The 5th Nikkei Asian Conference on Communicable Diseases 2018

‘Okinawa Communicable Diseases Statement 2018’

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1. Introduction

With progression of globalization, Japan and other countries, especially Asian countries, have become inseparable at every level, such as economics, society, and, culture. Threat of infectious diseases, such as outbreaks of Zika virus and Ebola virus infections, spread of tuberculosis and malaria, and raging of multidrug-resistant bacteria (AMR), are still major problems inside and outside the country.

With an increase in international recognition of infectious diseases as the background, industry-academia-government key persons of infection control gathered in Okinawa on February 2 and 3, 2018, from countries all over the world and held the 5th Nikkei Asian Conference on Communicable Diseases 2018. Through discussion, participants re-confirmed the necessity and effectiveness of promoting measures against infections threatening people's health and economic activity through Public-Private Partnership (P3), as confirmed in previous conferences. Nikkei Asian Conference on Communicable Diseases manages 'Asia Medical Innovation Consortium (AMIC)' comprised of several working groups throughout the year for the purpose of designing and executing P3.

In the plenary session of the 5th conference, 'AMIC Tuberculosis Working Group' reported that the TB-LAMP method of Eiken Chemical made major progress, such as acquisition of the recommendation for the use from the World Health Organization (WHO). The 'AMIC Malaria Working Group' prepared a proposal to the government referring to that prepared by the Tuberculosis Working Group. To establish a network of Asian bases for infection control including Okinawa and promote practical application of new techniques, 'AMIC Working Group for the Asian Communicable Diseases Clinical Research Centers' was founded last year. Its basic concept was discussed in the plenary session to make a proposal on the Asian Communicable Diseases Clinical Research Center to the society.

In addition, issues concerning overseas activity for Japanese therapeutic drugs applying the lessons learned from the outbreak of Ebola virus infection, actions taken to form the Okinawa Communicable Diseases Research Center, issues concerning promotion of infection control against multidrug-resistant bacteria (AMR), measures to improve public health, the importance of logistics for infection control, and the way of utilizing information and communication technologies (ICT) and artificial intelligence (AI) were discussed. In addition, the necessity of innovation contributing to international infection control was confirmed, and corresponding seeds from Japan were introduced. Through the discussions, expectation for development of this conference to contribute to global infection control not limited to Asia was expressed.

Participants agreed to 'Okinawa Communicable Diseases Statement 2018' as the achievement of the discussions. In addition to reporting the achievement of this conference to government-related conferences, the statement will be widely sent in not only Japan but Asia and worldwide. With deepening of international understanding, Japan will be needed to more strongly commit to worldwide infection control in the future. For the history of foundation of the Nikkei Asian Conference on Communicable Diseases and content of conferences, please refer to past statements.

http://ac.nikkeibp.co.jp/4thnac/okinawa2017/pdf/okinawastatement2017_ja.pdf
http://ac.nikkeibp.co.jp/3rdnac/tokyo2016/pdf/3rdnac_tokyo2016_statement_jp.pdf
http://ac.nikkeibp.co.jp/bio/okinawa2015/pdf/OkinawaCommunicableDiseasesStatement2015.pdf
http://ac.nikkeibp.co.jp/bio/okinawa0214/pdf/OkinawaCommunicableDiseasesStatement2014.pdf

2. Report on Progress of Public-Private Partnership (P3) in Japan

2.1 Tuberculosis

2.1.A P3 Initiative on Tuberculosis and its Background

As deaths from a single infectious disease, the number of deaths from tuberculosis is the highest in the world. In 2016, 10.4 million people newly developed tuberculosis and 1.7 million died. The number of patients in the world tends to decrease but tuberculosis outbreaks still continue mainly in developing countries, and the prevalence in Japan is still high. Moreover, emergence of multidrug-resistant Mycobacterium tuberculosis due to inappropriate use of antituberculous drugs has increased patients with difficulty in treatment. In 'End TB Strategy' formulated by the World Health Organization (WHO), 90% reduction of the number of deaths from tuberculosis and 80% reduction of the prevalence by 2030 setting the baseline at those in 2015 are targeted.

In Japan, countermeasures against tuberculosis after World War II succeeded because the network comprised of the Japan Anti-Tuberculosis Association and nationwide health centers functioned and access to patients improved through the national health insurance system covering the whole nation. In addition, simple and highly accurate diagnostic techniques and drugs against multidrug-resistant tuberculosis have been developed. These experience and innovation in Japan are expected to contribute to the world's countermeasures against tuberculosis.

The AMIC Tuberculosis Working Group attaches greater importance to the following items to end tuberculosis: (1) Development of a simple technique capable of accurately diagnosing tuberculosis which can be provided at a low-price and (2) reliable diagnosis of multidrug-resistant tuberculosis and proper prescription and reliable taking of antituberculous drugs. For these, they consider that it is essential to package diagnostic techniques and antituberculous drugs and realize a medical care delivery system capable of seamlessly providing the packages to developing countries. This Working Group proposed P3 Package for MDR-TB comprised of a simple and highly accurate genetic test (TB-LAMP, Eiken Chemical) for screening, multidrug-resistant genetic test (Genoscholar, NIPRO) capable of definitely diagnosing multidrug-resistant tuberculosis, and a new drug against multidrug-resistant Mycobacterium tuberculosis (Delamanid, Otsuka Pharmaceutical).

