U.S.-Japan Expert Meeting on AMR

Japan's Role in Addressing Global Antimicrobial Resistance (AMR)

Meeting Report

6 Goals and 14 Recommendations for the Promotion of the National Action Plan on AMR

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Health and Global Policy Institute

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Executive Summary

6 Goals and 14 Recommendations for the Promotion of the National Action Plan on AMR

Introduction

On April 18, 2016, U.S.-Japan Expert Meeting on AMR “Japan’s Role in Addressing Global Antimicrobial Resistance” was convened jointly with the Washington-based Center for Strategic and International Studies (CSIS). As AMR presents an increasingly serious threat to global public health, it is imperative that all stakeholders urgently coordinate and take necessary actions at national and international levels across both public and private sectors. As the follow up of Tokyo Meeting of Health Ministers on AMR in Asia, this meeting provided a platform for open multi-stakeholder discussions on AMR-related policy with active participation of experts from the private, public and academic sectors.

In particular, the conference explored 6 goals and outcome indices from the National Action Plan on Antimicrobial Resistance (AMR), which was published on April 5, 2016 by the Japanese Government. In this regard, this report will propose 14 recommendations that cover the 6 Goals of the National Action Plan on AMR by the Japanese Government.

This paper is a summary of the recommendations that were covered at the U.S.-Japan Expert Meeting on AMR.

【AMR Action Plan Field 1: Public Awareness and Education】

Goal1:
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

Opinions from the U.S.-Japan Expert Meeting on AMR

- Conduct awareness-raising activities for both healthcare providers (those who will prescribe drugs) and patients.
- Establish and promote consistent education on AMR, covering not only clinical knowledge, but also economic and social knowledge.
- Implement a multi-stakeholder approach to awareness raising activities that would allow each stakeholder to understand the entire scope of the problem.

Recommendation 1: Promote AMR Education Programs

- In addition to presenting clinical and basic medical knowledge, AMR education programs should offer increased content related to social medicine, pharmaco-economics, and other relevant areas in the social sciences. They should also reference international comparative studies to provide a wider perspective.

Recommendation2: Deepen Public Awareness about AMR

- Create a National Council on Countermeasures against AMR (tentative name) as a public awareness-raising working group. This body should be a multi-stakeholder group featuring collaboration among the private, public and academic sectors. It should comprise stakeholders, including healthcare providers, patient groups, insurers, members of the private sector, the Government, and professionals from other countries, and work to develop concrete public awareness campaigns.

【AMR Action Plan Field 2：Surveillance and Monitoring】

Goal2:

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 Care, Livestock and Fisheries

(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

Opinions from U.S.-Japan Expert Meeting on AMR

- Promote the Japan Nosocomial Infections Surveillance (JANIS) network in the Asian region, make a contribution to the world, and construct data analysis systems inside and outside of Japan.
- It is essential to keep aware of public opinion and to develop reasonable and accurate strategies to guide policy making that are based on a knowledge of the current situation of antimicrobial use in human and animals.
- Construction of an isolate-based surveillance system that collects and stores antimicrobial-resistant bacterial strains requires a certain level of facilities, effort and human resources: it would be difficult for the National Institute of Infectious Diseases to establish such a system alone.
- A lack of funding and human resources is a common problem of isolate-based surveillance systems across the world. It is important that stable backup systems be in place to ensure the continuation of such systems.
- It is essential that isolate-based surveillance systems led by governments be managed in collaboration with academic associations and the private sector.

- Construct a public-private-partnership mechanism for the storing of data on antimicrobial-resistant bacteria for further research and development.
- Establish a database that would connect data on antibiotic use, clinical data, and strain data, and follow up on this data through post-marketing surveillance and antibiotic usage monitoring activities.
- Develop a system that collects data from pharmacies to understand antibiotic use among outpatients.
- Promote the establishment of a case registration platform in the area of infectious diseases.
- Promote the establishment of a “Antimicrobial Resistance Research Center” (tentative name) to strengthen surveillance activities.
- Create a network to share data on high-risk antimicrobial-resistant bacteria between U.S surveillance system and JANIS.

Recommendation 3：Establish an Isolate-based Surveillance System

- It is essential that isolate-based surveillance systems led by governments be managed in collaboration with academic associations and the private sector.
- Establish a system to consistently secure various resources, including funding and staff members, by clarifying the roles of the Government and academic associations.
- Regarding the application and management of surveillance systems, it is recommended that Japan consider the establishment of a Surveillance Management Committee within institutions such as the National Center for Global Health and Medicine and the National Institute of Infectious Diseases.

