

## AMR Alliance Japan Recommendations Setting Appropriate Outcome Indices in the Next AMR Action Plan

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Globally, antimicrobial resistance (AMR) leads up to 700,000 deaths annually. In Japan, an estimated 8,000 people die annually from just bloodstream infections caused by two major AMR infections – methicillin-resistant *Staphylococcus aureus* and fluoroquinolone-resistant *Escherichia coli*. To prevent the spread of AMR, in April 2016, the Government of Japan enacted the “National Action Plan on Antimicrobial Resistance 2016-2020 (NAP 2016-2020).” The NAP 2016-2020 has been fundamental in establishing AMR measures, and has contributed to actions such the collection of AMR related data. Aiming to review this progress, AMR Alliance Japan held a roundtable expert discussion on the NAP 2016-2020. During this discussion, experts raised points to consider when setting outcome indices and numeric targets in the upcoming version of the National Action Plan on Antimicrobial Resistance (the “next NAP”). This discussion led to the recommendations described below.

This proposal consists of three sections. First, this proposal provides an overview of the outcome indices and corresponding numerical targets described in the NAP 2016 – 2020. Second, this proposal presents an intellectual framework for setting outcome indices and numerical targets in the next NAP. Third, based on this framework, specific outcome indices are provided for the human, animals, food, and environmental sectors.

The ongoing Coronavirus Disease 2019 (COVID-19) pandemic has demonstrated the importance of infectious disease policy, and accordingly, there are high expectations for the next NAP. It is hoped that this proposal can help with the formulation of the next NAP, toward the further strengthening of AMR countermeasures moving forward.

■ **Current situation: outcome indices and corresponding numerical targets in the NAP 2016 -2020**

**Human sector**

<b>Outcome Indices</b>	<b>Numerical targets</b>
Penicillin-resistance rate of <i>Streptococcus pneumoniae</i> in 2020	15% or below
Methicillin-resistance rate of <i>Staphylococcus aureus</i> in 2020	20% or below
Quinolone-resistance rates of <i>Escherichia coli</i> in 2020	25% or below
Carbapenem (Imipenem)-resistance rate of <i>Pseudomonas aeruginosa</i> in 2020	10% or below
Carbapenem-resistance rate of <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i> in 2020	0.2% or below
Daily antimicrobial use per 1000 inhabitants in 2020	Reduced to two-thirds of 2013 levels
Daily antimicrobial use per 1000 inhabitants of oral cephalosporins, fluoroquinolones, and macrolides in 2020	Reduced by 50% from 2013 levels
Daily intravenous antimicrobial usage per thousand population in 2020	Reduced by 20% from 2013 levels

**Animal sector**

<b>Outcome Indices</b>	<b>Numerical targets</b>
Tetracycline-resistance rate of <i>Escherichia coli</i>	33% or less
Third-generation cephalosporins-resistance rate of <i>Escherichia coli</i>	Meet level of G7 members in 2020
Fluoroquinolone-resistance rate of <i>Escherichia coli</i>	Meet level of G7 members in 2020

## ■ Future directions: intellectual framework for setting outcome indices and numerical targets in the next NAP

### Outcome indices and numerical targets in the NAP 2016 – 2020

- An analysis should be carried out on trends in antimicrobial resistance rates and antimicrobial use for each bacterial species throughout the NAP 2016-2020 timeframe. This should include analysis of the relationship between antimicrobial use and resistance rates, and the relationship between oral antimicrobial and intravenous antimicrobial use in the human sector. **This analysis should take place on a rolling basis, and outcome indices in the next NAP should be set and revised in accordance with analysis results. It is also important to ensure that numeric targets be set based on evidence.**
- **Numeric targets are not set with the purpose of simply reducing the total volume of antimicrobials used – they are set to discourage inappropriate antimicrobial usage.** Inappropriate antimicrobial use must be discouraged while encouraging appropriate use. For this reason, it would be better to avoid setting targets excessively low.
- Diagnostic tests are indispensable for distinguishing between the proper and improper use of antimicrobials. **Point-of-care testing (POCT) should be promoted concurrently with numerical targets** in order to evaluate the appropriate use of antimicrobials and to encourage antimicrobial stewardship.

### Outcome indices and numerical targets for the next NAP

- **Numerical targets in the next NAP should be set based on data and other information that has been collected up to this point.** In addition, it would be best to include longer-term, five year and out targets alongside regular numerical targets.
  - Examples of extant data sources in each sector:
    - Human sector: Japan Nosocomial Infections Surveillance (JANIS), AMR Bacteria Bank, National Epidemiological Surveillance of Infectious Disease (NESID), Japan Antimicrobial Resistance Bacterial Surveillance (JARBS), Japan Surveillance for Infection Prevention and Healthcare Epidemiology (J-SIPHE), Surveillance for Trend in Antimicrobial Use.
    - Animal sector: Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM), Survey on Methicillin-Resistant Staphylococcus aureus (MRSA) Infiltration, Survey on Antimicrobial Resistance Trends Expanded to All Cultured Fish Species, Survey on Antimicrobial Resistance in Pets.