2.1.B Status of Progress

Genoscholar, TB-LAMP, and Delamanid have acquired recommendation for the use from the World Health Organization (WHO). Regarding P3 Package, NIPRO and Eiken Chemical cooperatively performed primary screening of tuberculosis using TB-LAMP in the Philippines as a part of the JICA Collaboration Program with the Private Sector for Disseminating Japanese Technologies, and proposed an algorithm to diagnose drug-resistant tuberculosis using Genoscholar. Basic performance evaluation of each technique (Phase I) has been completed and it is now going to progress to evaluation of the algorithm (Phase II). In the JICA program, a project to replace the conventional method (culture test) with Genoscholar of NIPRO to shorten the time required for diagnosis is progressing in Indonesia, and P3 Package for MDR-TB into Afghanistan has already been introduced.

The public-private collaboration project started at various levels through approaches to the ministries and agencies. The AMIC Tuberculosis Working Group had an opportunity in the first ministerial-level meeting concerning tuberculosis held in November 2017 in Russia, in which a statement of measures previously taken aiming at ending tuberculosis was distributed, sending information to the countries.

Measures to make use of the techniques comprising P3 Package for countermeasures against tuberculosis have also been in full progress in various countries and regions. TB-LAMP has been confirmed to be highly sensitive compared with the conventional method (smear test) in a field test

performed in Cameroon and the Ministry of Heath decided on replacement. We have a good prospect for supply through utilizing the budget for The Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) and Global Drug Facility of Stop TB Partnership. Discussion on the spread of the test is underway in several countries and national projects are moving in 3 countries.

Delamanid was included in the WHO Model List of Essential Medicines in 2015 and its supply to about 100 countries through GDF became possible in 2016. Partnership with overseas pharmaceutical companies became realized in 2017, and acquisition of approval in highly burdened countries with high prevalence and population is planned. In addition, getting support by the Bill & Melinda Gates Foundation, development of a new regimen for tuberculosis based on delamanid and a novel therapeutic drug for tuberculosis (OPC-167832) will be proceeded.

The AMIC Tuberculosis Working Group will strengthen the public-private collaboration project by getting opportunities for encouragement in high-level meetings, such as those in the United Nations General Assembly held in September 2018.

2.2 Ebola

2.2.A Ebola P3 Initiative and its Background

Although it is currently calmed down, the risk of outbreak of Ebola virus infection is constantly present. Although large-scale outbreaks were controlled, Japan should continue to provide necessary support through public-private collaborative activity and have interest in cooperation with Asian and other countries worldwide.

In March 2017, a stock of ‘favipiravir (product name: Avigan)’ for about 2 million people, the upper limit of inpatients in estimation of the damage of novel influenza stipulated in the Government Action Plan was decided in the ‘Guidelines for Measures against Novel Influenza’ revised by the government. However, the stock is limited to the use against novel influenza and it cannot be used for other diseases. To prepare for not only re-outbreak of Ebola virus infection but also other infectious diseases, it is urgently needed to construct a framework enabling a swift response, such as a system in which unapproved potential medical drugs and indications in clinical study steps are closely examined beforehand and can be used irregularly for emergencies corresponding to the situation.

Ebola P3 Initiative is a public-private collaboration project which started in 2014 getting financial cooperation from the Ministry of Health, Labour and Welfare in response to a request for support from the government of Guinea, an Ebola virus infection-affected country, and request for collaborative research from a French research institute, Institut National de La Sante Et de La Recherche Medicale (INSERM). One pillar of the project was to conduct a clinical study demonstrating the treatment effect of favipiravir (product name: Avigan) on Ebola virus infection. Upon presenting the animal study results of Avigan to a French delegation in the WHO meeting on countermeasures against Ebola held in Summer 2014, a clinical study was planned in cooperation to utilize the drug against Ebola as early as possible. Agreement with Toyama Chemical for conduct of a phase II clinical study administering favipiravir was obtained. The study was conducted in cooperation with local medical NGO and INSERM taking responsibility for the execution under permission by the French and Guinean Regulatory authorities. In this public-private collaboration project, Cannon Medical Systems (former Toshiba Medical) and Nagasaki University provided the Ebola virus diagnostic drug and device employing the RT-LAMP method and performed verification tests in Guinea.

2.2.B Status of Progress

In the clinical study of favipiravir, favipiravir was administered to 126 patients between December 2014 and May 2015. Fifty-five patients with a low viral load before administration

survived, reducing the mortality rate as achievement of this clinical study, and 44 patients actually survived. The final report was published in March 2016. Getting funds from AMED, Nagasaki University, and Fuji Film/Toyama Chemical started the 'study toward development of treatment, diagnosis, and preventive methods against viral hemorrhagic fever' targeting Crimean-Congo fever, Marburg disease, and Lassa fever in 2018. Favipiravir is also expected to be an effective therapeutic drug for tick-borne 'severe fever with thrombocytopenia syndrome (SFTS). The clinical study was conducted being led by Masayuki Saijo, Director, Department of Virology 1, National Institute of Infectious Diseases, and Masataka Yasukawa, Vice President of Ehime University, and findings leading to the development of an effective treatment method were acquired. In response to this, a clinical trial aiming at acquisition of pharmaceutical approval is being prepared in Japan, and a clinical trial is also being planned in Korea.