Recommendation 4：Develop Surveillance Systems

- In order to accelerate the development of new drugs, data from the isolate-based surveillance system should be open to the public in principle. This would promote research and development via collaboration among the private, public and academic sectors.
- Promote the proper use of antibiotics by utilizing information technology to connect clinical data, strain data, and data on antibiotic use within surveillance systems. This would increase understanding of the current usage situation for each antibiotic.
- Integrate data related to the surveillance of human and animals, and then link this data with data from the U.S. surveillance system in order to promote a “One Health” approach to surveillance.

Recommendation 5: Facilitate an Understanding of the Current Situation of Antibiotic Use in Outpatient Setting

- Develop a system that collects data from pharmacies to understand antibiotic use among outpatients.

Recommendation 6: Strengthen Surveillance through Participation by Multiple Stakeholders

- Policies aimed at strengthening surveillance, such as the establishment of the Antimicrobial Resistance Research Center (tentative name) require not only the participation of the Government, but of academic associations and the private sector, to improve cooperation.

【AMR Action Plan Field 3: Infection Prevention and Control】

Goal 3:

Prevent the Spread of Antimicrobial-resistant Organisms by Implementing Appropriate Infection Prevention and Control

Strategies:

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

(3.2) Promote Infection Prevention and Control of Livestock and Fisheries, Veterinary Care and Food Chain

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

Opinions from the U.S.-Japan Expert Meeting on AMR

- Share data on the state of regular and antimicrobial-resistance infections via information technology in order to facilitate an understanding of the regional distribution of infection-sensitivity and epidemic organisms.

Recommendation 7: Use of Information Technology for AMR

- Promote the use of information technology to enable regional and institutional real-time information sharing.

【AMR Action Plan Field 4: Appropriate Use of Antimicrobials】

Goal 4:
Promote Appropriate Use of Antimicrobials in the Fields of Healthcare, Livestock and Fisheries
Strategies:
(4.1) Promote Proper Use of Antimicrobials at Medical Institutions
(4.2) Ensure Prudent Use of Antimicrobials for Animals in the Field of Livestock, Fisheries and Veterinary Care

Opinions from the U.S.-Japan Expert Meeting on AMR

- The promotion of appropriate antibiotic use requires institution-specific approaches for each type of institution (such as hospitals, clinics, or other long-term care facilities).
- The participation of long-term care facilities in Antibiotic Stewardship Programs is under consideration by the U.S. CDC.
- Establish systems to control antibiotic usage among outpatients, such as the introduction of a delayed antibiotic prescription system that would disallow the prescription of antibiotics on the same day as a medical consultation.
- In order to promote the appropriate use of antibiotics from the perspective of drug pricing policy, it is essential to develop a mechanism that would unlink usage and sales.
- Promote appropriate use of antibiotics by identifying antimicrobial-resistant bacteria with antimicrobial-resistant gene tests.
- Improve public awareness-raising activities and patient education concerning AMR in order to improve public understanding about the reduction of unnecessary antibiotic prescriptions.
- Further institutionalize vaccination to take a precaution to reduce unnecessary prescriptions of antibiotics.
- It is essential to think about the best combinations of antibiotic treatments and vaccines.
- It is necessary to aim not only to reduce unnecessary prescriptions of antibiotics but also to promote epidemiological studies on the effects of treatment that feature outcome indices.

Recommendation 8: Promote Complex Approaches for the Appropriate Use of Antibiotics

- Promote the appropriate use of antibiotics and the benefits of this through institution-specific approaches.
- Reduce unnecessary prescriptions of antibiotics by developing drug pricing mechanisms that would unlink usage and sales.
- Promote insurance coverage for antimicrobial-resistant gene tests to further encourage the appropriate use of antibiotics.

Recommendation 9: Promote a Vaccination Strategy

- Reduce the unnecessary use of antibiotics at elderly care facilities. It is important to promote appropriate vaccination practices that take into consideration patient immune systems.
- Promote antibiotic and vaccine usage that is appropriate in consideration of each patient's age and their immune system.

Recommendation 10: Promotion of Outcome Indices

- Regarding proper antibiotic usage, it is necessary to not only aim to reduce unnecessary prescriptions by volume, but also to promote evaluations that employ clinical effects and epidemiological outcomes as measures.

【AMR Action Plan Field 5：Research and Development】

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 AMR and its Socioeconomic Impact

(5.2) Promote Research on Public Awareness / Education on AMR, 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 (R&D) of Novel Methods for Prevention, Diagnosis and Treatment and Promote the Cooperation of Industry, Academia and Government

(5.5) Promote Global Research Collaboration on AMR and R&D of Novel Methods for Prevention, Diagnosis and Treatment of Antimicrobial-resistant Infections

Opinions from the U.S.-Japan Expert Meeting on AMR

- Encourage a virtuous cycle in which the promise of patents provides incentives for the promotion of research and development and innovation, and ultimately improves access to medicine.
- Bolster infrastructure to promote drug development, and create win-win relationships between people working for drug development and drug review.
- Regarding the establishment of development incentives, promote both push (grants, tax exemption, etc.) and pull (redemption, patent term extension, etc.) mechanisms.
- Encourage PK/PD modeling and simulation work that can make it possible to implement clinical trials even with a limited number of patients.
- Collect data on safety and effectiveness through constant post-marketing surveillance.
- Promote measures to apply the existing “Scheme of Rapid Authorization of Unapproved Drugs” to reviews of antibiotics.