- Furthermore, the next NAP should include **indicators that assess behaviors at each stage of AMR control measures (“process indicators”) and indicators that assess the final results of AMR control measures (“outcome indicators”)** in line with each long- and short-term target.
- When setting each indicator and target, it is important to recognize that there are regional variations in antimicrobial use and the distribution of antimicrobial resistant bacteria. **Consideration should be given to frameworks for information collection, evaluation, and assessment on a prefecture, primary or secondary care area, healthcare institution, or prescriber basis.**
- The setting of indicators and targets in itself helps to communicate the necessity of action and importance of AMR countermeasures. To facilitate such communication, it is important that each indicator and target be simple and exceptionally easy to understand.
- Consideration should be given to the construction of a system to research and collect information on the incidence of community-acquired antimicrobial resistant infections, the prevalence of healthy carriers of antimicrobial-resistant organisms, the cost of AMR measures, and the impact of AMR on socioeconomic activities.

#### **Ensuring the next NAP contains a One Health perspective spanning the human, animal, and environmental sectors**

- **Efforts should be made to comprehensively assess and analyze the state of AMR organisms in the human, animal, and environmental sectors.** It is important to conduct appropriate risk assessments of organisms originating from the animal and environmental sectors that may impact human medicine and health. Furthermore, consideration should be given to the creation of a framework for the occasional review and revision of indicators and targets in the NAP to appropriately reflect any risks discovered through such assessments.
- Japan imports many food products, including ingredients that go toward the production frozen foods and other products. In light of that, efforts should be taken to **establish effective monitoring methods that can determine whether AMR organisms are being imported from abroad via food.**

Please note, the term “animal sector” in this document mainly refers to livestock for human consumption (cows, pigs, chicken), fish, and pets.

## ■ Specific recommendations: outcome indices for the next NAP

The following items are proposed as outcome indices in the next NAP based on the considerations listed above, continuity with the NAP 2016 – 2020, and the ultimate objective of AMR countermeasures.

### End Goals

- Lower number of patients infected with antimicrobial resistant organisms (based on NESID)
- Lower number of deaths from antimicrobial resistant infections (based on vital statistics)

### Human sector (1/2): Recommendations based on continuity with the previous NAP

Process indicators: The following indicators should be established in light of the major role that antimicrobials play in the treatment of infectious diseases in clinical settings. Since the use of antimicrobials varies from region to region, a system should be established that can analyze and evaluate these indicators on a prefecture, primary or secondary care area, healthcare institution, and prescriber basis.

- Daily use of antimicrobials per 1000 inhabitants (based on data from Japan Antimicrobial Consumption Surveillance (JACS) and other sources)
  - Daily use of oral third-generation cephalosporins per 1000 inhabitants (based on data from JACS and other sources)
  - Daily use of oral quinolones per 1000 inhabitants (based on data from JACS and other sources)
  - Daily use of oral macrolide per 1000 inhabitants (based on data from JACS and other sources)
  - Daily use of intravenous antimicrobials per 1000 inhabitants (based on data from JACS and other sources)
- Outcome indicators: As the situation of antimicrobial resistant organisms varies from region to region, it will be necessary to establish an analysis and evaluation system that can monitor antimicrobial resistant organisms nationwide, in primary and secondary care areas, and within each medical institution. The following indicators should be established in relation to antimicrobial resistance rates and the distribution of antimicrobial resistance.

- Antimicrobial resistance rate and distribution of penicillin-resistant *Streptococcus pneumoniae* (based on data from Japan Nosocomial Infections Surveillance (JANIS) and other sources)
- Antimicrobial resistance rate and distribution of methicillin-resistant *Staphylococcus aureus* (based on data from JANIS and other sources)
- Antimicrobial resistance rate and distribution of quinolone-resistant *Escherichia coli* (based on data from JANIS and other sources)
- Antimicrobial resistance rate and distribution of third-generation cephalosporins-resistant *Escherichia coli* (based on data from JANIS and other sources)
- Antimicrobial resistance rate and distribution of carbapenem (imipenem)-resistant *Pseudomonas aeruginosa* (based on data from JANIS and other sources)
- Antimicrobial resistance rate and distribution of carbapenem-resistant *Escherichia coli* (based on data from JANIS and other sources)
- Antimicrobial resistance rate and distribution of carbapenem-resistant *Klebsiella pneumoniae* (based on data from JANIS and other sources)