Cannon Medical Systems has also provided for free the diagnostic kit employing the RT-LAMP method for 10,000 tests and 9 diagnostic devices to the Guinean government through the Ministry of Foreign Affairs of Japan by 2017. However, there is no prospect of sales of the Ebola virus diagnostic kit after 2018. With the financial cooperation of AMED, the company started development of a Zika fever diagnostic kit in collaboration with Nagasaki University in June 2016. A clinical study was conducted from March 2017 in Brazil with many infected patients and it was completed in November 2017. Approval for manufacturing and sales as a Zika fever diagnostic kit was applied in January 2018 in Japan.

In addition to development of new treatment methods of emerging and re-emerging infectious diseases, institutional measures based on the lessons from the Ebola outbreak are also being discussed. Since favipiravir was approved as an anti-influenza drug, it was difficult to immediately support overseas in the outbreak of Ebola virus infection. To solve this problem, 'Scheme to provide unapproved drugs to developing countries in an emergency' was constructed under the initiative of the Prime Minister's office in cooperation with the Ministry of Foreign Affairs and Ministry of Health, Labour and Welfare and 'adjustment meeting of the ministries concerning providing unapproved drugs overseas' and 'expert committee' thereof were held in July 2017.

2.3 Malaria

2.3.A Malaria P3 Initiative and its Background

The number of malaria-infected persons reached 200 million in 2016, and the number of deaths reached 440,000. Five percent of deaths of infants aged 5 years or younger were due to malaria, and it reached 10% in Sub-Saharan Africa. The Asia Pacific Leaders Malaria Alliance holds a high target in a roadmap: elimination of malaria from 6 countries and prevention of infection of 40.3 million people by 2016-2020 and elimination from 22 Asian countries by 2026-2030.

For elimination of malaria, Japan is able to provide a comprehensive solution by integrating techniques of private companies in 3 fields: tests/diagnosis, development of new drugs, and vector control for prevention. Supply of necessary medical drugs and medical devices depends on international supporting institutions such as the Global Fund, but these institutions request acquisition of WHO-PQ certificate in many cases, for which the following items are essential: (1) Verification of the usefulness based on evidence data and application, (2) winning nomination by the recipient country, and (3) construction of a permanent network with international institutions, such as WHO and Global Fund. However, these are difficult to realize by private companies alone. Formation of P3 Initiative as seamless industry-academia-government collaboration is important.

2.3.B Status of Progress

The AMIC Malaria Working Group established in September 2016 has had many discussions and pointed out the importance of integration of the fields of tests/diagnosis, development of new drugs, and vector control for prevention, and it was agreed that achievement being acquired in Asia should be ensured and at the same time, active countermeasures are essential for the malaria endemic zone

centering Africa.

However, the situation concerning malaria is different between Asia and Africa. Thus, after discussion in the 4th conference, the Asia Task Force and Africa Task Force were established and issues were discussed corresponding to the situation in each region. In the Asia Task Force, a specific strategy for acquisition of WHO-PQ certificate was discussed, and the results of a study on application of a high-sensitivity test system developed by SYSMEX and Eiken Chemical were shared. In addition, the Africa Task Force shared the results of a study in which therapeutic drugs were administered in all regions with accumulated malaria patients, such as Kenya, and elimination succeeded.

Regarding high-sensitive high-speed diagnostic techniques, in Japan, SYSMEX developed a multichannel automated blood cell analyzer utilizing flow cytometry and Eiken Chemical developed a high-sensitive test system adopting the LAMP method capable of amplifying genes even in outdoor fields. Regarding therapeutic drugs, Neopharma suggested that 5-aminolevulinic acid (5-ALA) being developed may be combined with artemisin, for which acquisition of resistance has recently been problematic. Getting support from GHIT Fund, Osaka University and Nobelpharma completed preparation for initiation of a new clinical study of BK-SE36 vaccine with adjuvant in Burkina Faso and Germany. For vector control, Sumitomo Chemical developed a long-lasting insect-controlling net, long-lasting indoor spray, and mosquito larvicide, and proposed comprehensive vector control. The long-lasting indoor spray acquired WHO-PQ certificate in 2017.

3. New Challenges and Actions Needed

3.1 Tuberculosis P3 Initiative: Issues and Actions Needed

[Issues]

Toward full-scale application of P3 Package, introduction should be proceeded corresponding to culture, language, and medical delivery system of each country in cooperation with local key opinion leaders (KOL). In addition, it is difficult to continue the project in a profitable way by individual companies alone. To continuously provide diagnostic techniques and therapeutic drugs, it is important to acquire support from the government and external funds. Moreover, differences in the procedure and conditions of application for approval among nations are obstacles of the spread. Acceleration of research and development of new innovation aiming at ending tuberculosis is also needed.

[Actions Needed]

<For Consortium and Companies>

1) The AMIC Tuberculosis Working Group should develop close coordination with persons concerned in Japan as well as sufficient coordination with target countries to facilitate providing P3 Package in a way appropriate for the condition of each country. The group should also acquire cooperation from the government and external funds to continue the project.
2) It is necessary to accelerate development of a novel diagnostic technique (Fuji Film) to detect a component of Mycobacterium tuberculosis, lipoarabinomannan (LAM), in urine and therapeutic drugs including OPC-167832 (Otsuka Pharmaceutical) with a novel action mechanism inhibiting cellular synthetic enzyme of Mycobacterium tuberculosis.
3)Exploring new expansion of P3 projects is necessary.