- Encourage participation by academic associations in the creation of clinical evaluation guidelines when developing new antibiotics.
- Create a network to share clinical and post-market data among medical institutions.
- In order to encourage the consistent collection of data on drug safety, expand the implementation of post-marketing surveillance and post-market follow up studies by utilizing patient registries.
- Develop drug-pricing policies that grant incentive packages to companies that developed new drugs addressing high unmet medical needs. This could include measures offering concessions on price maintenance proposals by the company for drugs outside of the those with high unmet medical needs.
- Promote the development of highly specific diagnostic methods to allow physicians the choice of not using antibiotics.
- Develop a framework for the further clarification of new drug indications (this is also under consideration in the U.S.). Such a framework should allow for conducting additional clinical trials after approval.

Recommendation 11: Establish an Evaluation and Review System to Promote Research and Development

- Encourage PK/PD modeling and simulation work that can make it possible to implement clinical trials even given a limited number of patients.
- Establish electronic information networks to gather information on new antibiotics, including on their effectiveness, and their safety from development to the post-market period.

Recommendation 12: Create Diversified and Effective Incentives for Research and Development

- Grant various incentives regarding research and development (pull, push, cap-and-collar, etc.).
- Expand drug pricing policies that promote the development of drugs with high unmet medical needs.

Recommendation 13：Establish a Consortium of Organizations from the Private, Public and Academic Sectors to Promote Drug Development

- Create a consortium in the Government, which will hold multi-stakeholder discussions involving private, public and academic sector members related to antibiotic research and development, incentive grants, review systems, and clinical usage.

※PK / PD：PK, or pharmacokinetics, indicates a temporal variation of the concentration of antibiotics in a body. PD, or pharmacodynamics, indicates the relationship between antibiotic concentration in a body and its effect. Understanding pharmacokinetics and pharmacodynamics by PK / PD allows establishing antibiotic use that prevents the emergence of antimicrobial resistance.

※Modeling and simulation (M&S): a method to achieve an efficient clinical study for drug development. By analyzing each model's accumulated expertise and data, it is possible to select an appropriate test model for every phase.

※Post-marketing surveillance (PMS): a system that collects data of new drugs such as secondary effects after it has been released on the market. Because there are not sufficient numbers of cases at clinical study of new drugs for rare diseases, it collects data from all patients after approval.

※Scheme of Rapid Authorization of Unapproved Drugs：a system indicated by 'The Strategy of SAKIGAKE' that is drawn up in June 2014. Although only drugs that had been approved in Western countries could be reviewed, this system expands the scope on unapproved drugs in Western countries.

※Indication：specific treatments or drugs that are advised to use.

*Cap-and-collar mechanisms: a financial concept whereby maximum and minimum interest rates are set. In this report, it is referred to as a way of securing a minimum level of sales for medical products.

【 AMR Action Plan Field 6：International Cooperation】

Goal 6：
Enhance Global Multidisciplinary Countermeasures against Antimicrobial Resistance
Strategies:
(6.1) Strengthen Japan's Leadership for Global Policies on Antimicrobial Resistance
(6.2) Implement International Cooperation to Achieve a Global Action Plan on Antimicrobial Resistance

Opinions from the U.S.-Japan Expert Meeting on AMR

- The Tokyo Meeting of Health Ministers on AMR in Asia was of great significance in that it facilitated discussion between developed and developing countries in the Asia-Pacific region, which is experiencing remarkable economic growth within a period of changing public mindsets.
- It is important to support trends in the international community such as the reports from WHO and framework agreements in order to change public perception of AMR in each country.
- The U.S. is also focusing on international collaborations to combat AMR.
- Each stakeholder should work for international cooperation in each country that takes into account the current situation of AMR countermeasures in developing countries
- JANIS requires strategies to tackle funding and human resources issues if it is going to expand in Asia.

Recommendation 14：Lead on AMR in the Asia-Pacific Region

- Looking to the Tokyo Meeting on Health Ministers on AMR in Asia as a good example, consistently promote international cooperation frameworks between international organizations and other Asian countries.
- Raise public awareness internationally by utilizing international trends and agenda setting efforts.
- Secure the resources needed for JANIS to expand into Asia and contribute to the region.