### **Human sector (2/2): Recommendations from the perspective of the end goals of AMR measures**

- Process indicators: Antimicrobial stewardship is fundamental to AMR countermeasures. To further promote antimicrobial stewardship, it is important to understand the current status of inappropriate antimicrobial use, knowledge and behaviors that impact the way the public seeks and receives medical care, and the extent that AMR countermeasures are being reimbursed by the Japanese healthcare system. In addition to promoting AMR countermeasures, efforts should be made to secure more human resources in the field of infectious diseases and promote appropriate infectious disease countermeasures in general. Based on that perspective, the following indicators should be established.
  - Percentage of patients with upper respiratory tract inflammation or common cold that are treated with antimicrobials (based on data from the Health Insurance Claims and Specific Health Checkups of Japan (NDB) and other sources)
  - Percentage of the public that possesses accurate knowledge on AMR and antimicrobials (based on survey data from the National Center for Global Health and Medicine and other sources)
  - Number of healthcare professionals with professional certifications related to infectious diseases (based on data from the Japanese Association for Infectious Diseases, the Japanese Society of Chemotherapy, the Japanese Society of Hospital Pharmacists and other sources)

- Number of reimbursements related to antimicrobial stewardship premiums in the medical fee system (based on data from NDB and other sources)
- Number of reimbursements related to antimicrobial stewardship premiums for the pediatric field in the medical fee system (based on data from NDB and other sources)
- Number of reimbursements related to regional cooperation for infectious disease control in the medical fee system (based on data from NDB and other sources)
- Number of new antimicrobials on the market (based on data from the pharmaceutical industry and other sources)

### **Animal sector (1/2): Recommendations based on continuity with the previous NAP**

- Outcome indicators: The following indicators should be established to assess the antimicrobial resistance rate of organisms that could potentially impact human health. In particular, tetracycline is the most frequently used drug in animals and requires continuous monitoring.
  - Tetracycline-resistance rate of *Escherichia coli* in livestock (based on the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) and other sources)
  - Third-generation cephalosporin-resistance rate of *Escherichia coli* in livestock (based on JVARM and other sources)
  - Fluoroquinolone-resistance rate of *Escherichia coli* in livestock (based on JVARM and other sources)

### **Animal sector (2/2): Recommendations from the perspective of the end goals of AMR measures**

- Process Indicators (particularly for livestock): The following indicators should be established in relation to antimicrobial resistance rates.
  - Amount of animal-use tetracycline used (based on JVARM and other sources)
  - Amount of animal-use third-generation cephalosporin used (based on JVARM and other sources)
  - Amount of animal-use fluoroquinolone used (based on JVARM and other sources)
  - Amount of colistin used (based on JVARM and other sources)
  - Total use of antimicrobials used in the animal sector (based on JVARM and other sources)
- Outcome indicators (livestock): The following indicators should be established to understand the antimicrobial resistance rate of organisms that could potentially impact human health.
  - Prevalence of methicillin-resistant *S. aureus* (based on JVARM and other sources)
  - Antimicrobial resistance rate of major bacterial species to fluoroquinolones, third-generation cephalosporins, colistin, etc. (based on JVARM and other sources)

- Outcome indicators (pets): The following indicators should be established to understand the antimicrobial resistance rate of organisms that could potentially impact human health.
  - Antimicrobial resistance rate of major bacterial species to fluoroquinolones, third-generation cephalosporins, etc. (based on JVARM and other sources)
- Outcome indicators (fish):
  - Antimicrobial resistance rate of major bacterial species found in fish for human consumption

#### **About AMR Alliance Japan**

AMR Alliance Japan was established in November 2018 as multi-stakeholder, collaborative organization dedicated to the improvement of public health through the promotion of AMR countermeasures. As of October 2021, its members include, in alphabetical order: Children and Healthcare Project; The Japan Medical Association; The Japan Pharmaceutical Association; The Japan Pharmaceutical Manufacturers Association; The Japan Society of Hospital Pharmacists; The Japanese Association for Infectious Diseases; The Japanese Society for Chemotherapy; The Japanese Society for Clinical Microbiology; The Japanese Society for Medical Mycology; The Japanese Society for Pediatric Infectious Diseases; The Japanese Society of Infection Prevention and Control; The Japanese Society of Pharmaceutical Health Care and Sciences; The Japanese Society of Therapeutic Drug Monitoring; MSD K.K.; Shionogi & Co., Ltd.; Nippon Becton Dickinson Co., Ltd.; Pfizer Inc.; The Pharmaceutical Society of Japan. The Health and Global Policy Institute serves as the Secretariat of AMR Alliance Japan.

*The perspectives described in this document were developed by the AMR Alliance Japan Secretariat reflecting sentiments uncovered during roundtable discussions held by AMR Alliance Japan on the next NAP. They should not be interpreted as the position of any individual organization or stakeholder.*