<For Academia>

Measures to promote studies aiming at developing new diagnostic techniques and therapeutic drugs for the future, such as construction of a genomic database of Mycobacterium tuberculosis, should be performed by the National Institute of Infectious Diseases, Japan Anti-Tuberculosis Association, and National Center for Global Health and Medicine in cooperation with each Asian country.

<For Government>
1) The government should constantly support the continuation of the project.
2) Harmonization of regulatory affairs with countries with high burden of tuberculosis, such as developing countries, and preparation of a system to simplify examination in the target countries, if approval has been acquired in Japan, are needed.

3.2 Ebola P3 Initiative: Issues and Actions Needed

Companies are performing clinical studies to make use of their products for not only Ebola virus infection but also diagnosis and treatment of other new emerging and re-emerging infections. Although the Ebola outbreak in West Africa has converged, the issues below were raised. By investigating dealing with regulations and systems and support for companies, more effective control of new emerging and re-emerging infections becomes possible.

[Issues]

1) The main organization responsible for fund-raising, planning, and execution of the clinical study of favipiravir against Ebola virus infection in Guinea is INSERM, and INSERM took initiative with regard to the timing of disclosing the study results. Since the organization responsible for executing the clinical study was not a Japanese government agency, grasping information and negotiation for executing the study at the local site were difficult for one company.
2) Since Avigan is unapproved for treatment of Ebola virus infection, it was difficult to support in the pandemic of Ebola virus infection.
3) There is no prospect of sales of the RT-LAMP kit as an Ebola virus diagnostic kit after 2018. Since the market was temporary and unstable and it was an emergency action after the occurrence of the pandemic, construction of a business model was difficult.

[Actions Needed]

1) For execution of clinical studies overseas by companies, active involvement of the Japanese government and cooperation with the government and regulatory authority of each country are needed.

'Scheme to provide unapproved drugs to developing countries in an emergency' was established in 2017 under the initiative of the Prime Minister's office. It needs an expeditious response, such as preparation in which unapproved medical drugs in clinical study steps and drugs with the possibility of use without approval are closely examined beforehand in cooperation with pharmaceutical companies to realize the plan to cope with infectious diseases for which no treatment method has been established. In addition, cooperation with the governments of countries with high incidences of infection is important.
2) Consideration of procurement of drugs for infectious diseases and diagnostic kits by the Japanese government and construction of the minimum market in Japan are necessary.
3) The government should further promote support for incorporation into the supply process of international institutions, such as acquisition of WHO-PQ certificate.
4) Development of P3 Projects to target new emerging and re-emerging infections based on experience of Ebola P3 project is necessary.

3.3 Malaria P3 Initiative: Issues and Actions Needed

[Issues]

Countermeasures against malaria are now facing 4 issues: 1) Detection and treatment of asymptomatic plasmodium carriers, 2) countermeasures against drug resistance/insecticide resistance 3) securing financial resources, and 4) strengthening of health system. WHO also recognizes the necessity of innovation overcoming these 4 issues. Japan is expected to take actions through P3 centering Issues 1) and 2).

1) Detection and treatment of asymptomatic plasmodium carriers: The presence of asymptomatic malaria parasite carriers undetectable by the conventional diagnostic technique has been clarified. It has been pointed out that although they are asymptomatic, they may develop the disease or serve as a new source of infection, proposing the importance of high-sensitivity testing and early initiation of treatment. At present, WHO attaches greater importance to the presence of evidence for reduction of infection and death by intervention of asymptomatic cases. It is important to construct evidence for the significance of high-sensitivity testing and early treatment.
2) Countermeasures against drug resistance/insecticide resistance: Emergence of vector mosquito resistant to existing insecticides and malaria parasites resistant to anthelmintic has been confirmed. For countermeasures, surveillance of drug sensitivity and introduction of a new drug are needed. Since research and development of an insecticide requires 10 years, a scheme to recover the investment for research and development is needed.
3) Securing financial resources: Disparity of countermeasures against malaria is expanding between Western countries which succeeded in elimination and some African and Asian countries. Difference in investment has been pointed out as a cause of this bipolarization. Foundation to improve health care is insufficient in many developing countries requiring countermeasures against malaria, and they inevitably depend on support from international aid organizations, such as WHO and Global Fund.
4) Strengthening of health system: Health system necessary for malaria control is vulnerable in countries with the spread of malaria.

[Actions Needed]

<For Consortium and Companies>

For detection and treatment of asymptomatic parasite carriers and countermeasures against drug resistance /insecticide resistance described above, consortium and companies are needed to provide comprehensive solutions for the following 3 fields: ‘Vector control exerting a strong effect on insecticide-resistant mosquitoes’ which has been performed, in addition to ‘high-sensitive rapid diagnosis’, ‘development of a new drug with high safety and effect on drug-resistant plasmodium’. All fields require various lobbying activities and verification data collected in local regions to acquire the certificate of the WHO prequalification program (PQ). In addition, private companies have to continue long-term investment while strengthening cooperation with academia.

<For Government>

To acquire WHO-PQ certificate, making efforts by private companies alone is limited, and industry-academia-government collaboration is necessary. To perform a clinical study in Africa with the most serious damage by malaria, construction of an implementation system, development of human resources for negotiation with local medical institutions and communities, and cooperation with policy advisors are important. To recover the high research cost, Japan-led establishment of a procurement support route, such as support by buying out products which acquired WHO-PQ certificate, is necessary.