U.S.-Japan Expert Meeting on AMR Meeting Report

U.S.-Japan Expert Meeting on AMR

Japan's Role in Addressing Global Antimicrobial Resistance

Meeting Executive Summary

U.S.-Japan Expert Meeting on AMR "Japan's Role in Addressing Global Antimicrobial Resistance" was convened jointly with the Washington-based Center for Strategic and International Studies (CSIS). As antimicrobial resistance presents an increasingly serious threat to global public health, it is imperative that all stakeholders urgently coordinate and take necessary action at national and international levels across both public and private sectors. This meeting provided a platform for open multi-stakeholder discussions on AMR-related policy with active participation of experts from the private, public and academic sectors.

Panel Discussion 1 "Regional and Global Capacity-Building to Combat AMR"

In response to the rising urgency of antimicrobial resistance, there has emerged a strong global political will to identify and implement solutions. This session focused on regional and global initiatives including WHO AMR Global Action Plan and National Action Plans from U.S. and Japan. Experts and government representatives discussed existing and future bilateral and multilateral collaborations and explored ideas for G7 action.

Panel Members

Lawrence Kerr (Director, Office of Global Health Security, Office of Global Affairs, Department of Health and Human Services)

Kazunari Asanuma (Director, Tuberculosis and Infectious Diseases Control Division, MHLW)

Yoshichika Arakawa (Professor, Graduate School of Medicine, Nagoya University)

Tomohiko Makino (Medical Officer, WHO West Pacific Regional Office)

(Moderator: Audrey Jackson (Senior Fellow, CSIS))

(titles omitted / in no particular order)





- **Stakeholder's Action to Tackle AMR**

Asanuma (MHLW): An Action Plan on AMR has been drawn up by WHO. Japan was the last country among G7 countries to release its own Action Plan. In addition to the five goals proposed by WHO (i.e. public awareness and education, surveillance and monitoring, infection prevention and control, appropriate use of antibiotics, and research and development), Japan's National Action Plan integrated a sixth one, which is international cooperation. In the area of proper antibiotic usage, we will try to clarify numerical targets, and also focus on collaborations with veterinary medicine and agriculture.

Makino (WHO): The Tokyo Meeting of Health Ministers on AMR in Asia convened by Japan and WHO was greatly significant in consideration of three areas: (1) The Asia-Pacific region is experiencing remarkable economic growth; (2) Society in the region has matured, and public awareness has gradually changed; and (3) The meeting showed that every country (developed and developing) needs to tackle AMR. In relation to all of this, WHO added three points into the agreement that are in line with the ultimate purpose of the existing concept of One Health. These were calls for: (1) UHC (Universal Health Coverage) for the proper use of antibiotics; (2) the engagement of the human and animal health sectors in common efforts

under the One Health approach; and (3) the application of a framework for SDGs (Sustainable Development Goals) covering not only the human and animal sectors, but also a wider range of fields.

Kerr (HHS): The U.S., like Japan and other countries in the world, considers AMR a serious threat, and President Obama has promoted measures that position AMR as a key issue of national security. U.S. efforts focus particularly on international cooperation, with the aim of controlling AMR through joint efforts with international organizations such as the G7, WHO, FAO (Food and Agriculture Organization), and OIE (World Organization for Animal Health), as well as 40 countries around the world.

Arakawa (Nagoya University / Academia): JANIS (the Japan Nosocomial Infections Surveillance network) was launched after the initiation of national surveillance in 2000. The system has been improving year by year, by taking measures to lessen the workload of health care providers in clinical practices. It is now possible to gather data from all over the country and use them for policy making. Moreover, participating medical institutions can not only review continuous trends, but also objectively compare their data with national averages. In the future, JANIS is expected to expand this system in Asian countries in order to share data, which would contribute to efforts to tackle AMS.

- **Necessary Steps for Capacity Buildings against AMR**

Asanuma (MHLW): Even prior to the creation of the Action Plan, Japan was leading the world in terms of its countermeasures against AMR thanks to efforts taken by medical professionals. What is particularly important is the promotion of activities to raise public awareness about proper antibiotic use. It is essential to conduct awareness-raising activities for both the healthcare providers who prescribe drugs and patients.

Makino (WHO): When discussing countermeasures against AMR, it is not enough just to discuss AMR. We must also have oversight that ensure proper medical care, monitor prescribing behavior, and consider ways to promote UHC, which will help us construct a sustainable medical care system. Additionally, discussion should touch upon not only the

efforts made by physicians in medical institutions, but also the commitment from various other actors, such as policy makers.

Kerr (HHS): The prime concern of low-income countries should be to understand the current situation. When considering technology transfers, it is important to recognize the disease burden of AMR on the receiving countries. In middle-income countries, the improvement of laboratory capabilities for the detection of AMR is indispensable. Each country should contribute to international cooperation in accordance with level of capacity they have. Furthermore, more education and public awareness about AMR is needed. Patients are often unaware of the dangers associated with AMR, and health care providers find it easier to prescribe antibiotics than to educate their patients about their unnecessary prescriptions. A study from the CDC has demonstrated that prompting physicians with a simple sign questioning whether antibiotics were really needed in a patient encounter resulted in a 30 percent drop in antibiotic prescriptions.

