activities, promote access to antimicrobials and their appropriate use to preserve their effectiveness, and enhance laboratory functions through the technical cooperation of JICA

[98] Global Action Plan on Antimicrobial Resistance, World Health Organization 2015, ISBN 978 92 4 150976 3.
[99] E.g. Japan Nosocomial Infections Surveillance (JANIS), Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM), AMR genome database (GenEpid-J)

- Promote international cooperation for elimination of drug-resistant tuberculosis utilizing new diagnostic methods and therapeutics for drug-resistant tuberculosis developed in Japan and endorsed by WHO

■ International cooperation in animal health

- Support the promotion of international cooperation by OIE concerning AMR measures, particularly in the Asian region
- In collaboration with the OIE, promote international cooperation by holding international seminars concerning surveillance and monitoring, utilizing the collaborating center function of the National Veterinary Assay Laboratory (NVAL), as well as the outreach forum of the Veterinary International Conference on Harmonization (VICH).

RELATED MINISTRIES, AGENCIES AND INSTITUTIONS

Office of Healthcare Policy, Cabinet Secretariat (CAS); 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 AMR

OUTCOME INDICES FOR THE ACTION PLAN

The following outcome indices are specified for this action plan.

HUMAN-RELATED INDICES

1. Lower the penicillin resistance of *Streptococcus pneumoniae* to 15% or less in 2020[100]
2. Lower the methicillin resistance of *Staphylococcus aureus* to 20% or less in 2020[101]
3. Lower the fluoroquinolone resistance of *Escherichia coli* to 25% or less in 2020[102]
4. Lower the carbapenem (imipenem) resistance of *Pseudomonas aeruginosa* to 10% or less in 2020[103]
5. Maintain the carbapenem resistance of *Escherichia coli* and *Klebsiella pneumoniae* at 0.2% or less in 2020[104]
6. Reduce the antimicrobial use per day per 1,000 inhabitants in 2020 to two-thirds of the level in 2013[105]
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
8. Reduce the use of intravenous antimicrobials per day per 1,000 inhabitants in 2020 by 20% from the level in 2013

[100] 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.

[101] 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 of the same level as in other developed countries.

[102] 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 of the same level as in other developed countries.

[103] 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 of 10% or less. by accelerating the lowering rate to 1 to 2%.

[104] 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 at the same level through adequate measures.

[105] 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. 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

1. Lower the tetracycline resistance of *Escherichia coli* to 33% or less[106]
2. Maintain the third-generation cephalosporin resistance of *Escherichia coli* at the same level as in the other G7 countries as of 2020[107]
3. Maintain the fluoroquinolone resistance of *Escherichia coli* at the same level as in the other G7 countries as of 2020[107]

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 Ministerial Meeting on Measures on Emerging Infectious Diseases. The outcome indices should be evaluated by issuing the annual One Health Surveillance Report on AMR (tentative name).

[106] 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 by implementing this action plan, and the target is set at 33% or less in 2020.

[107] In the "Ranking of the Importance of Antimicrobials against Bacteria which Affect Human Health through Food", 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 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 prohibition thereof in cases where other veterinary antibiotics are effective, 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.

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 ARGs to originally antimicrobial-susceptible bacteria, through mechanisms such as transformation (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 production 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 production 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 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, figures calculated by dividing the amounts by the number of persons/animals, by the days of administration (for humans only), by average weight (for animals only), etc. are used as indices. For humans, the Antimicrobial Use Density (AUD) and the Days of Therapy (DOT) are used. For animals, a density index (mg/Population Correction Unit (PCU)) is used, which is calculated by dividing the amount of use by weight after correcting the amount of sales of agent (in pure powder) by population.

- **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 test) or genotypic testing (typing of (the products of) ARGs). While phenotypic testing evaluates the reactivity of organisms to actual agents, genotypic testing evaluates specific 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.

MEMBERS FOR FORMULATING THE ACTION PLAN

EXPERTS

This action plan was formulated through discussion, based on inputs provided by the following invited experts (alphabetical order; last name, first name);

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RELATED MINISTRIES AND AGENCIES

Cabinet Secretariat (CAS), Food Safety Commission of Japan (FSC), Ministry of Foreign Affairs (MOFA), Ministry of Education, Culture, Sports, Science and Technology (MEXT), Ministry of Health, Labour and Welfare (MHLW), and Ministry of Agriculture, Forestry and Fisheries (MAFF), Ministry of the Environment (MOE)

RELATED INSTITUTIONS

National Institute of Infectious Diseases (NIID), National Veterinary Assay Laboratory (NVAL), Japan International Cooperation Agency (JICA), Pharmaceuticals and Medical Devices Agency (PMDA), Fisheries Research Agency (FRA), 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), Japan Council for Quality Health Care