4. New Challenges

4.1 Asian Communicable Diseases Clinical Research Center

[History and Current Status]

To proceed specific discussion to construct the Asian Communicable Diseases Clinical Research Center and Okinawa Communicable Diseases Research Center, ‘Working Group for the Asian Communicable Diseases Clinical Research Center’ was founded in 2017 as a new AMIC working group. The working group proposes the basic concept of the Asian Communicable Diseases Clinical Research Center as follows. This concept is consistent with ‘Asia Human Well-Being Initiative’ promoted by the government.

[What is a clinical study?]

Clinical study is defined as 'an intervention study with humans' in this concept. This is an essential step in the research and development of new drugs and medical techniques. To develop diagnostic and new drugs, cooperation with regions with actual incidences of infection is necessary. To establish the Asian Communicable Diseases Clinical Research Center and get their work on track, it is important to proceed multinational clinical studies by the spirit that Japan and each Asian country are equal partners.

For new drugs developed in Japan, clinical studies up to the phase I study confirming the safety will be performed in Japan, for which strengthening of cooperation with base institutions, such as the National Center for Global Health and Medicine and Nagasaki University.

Phase II and later phase clinical studies judging the effect of new drugs have to be performed in cooperation with each Asian country with many infected persons. Based on the data collected in this way, approval of sales in each country and WHO-PQ certificate can be acquired and spread of the new drug can be accelerated. Based on these results, phase III clinical study will be performed to apply it in actual clinical care in local regions, and inclusion in the infection control guidelines in the country is also important. For preparation of the phase II and III study protocols, cooperation and agreement between countries including the regulatory authorities is desirable.

SATVI in South Africa is a preceding example of the Asian Clinical Research Center specialized in clinical studies of tuberculosis vaccines. Clinical trials from Phase II and later phases of tuberculosis vaccine of the whole world are performed at this center.

[Issues]

Japan founded bases of basic studies on infection in Asia and Africa, mainly in universities, through projects of JGRID and SATREPS. The Japan International Cooperation Agency (JICA) also supports infection research facilities in other countries. In addition, the Japan Anti-Tuberculosis Association has developed human resources for countermeasures against tuberculosis by inviting physicians and researchers from all over the world with a focus on Asian countries for more than 50 years. In addition, the National Center for Global Health and Medicine started a project to form a global clinical research network center in 2016 and clinical research and clinical trial centers are being formed in Asian countries.

However, cooperation with these centers and their capacity are not necessarily sufficient, and the cooperation system is fragile in Asia. In addition, for P3 Projects aiming at elimination of malaria which has started, study concerning strengthening of similar base and network construction is necessary for Africa with the most serious damage by malaria.

[Actions Needed]

<For neighboring Asian countries>

The consensus process for this proposal will be initiated in close collaboration with countries concerned as an industry-academia-government collaboration project.

<For Japan>

1) Strengthening of collaboration with the global clinical research network center formation project of the National Center for Global Health and Medicine and Nagasaki University

2) Preparation of a system to perform clinical study and animal study using primates at the same time in cooperation with the Tsukuba Primate Research Center, National Institutes of Biomedical Innovation, Health and Nutrition

3) Formation of network of researchers preparing clinical study plans and assay systems for each target disease to support the Asian Communicable Diseases Clinical Research Center.

4) Feasibility of establishing the Asian Communicable Disease Clinical Research Center should be studied by all Japanese ministries.

5) Further discussion on the above items in the working group and close consideration of the specific picture of the Asian Clinical Research Centers including request to the government are necessary.

6) The AMIC Malaria Working Group has to elaborate the concrete image of the Clinical Research Center in Africa.

7) In addition, to realize the above, early operation of BSL4 in Nagasaki University is needed.

4.2 Formation of Okinawa Communicable Diseases Research Center

[History and Current Status]

Since Okinawa Prefecture is tourism-oriented, with the number of tourists visiting being in the region of 9.40 million (including 2.54 million from abroad), and engaged in international distribution connecting 11 cities in Japan and other countries centering on Naha Airport, ranked 4th in the international cargo volume in Japan, the risk of emerging and re-emerging infectious diseases coming into the prefecture is high and infection control is an urgent issue. In addition, Okinawa is rich in biodiversity due to the natural characteristics of subtropical climate and creation of new industries utilizing the bioresources, such as development of vaccines against infections and therapeutic drugs, is expected. Okinawa also has a history of eradicating malaria and filaria. Making use of these experiences and techniques is expected for international contribution and cooperation. With this background, formation of Communicable Diseases Research Center is promoted based on the comprehensive plan of the prefecture, “Okinawa 21st Century Vision Plan”.

In the national plan, setting the core at University of the Ryukyus Faculty of Medicine and Hospital, scheduled to move to the former residential area in west Futenma in 2024, preparation of bases of health and medical care in Okinawa is aimed at. In the Cabinet Office Council report compiled in April 2017, infection control is positioned as a pillar together with the bioinformation bank and bioresource library.

Okinawa Communicable Diseases Research Center and bases of health and medical care in Okinawa should be prepared to contribute to improvement of health and medical care and welfare for residents of Okinawa Prefecture. It is necessary to review the way of their function and collaboration should be from these viewpoints.

[Issues]
Specific consideration of the following items is necessary.