Arakawa (Nagoya University / Academia): In developed countries, carbapenem and cephalosporin tend to be excessively prescribed for humans, and colistin is used for animals. It is essential to assess each situation delicately, and to establish strategies and set goals rationally and accurately. This should guide policy making around AMR.

- **The Necessity of Working with Multiple Stakeholders, the Benefits of Cooperation**

Kerr (HHS): As someone who belongs to the U.S. Government, I would like to request that each stakeholder understand the whole picture of the problem. At the same time, it is important to understand that it is impossible for the Government to solve the problem alone. Proper antibiotic usage will be promoted through the engagement of various sectors, as well as medical education, awareness-raising activities for patients and the food and agriculture industries.

Makino (WHO): Although we live in the era of PPP (Public Private Partnerships), the private sector still rarely participates in discussions at WHO. But the future participation of the private sector is inevitable in this era. Because WHO has a large influence on public opinion in each

country, it is essential to create discussion that can bring about a paradigm shift. Although AMR is mainly discussed as a security issue, it should be positioned within the medical system. PPP is also important for the development of new drugs. By promoting public and private partnerships, this area should seek to lessen development costs.

- **Commitment from Industry regarding Intellectual Property and the Delivery of Pharmaceuticals**

Makino (WHO): Although the patent system is designed to promote the sharing of scientific discoveries throughout the world, certain actors in the health sector think that patents restrict access to medicine. However, license fees allow further research and development, as well as information sharing, which bring about a spillover* effect, i.e. they maintain access to medicine. Actors in the health sector should understand the mechanisms of innovation and spillover. Some activities carried out by those in non-governmental sectors that aim to improve access to medicine are actually lessening incentives for pharmaceutical companies.

*Spillover: This term refers to a situation in which innovation is brought about through the use of information and technology from many different areas.

Kerr (HHS): Only the pharmaceutical industry is capable of developing new drugs and antibiotics. Therefore, it is important to maintain a balance that ensures incentives to bring drugs to market and promote access to medicine, so that pharmaceutical companies can develop new drugs and function as an industry.

- **Expansion of JANIS in Asia and the Establishment of an Isolate-based Surveillance System**

Arakawa (Nagoya University / Academia): JANIS needs funding and human resources in order to expand in Asia. It is essential to consider how to secure these resources. Moreover, in addition to the expansion by JANIS, in terms of surveillance systems based on laboratory data, we need to establish an isolate-based surveillance system. To build a database that gathers data on AMR pathogens, a certain level of facilities, experts, and human resources are needed. It would be difficult for the National Institute of Infectious Diseases to establish such a system alone. Therefore, related societies focusing on infectious diseases that are

comprised of many leading experts in the field of AMR should cooperate, support, and manage such a system together with the National Institute of Infectious Diseases.

Comment from the audience (Academia): Although an isolate-based surveillance system is currently being developed in collaboration with the Japanese Association for Infectious Diseases, Japanese Society of Chemotherapy, and Japanese Society for Clinical Microbiology, the lack of funding and human resources is a problem. We need to create a stable backup system to ensure its continuation. In that regard, it is recommended that the surveillance system be led by the Government with help from related academic associations.

Asanuma (MHLW): To strengthen surveillance, we are planning to establish an Antimicrobial Resistance Research Center (tentative name). The assistance of experts from academia and related academic associations is indispensable. We would like to continue our collaborations with the private, public and academic sectors.

Kerr (HHS): In the U.S., we are combining data from the AMR surveillance systems of civilian, military, animals, food, and so on, and we plan to collaborate with those managing surveillance systems in other countries in order to create a framework to share information regarding high-risk antimicrobial-resistant bacteria and send out alerts about them.

- **The Shift from Treatment with Antibiotics to Prevention via Vaccines**

Asanuma (MHLW): It is possible to reduce unnecessary prescriptions of antibiotics by giving pneumococcal vaccines to elderly people. We recognize the importance of further institutionalizing vaccines. The excessive use of antibiotics in long-term care facilities and nursing homes should be paid attention to. We need countermeasures related to this in particular.

Arakawa (Nagoya University / Academia): There are only so many vaccines available. They are effective among young and healthy people who have immune systems that are functioning properly. However, the same effect cannot be expected for patients or elderly people with compromised immune systems. Therefore, it is necessary to use both vaccines

and antibiotics for in-patients and people with compromised immune system to control nosocomial infections.

Makino (WHO): This same AMR problem could occur for vaccines as well. Therefore, it is essential to think about the best combination of antibiotic treatments and vaccines.