1) Preparation of an infectious disease epidemiology system (introduction of IT) by making use of the characteristic of the prefecture, islands

2) Construction of bases contributing to improvement of health and medical care and welfare for residents of Okinawa prefecture and superiority of the bases able to appeal to the world
Examples
• Strategic logistic base in response to infection crisis utilizing the logistic hub
• Preparation of a tropical and subtropical infectious disease surveillance system and collaboration with bio-information bank
• Foundation of Communicable Diseases Diagnosis Center (tentative name) and improvement of the function of infection control
• Development of human resources, such as physicians specialized in infection
• Establishment of a diagnostic and treatment system covering the entire prefecture

3) Collaboration with infection research bases in Japan and other countries, such as the National Institute of Infectious Diseases

4) Utilization of bioresources in Okinawa

5) Strengthening of collaboration with research and medical institutions, such as Okinawa Institute of Science and Technology Graduate University and infection-related companies

[Actions Needed]

Based on the above items, the way that the Okinawa Communicable Diseases Research Center should be will be further discussed in the working group and proposed in the 6th conference.

4.3 Measures against Multidrug-Resistant Bacteria (AMR)

[History and Current Status]

Emergence of drug-resistant bacteria due to improper use of antimicrobial drugs has recently been a social problem and many patients die due to drug-resistant bacteria, becoming a threat of mankind. In May 2015, a global action plan concerning drug resistance was adopted in the annual general meeting of WHO, and member nations were required to formulate an action plan. In addition to formulation of an action plan, international industry-academia-government actions to promote research and development of new antimicrobial drugs are progressing in each country.

In Japan, 'Action plan of countermeasures against drug resistance' (2016-2021) was formulated in April 2016, which presented the policy of taking countermeasures against drug resistance by public-private union in cooperation between the agricultural and medical fields under the "one health" concept. In the medical field, under this plan, 'AMR Clinical Reference Center' was launched in the National Center for Global Health and Medicine, 'Drug-resistant infectious disease control research center' was launched in the National Institute of Infectious Diseases, and implementation of educational programs for medical care workers is progressing. Specific actions have become full progress, such as that 'Antimicrobial Stewardship The 1st Edition' was published in June 2017, guidelines for proper treatment of infectious diseases for medical care workers were presented, and medical treatment fee was set for explanation of antimicrobial drug prescription to patients. Measures against multidrug-resistant bacteria reached the step of specific "active move" from "idea".

[Issues]

Further change in consciousness in the medical, agricultural, and environmental fields is necessary in addition to that in general people. Moreover, although research and development of novel antimicrobial drugs, which once slowed down, is rising, the absolute number is still small and funding to support research is insufficient. Industry-academia-government cooperation for research and development of antimicrobial drugs and vaccines is a necessary step present ahead. Development and spread of diagnostic drugs, thorough surveillance, and cooperation with the agricultural and environmental fields are also needed.

[Actions Needed]

1) Improvement of awareness of AMR threat by workers engaged in the medical care, agriculture, forestry, fishery, and livestock industries and general people
2) Education and enlightenment of medical care workers and general people in public health and use of antimicrobial drugs
3) Thorough execution of standard infection control (standard precaution) at medical practice sites
4) Change in consciousness of workers in the food industry, such as introduction of HACCP
5) Drastic change in consciousness of workers in the agriculture, forestry, fishery, and livestock industries and attendance of Ministry of Agriculture, Forestry and Fisheries officials at the next conference
6) Promotion of development of new antimicrobial drugs and vaccines including push- and pull-type supports
7) Promotion of development of rapid diagnostic techniques
8) Full-scale research and development with international industry-academia-government cooperation, such as activities of the Japan Pharmaceutical Manufacturers Association
9) Development and thorough strengthening of an international multidrug-resistant bacteria surveillance system

4.4 Public Health and Infection Control

[History and Current Status]

To secure safe water and apply it to infection control in Asia and Africa, approaches from 2 viewpoints: improvement of water infrastructure and hygienic behavior, are needed. The former represents measures to improve sanitary facilities including waterworks and the latter includes promotion of understanding hygienic behavior by residents, such as washing hands with soap and maintenance of cleanliness around water supply facilities. At present, it is estimated that 663 million people cannot access clean water in the world, and 2.4 billion people live in regions in which they cannot continuously use sanitary facilities such as a toilet.

When tap water was not developed before or immediately after the end of World War II, Japan had problems with outbreaks of infectious diseases, such as cholera, dysentery, typhoid, and paratyphoid. However, incidences of drinking water-borne infectious diseases and death of infants drastically decreased with the spread of waterworks supplying safe drinking water. Saraya has spread hygienic habits, such as disinfection of the fingers and washing hands, in developing countries.

[Issues and Actions Needed]

To connect improvement of water infrastructure to improvement of public health including infection control, improvement of water infrastructure is insufficient. To achieve the target, it is necessary to cope with issues below:

1) Integrated design of waterworks, sewage, and waste disposal: It is necessary to integrate water and sewer services and residential waste processing in the design, such as improvement of waterworks increases the inflow water volume into sewage. Construction of P3 realizing cooperation beyond business entities is essential.
2) Strengthening of hygienic education of general people: It is necessary to promote it utilizing the school health program, such as encouraging washing of hands.
3) Proper operation of sanitary facilities and strict enforcement of maintenance
4) Stable utilization of financial resources: JICA promotes development of water infrastructure over the world, but overall improvement cannot be achieved by this activity alone. To promote water infrastructure development in broader regions, securing of funds is necessary.
5) Innovation in the public health field

4.5 Contribution of Logistics to Infection Control

[History and Current Status]

In the outbreak of Ebola virus infection in 2014, insufficient distribution network supplying drugs and medical devices and capacity of warehouses, lack of information related to the supply and demand of materials, limited access to regions with infection due to closure of national borders, and overlap and inefficiency of support due to insufficient public-private cooperation were problematic.