- **Antimicrobial Stewardship in Outpatient Settings and Long-term Care Facilities**

Kerr (HHS): Proper antibiotic usage requires institution-specific approaches for each type of institution, such as hospitals, clinics, or long-term care facilities. In the U.S., the hospitals that participate in the antibiotics stewardship program can receive reimbursements from Medicare and Medicaid. We are planning for the participation of long-term care facilities into the stewardship program in 2018.

*Stewardship program: a program set up by the U.S. CDC to promote the appropriate use of antibiotics in hospitals and other facilities.

Asanuma (MHLW): Because outpatients often receive their medications via prescriptions, it is important to develop a system that collects data from pharmacies to monitor antibiotic usage in outpatient settings. The current situation of antibiotic usage in elderly care facilities in particular needs to be clarified.

Arakawa (Nagoya University / Academia): Although Japan's Action Plan aims for the reduction of unnecessary antibiotic use among outpatients, antibiotics are indispensable for cases such as viral upper respiratory tract infections and other bacterial superinfections. The U.K. achieved the control of antibiotic use through the introduction of elective prescriptions that prevent prescriptions of antibiotics being filled on the same day as a consultation. It is essential to control antibiotic use not only in medical institutions but also through policy making.

Panel Discussion 2 "Accelerating Research and Development of Drugs to Combat AMR"

AMR is an immediate global threat which calls for multi-stakeholder partnership. As antibiotic development has slowed over the years, innovative mechanisms are urgently needed to promote both development of new antibiotics and appropriate access and use. In this session, experts discussed possible R&D frameworks for public-private-academia partnership to address the gaps in economic incentives for antimicrobials development.

Panel Members

Kazuhiko Mori (Councilor for Pharmaceutical Affairs, Minister's Secretariat of MHLW)

Satoshi Iwata (Professor, Department of Infectious Diseases, Keio University School of Medicine)

Takeo Morooka (Executive Officer, Head of Health Policy and Corporate Support, MSD K.K.)

Takuko Sawada (Director of the Board, Senior Vice President, Corporate Strategy Division, Shionogi & Co., Ltd.)

(Moderator: Ryoji Noritake (Vice President, Health and Global Policy Institute))

(titles omitted / in no particular order)





- **Each Stakeholder's AMR Countermeasures**

Mori (MHLW): It is essential to draw up guidelines for drug evaluations. Regarding AMR, it is also important to update guidelines for the development of antibiotics internationally. Additionally, there is a need to enhance infrastructure in such a way as to promote development and maintain win-win relationships between those working for drug development and drug review. To that end, we need to see the improvement of networks that gather data on the effectiveness of new drugs and their side effects, as well as collaboration

with academia. We are considering how to promote incentives for drug development.

Iwata (Keio University / Academia): People in academia are focused on education and research. There hasn't been much work done to promote education on infectious diseases from the perspectives of clinical expertise as well as economic and social expertise. It would be best if health care practitioners could provide feedback about the reality of their clinical practices to people working in research and development. There needs to be public, private, and academic sector collaboration on the indices used to evaluation clinical trials and medications.

Morooka (Global Pharmaceutical Company): There are some factors that prevent the research and development of new drugs: (1) Pricing and refund systems do not provide sufficient returns for the time and cost involved – it is essential to promote both push (grants, tax exemptions, etc.) and pull (reimbursements, patent term extensions, etc.) mechanisms; additionally, the Government should secure a minimum level of sales through a cap-and-collar mechanism*. (2) Because cases of AMR are sporadic and limited, it is necessary to set separate standards for international clinical assessment guidelines that differ from existing ones. (3) Regarding the appropriate use of antibiotics, it is not enough just to aim for the reduction of unnecessary antibiotic prescriptions, as is written in the Action Plan; we must introduce an evaluation system that employ clinical effects and epidemiological outcomes as measures.

*Cap-and-collar mechanisms: a financial concept whereby maximum and minimum interest rates are set. In this report, it is referred to as a way of securing a minimum level of sales for medical products.

Sawada (Japanese Pharmaceutical Company): The support system for research and development in Japan is not developed enough compared to that in Europe and the United States. Although there are a sufficient number of AMR Gram-positive patients in Japan, the number of AMR Gram-negative patients is limited, so there is a need to develop clinical trials globally. This is true of other countries as well; no one country can supply the total package for clinical trials. One barrier is that the requirements for clinical trials, and the indications that can be studied, vary from country to country. In this context, it is difficult to implement any clinical development that recommends international indications of new drugs. It is thus essential to design harmonized clinical guidelines for antibiotic development. Furthermore, it

is important to establish a clinical trial network that can share data between medical institutions, as well as set indications* for antibiotics in accordance under careful stewardship*.

*Indication: This term refers to the patients and diseases that a specific medication or drug is expected to have a clinical effect on.