Learning from this lesson, international organizations, such as the United Nations World Food Programme (WFP), WHO, and United Nations Children's Fund (UNICEF), and private companies, such as Johnson & Johnson of the US and NEC, participated from 2015 and formed 'Global Pandemic Supply Chain Network (PSC network)'.

Material supply chain is the basis of all emergency support activities. Formation of a system to efficiently supply materials at an appropriate timing is essential in preparation for outbreaks in the future. Utilizing the geographical advantage of Okinawa prefecture, close location to Asia, formation of a major base of logistics, such as a 24 hour-operating airport, has been aimed at. Utilizing this distribution network for pharmaceutical logistics, synergy between the bases of health and medical care in Okinawa and Communicable Diseases Research Center can be expected. Okinawa Prefecture clarified a plan to form an international distribution center by concentrating on the airport/harbor site industries aiming at storage and distribution of high value-added products, such as drugs, in the "Okinawa 21st Century Vision Plan (revised)" in May 2017.

[Issues]

1) (For drugs to be handled at a low temperature) The cold chain management system is inefficient.
2) Procuring international organizations are vertically segmented.
3) Emergency relief supply may be stopped in the custom of the country to be supported.
4) Information concerning supply demand of materials is lacking.
5) Formation of stockpile centers of anti-viral and antimicrobial agents in Japan and other countries is necessary.

[Actions Needed]

<For global>

1) Construction of an efficient cold chain management system
2) Strengthening of collaboration among international organizations involved in procurement and logistics
3) Strengthening of logistics support system in Japan in usual time in preparation for pandemics
4) Commonalization of custom codes concerning emergency relief supply

<For Japan>

1) Realization of formation of the international stockpile and logistic centers utilizing the geographic advantage of Okinawa (under the initiative of private sector)
2) Verification experiment of new logistic techniques in Okinawa (cold chain, E traceability, and drone in remote islands)

<Common>

1) Improvement of social recognition of the importance of the role of cold chain and pharmaceutical wholesalers
2) Giving incentive to companies to promote creation of many innovations
3) Disclosure of information on the use of public budgets and information concerning cold chain management

Participation in the 6th conference will be requested to pharmaceutical wholesalers to dig into specific measures.

4.6 Contribution of ICT and AI to Infection Control

[Current Status and Issues]

Information and communication technologies (ICT) and artificial intelligence (AI) may bring about a revolution in infection control. For example, the following items are expected: 1) Speed up of disease report in the early stage of a pandemic, 2) realization of remote medical care in regions lacking resources, 3) shortening of the time required for research and development of new drugs.

However, a high-quality database or data set has not been constructed despite ICT and AI techniques being available and human resources who uses these are also lacking. Research funds to connect ICT and AI to information of infectious diseases are also insufficient. Moreover, no legal, social, or ethical framework has been established.

[Actions Needed]

In addition to construction of a high-quality database and data set, development of human resources is essential, and launch of funds by the government to support these is needed. To promote acquisition of regulatory approval of medical devices, deepening of discussion on regulatory science is also important. In addition, it is necessary to raise discussion on legal, social, and ethical frameworks while obtaining the understanding of general people.

This will also be selected as a topic of the 6th conference in consideration of its importance.

4.7 New seeds of technology

In this conference, seeds of technology from Japan which may contribute to infection control in Asia were presented. It is necessary to determine whether development of the seeds of technology below should be supported after reliable evaluation of the impact of these on infection control.

<Innovation needed>

1) UNICEF
2) UNITAID
3) Global Fund
4) GHIT Fund

<Innovation from Japan>

5) Development of antibodies using the EB virus method (Evec)
6) Antibody production using transgenic silkworms (Rimco)
7) Data analysis technique for the immunology field (KOTAI Biotechnologies)
8) Compound against drug-resistant H. pylori (KyotoBiken Laboratories), living marine resource-derived compounds (OP Bio factory)
9) Genomic analysis technology for development of advanced medicine (SENTAN PHARMA)
10) Mobile biosensor (Japan Radio)

4.8 Incentive Promoting Private Sector Investment

[Current Status and Issues]

In the 5th Nikkei Asian Conference on Communicable Diseases 2018, problems with each disease: tuberculosis, emerging and re-emerging infectious diseases (Ebola, SFTS), malaria, influenza, and AMR, and infrastructure of infection control: Asian Communicable Diseases Clinical Research Centers and Okinawa Communicable Diseases Research Center, public health, logistics, ICT, and AI were discussed.

It was clarified through discussion by experts for 2 days that incentive promoting private sector investment for infectious diseases is weak in all issues, and companies inevitably hesitate to cope with problems with infection in Asia and Africa.

The Global Antibiotic Research & Development Partnership (GARDP) proposed De-Risk (division of research and development expenditure by 3rd-party fund and company) and De-Link (separation between the drug price and reward received by company) as an attempt to solve these problems, and development of antimicrobial drugs is progressing.

[Actions Needed]

Legal framework to correspond to these, for example, harmonization of regulations and international standardization of product specification, should be included in discussion. Further deepening of discussion on specific measures necessary to promote P3 is needed by the next conference.