*Stewardship: This term refers here to a clinical or educational intervention by an in-hospital expert on the proper use of antibiotics.

- **International Harmonization and Incentives for New Drug Development**

Mori (MHLW): Although it has been nearly 30 years since the international community started trying to establish internationally harmonized guidelines, we have not yet achieved them. As is written in the Action Plan, it is essential for Japan to recognize its role and take initiative in the world. Although it is difficult to conduct large-scale comparative clinical trials for antibiotics, it is possible to efficiently assess the efficacy of drugs by utilizing PK/PD* models and simulations*. Moreover, it is important to establish electronic information networks to gather information on new antibiotics, including information on their efficacy/effectiveness and safety from the developmental stages to the post-market stage. This network should connect the medical institutions using such antibiotics. It should be possible to apply the existing 'Scheme of Rapid Authorization of Unapproved Drugs' for the establishment of grants as incentives.

*PK/PD: PK, or pharmacokinetics, refers to the temporal variation in the concentration of antibiotics in a body. PD, or pharmacodynamics, refers to the relationship between the concentration of an antibiotic in a body and its effect. An understanding of pharmacokinetics and pharmacodynamics for an antibiotic can help prevent the emergence of antimicrobial resistance.

*Modeling and simulation (M&S): This term refers to a range of methods that can help to enable efficient clinical studies for drug development. Modeling and simulation practices make it possible to select the best clinical model at each phase of development by analyzing the accumulated knowledge and data from clinical trials.

*Post-marketing surveillance (PMS): This term refers to efforts to collect data about new drugs, such as secondary effects after it has been released on the market. Because there are not sufficient numbers of cases at clinical study of new drugs for rare diseases, it collects data from all patients after approval.

*Scheme of Rapid Authorization of Unapproved Drugs: a system described in the 'The Strategy of SAKIGAKE' that was drawn up in June 2014. Although the system originally only applied to approved drugs from Western countries, it was expanded to drugs that are unapproved in these countries as well.

Iwata (Keio University / Academia): Since it is foreseeable that it would be possible to undertake more effective drug development based on PK/PD information, academic associations and the Government are now drawing up guidelines on this issue. As it is difficult to assess safety with a limited number of clinical trials. It is important to gather post-market information on products. For drugs for which there is high medical need, it is also worthwhile to think about incentives related to drug prices.

Morooka (Global Pharmaceutical Company): In order to improve the platform for drug development in this country, it is recommended that public institutions store antimicrobial-resistant bacteria isolates, and use this kind of isolate bank for research and development. In improving incentives, it is important to use both push and pull mechanisms. In order to promote the appropriate use of antibiotics through drug pricing policy, it is essential to develop a mechanism that would unlink revenue from the volume of products sold, which would be different from the existing system in which the more you sell, the more revenue you earn.

Sawada (Japanese Pharmaceutical Company): In terms of platforms for research and development, it is essential to establish a follow-up system for the time after medical products have been released on the market. In order to monitor whether there is good stewardship related to product use, it is important to establish a database that can connect data on antibiotic use, clinical data, and strain data. There is a problem with the price mechanism related to antibiotics (i.e. they are more expensive than other medicines) and the amount they are prescribed (i.e. the volume of prescriptions is lower than other medicines because of their short administration period). Therefore, it is difficult to develop antibiotics for AMR bacteria without establishing a new drug pricing mechanism. Additionally, I would recommend that efforts be made to promote schemes for rapid authorization in this country and to unify clinical packaging around the world.

Mori (MHLW): Drug price increases may increase the financial burden that falls on patients. However, the scheme of rapid authorization of unapproved drugs proposes grants as incentives for companies that develop new drugs for which there is high medical need in that

it proposes that we accept price maintenance efforts for other drugs outside of the new drug. It is essential that we establish an ideal atmosphere for reasonable research and development by applying these existing systems.

- **Importance of Diagnosis in AMR**

Iwata (Keio University / Academia): It is important to 'know the enemy' when using antibiotics. Because it takes a few days to get the results when using current drug susceptibility tests, antibiotics are often employed as empirical therapy*. However, if it were possible to use genetic tests to identify AMR, it would be possible to better promote the appropriate use of antibiotics. As it is technically possible, it is recommended to make genetic testing covered under health insurance.

*Empirical: Empirical therapy here refers to what is sometimes called, 'therapy based on experience,' which is the act of starting therapy in the absence of a diagnosis. For infectious diseases, there are cases where medicines are prescribed before pathogenic microbes have been identified.

Comment from the audience (Academia): In addition to expediting diagnosis of pathogenic microbes, it is also important to allow for the decision to not use antibiotics. The development of diagnostics with high specificity would reduce unnecessary prescriptions, as it is written in the Action Plan.

*Specificity: This term refers to one of the indices used to determine the type of clinical trial to be undertaken. It determines 'the proportion of negative values detected given that it is known that the result is negative'.

Mori (MHLW): Innovation in the area of diagnostics is needed. It is crucial that we understand regional mappings of antibiotic susceptibility and epidemic strains through the use of information technology and sharing of data throughout the country. The Government needs to invest in the establishment of a platform that would be able to apply such data for clinical practices. Patient registries should be created and used for infectious diseases as they are with other diseases.

Comment from the audience (Academia): The problem with the issue of diagnostics is the lack of laboratory capacity. Without high quality microbiology laboratories in hospitals, it is

difficult to promote stewardship. Moreover, it is important to note that nowadays, it is less common to see young physicians prescribe antibiotics in an inappropriate way. They are moving towards the more prudent use of antibiotics.

- **Global Outlook on Harmonized Guidelines and of Post-marketing surveillance**

Comment from the audience (Participant from the U.S.): The creation of a process for the authorization of unapproved drugs is also a problem in the U.S. We attempt to clarify the indications of new drugs and conduct additional clinical trials in the post-market phase.

Mori (MHLW): Drug approval despite a limited number of studied cases has been discussed in the U.S. Congress (i.e. the 21st Century Cures Act). As Japan and the U.S. have a common concern in this regard, the FDA, MHLW, and PMDA will continue to discuss the issue. More and more, people around the world are coming to accept the drug assessments utilizing a limited number of cases through the use of PK/PD models.

*21st Century Cures Act: an act introduced in the U.S. House of Representatives in May 2015. It aimed to develop data to support the approval of new drugs, as well as research and development, by focusing on patients treated with early interventions using medical equipment.

- **Multiple Drug Therapy in Infectious Diseases**

Sawada (Japanese Pharmaceutical Company):Multi-drug therapy is commonly used for the treatment of HIV, but it is not always easy to use it when there are different patents involved, requiring contracts with several pharmaceutical companies. However, since more and more joint development is now occurring in areas like oncology for the development of anti-cancer drugs, I think that similar efforts can be undertaken for this issue if the need for such efforts is recognized.

*Patent: patents for medical products are granted from 20 years from the date they were filed. Since development and research normally takes about 10 years, market exclusivity only applies for less than 10 years in many instances. Because of the patent system, complementary drugs are usually formulated within single pharmaceutical companies.

- **In Conclusion**

Sawada (Japanese Pharmaceutical Company): Because AMR is a global issue, it is

important to agree on the harmonization of development package, indication, and post-marketing surveillance efforts, in order to promote the proper use of antibiotics. We hope that Japan will play an important role in the international community.

Morooka (Global Pharmaceutical Company): Regarding the establishment of development incentives, it is vital to use both push and pull mechanisms, in order to ensure sustainability. As a leading company in the pharmaceutical industry, we would like to contribute to the public private partnerships involving both Japanese and foreign companies.

Iwata (Keio University / Academia): With the wealth of knowledge available in academic associations, we would like to contribute to the establishment of internationally harmonized standards for clinical evaluations of new drugs. Since research requires a great amount of funding, we would like the Government to position infectious disease as a key research topic.

Mori (MHLW): With ICH*, the Japanese Government is working on the international harmonization of clinical evaluation. There is momentum for this right now, in that regulatory bodies in each country are each proposing new systems to promote innovation, and this is driving positive competition. In fact, the harmonization of regulatory guidelines and competition between regulatory bodies is pushing forward innovation. Even as a regulatory authority, our role is to bring the seeds of research out of the laboratory and into clinical practice, and to deliver new medical products to patients.

*ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use): A project undertaken between Japan, the U.S., and Europe that aims to unify drug registration standards. By conducting efficient non-clinical and clinical trials, it aims to prevent any delay in the availability of new medicines. It was created in April 1990.

Program

Date and Time:	14:00-18:00, Monday, 18 April, 2016
Venue:	Banquet Room Sirius, Hotel New Otani. Tokyo
Joint Organizers:	Center for Strategic and International Studies (CSIS) Health and Global Policy Institute (HGPI)
Special Sponsorship:	MSD K.K. and Shionogi & Co., Ltd.

14:00-14:15	**Welcoming Remarks** Kiyoshi Kurokawa (Chairman, HGPI) Audrey Jackson (Senior Fellow, CSIS)
14:15-14:30	**Keynote Address** “Tokyo Declaration on AMR, Japan’s role and the coming G7 meeting” Ministry of Health, Labour and Welfare, Japan
14:30-16:00	**Panel Discussion 1** “Regional and Global Capacity-Building to Combat AMR”
16:15-17:45	**Panel Discussion 2** “Accelerating Research and Development of Drugs to Combat AMR”
17:50-18:00	**Closing Remarks** Keizo Takemi (Councilor)