5. Conclusion

In the present conference, AMIC Working Group for the Asian Clinical Research Centers, the basis of infection control, was inaugurated and Working Group aiming at forming Infectious Disease Research Center in Okinawa which acts in cooperation with the former was also established. In addition, new technologies and functions contributing to infection control, such as logistics, ICT, and AI, were included in discussion from this conference.

Regarding measures against infectious diseases by industry-academia-government collaboration, achievement of certain results within a short time was confirmed. However, there are still many issues to be overcome.

The time has come to change the name of this conference from Conference on Asian Communicable Diseases to a name reflecting the global viewpoint because frameworks of public-private collaboration for the tuberculosis and malaria projects have spread to Africa and global actions are needed for ICT, AI, and logistics.

Concrete progress through efforts and strengthening of cooperation among persons concerned by the 6th conference is expected (the contents of subcommittees are attached as appendices of this statement).

End

[The 5th Nikkei Asian Conference on Communicable Diseases 2018]

- Organizer: Nikkei Inc.
- In cooperation with: Nikkei Business Publications, Inc., Nikkei Medical Publishing, Inc.
- Assistance from: Okinawa Prefecture
- Official Support: Ministry of Foreign Affairs, Ministry of Economy, Trade and Industry, Ministry of Health, Labour and Welfare, Ministry of Education, Culture, Sports, Science and Technology
- Sponsors with lunch/breakout session: Fuji Film/Toyama Chemical Co., Ltd., Neopharma Co., Ltd., Daiichi Sankyo Co., Ltd., Saraya Co., Ltd., Shionogi & Co., Ltd., Sumitomo Chemical Co., Ltd., SYSMEX Corporation
- Sponsors: Eiken Chemical Co., Ltd., Global Health Innovative Technology Fund (GHIT Fund), Sumitomo Dainippon Pharma Co., Ltd., Takeda Pharmaceutical Company Limited, Mitsubishi Tanabe Pharma Corporation, NIPRO, UNITAID

<Appendix>

Content of the 5th Nikkei Asian Conference on Communicable Diseases Luncheon session / subcommittee meeting

Luncheon session 1 (FUJIFILM • TOYAMA CHEMICAL)

"Approaches to emerging infectious diseases by industries, government, and academia in China, Japan, and Korea in the episode of Severe Fever with Thrombocytopenia Syndrome (SFTS)

"Severe Fever with Thrombocytopenia Syndrome (SFTS)" is an infectious disease caused by virulent virus. The same virus strain was identified in Japan, Korea, and China. Findings of favipiravir leading to development of an effective treatment method have been acquired in a study led by Masayuki Saijo, Director, Department of Virology 1, National Institute of Infectious Diseases, and Masataka Yasukawa, Vice President of Ehime University. In response to this, FUJIFILM and TOYAMA CHEMICAL are preparing for initiation of a clinical trial aiming at acquiring approval for the indication.

However, it is desirable to perform a global clinical trial in China, Japan, and Korea because the number of patients is limited. The companies plan to initiate the trial in Japan, and preparation for a trial is also progressing in Korea. Harmonization of the trials in the 2 countries is necessary. P3 in China, Japan, and Korea is expected for the future.

Progression of studies on prevention, early diagnosis, and vaccine including those of Crimean-Congo hemorrhagic fever is expected.

Luncheon session 2 (Neopharma)

"What is Japan's aim for measures against emerging and re-emerging infectious diseases?: Toward platform construction concerning utilization of therapeutic drugs and vaccines in developmental step"

To develop therapeutic drugs and vaccines from Japan to overcome emerging and re-emerging infectious diseases, clinical studies and examinations for pharmaceutical affairs have to be performed at local sites, and providing these therapeutic drugs and vaccines to local residents by private companies alone is limited. Preparation by the country is needed, such as preparation of a system to rapidly supply candidate compounds in response to occurrence of outbreak in Asia and Africa and appropriately extrapolate the clinical data into development and becoming a reference country to expand unapproved novel candidate therapeutic drugs in Asia and Africa and rapidly acquire approval.

It is also difficult for manufacturers to keep large stock for overseas outbreaks because prediction of the time of occurrence is difficult. In addition, it is needed to expand measures to compensate for adverse events accompanying the use of unapproved drugs by having the country involved, not burdening on only companies. To overcome these issues, platform construction by industry-government-academia collaboration including PMDA is necessary.

Subcommittee meeting A-1 (Saraya)

"Let's confront AMR! Possibility of HAND HYGIENE approach"

In Vietnam, more than 60% of the population is infected with drug-resistant ESBL-producing E. coli, and more than 50% of livestock and marine products are contaminated. Colistin overdosing in chickens has been confirmed. An intervention study on washing hands with water and soap was performed in Vietnam and clarified that both knowledge and practice were insufficient to prevent the infection. Continuous training and monitoring and education of children are essential. In addition, the "one health" approach across the boundary between humans and animals should be adopted. Introduction alcohol-based hand rub (ABHR) is also valuable. At the same time, guidelines for livestock facilities, supermarkets, and restaurants are also important to establish regional policies and systems following the certification concerning food safety, HACCP.

To improve the state in Vietnam, Saraya plans to cooperate with the government of Vietnam. They already initiated discussion on details of a pilot project and requested the Ministry of Agriculture of Vietnam to join the discussion.

Subcommittee meeting A-2 (Okinawa Prefecture)
"Approaches to form the Okinawa Communicable Diseases Research Center and Prospects"

The functions and roles needed for the Okinawa Communicable Diseases Research Center are as follows: 1) Strengthening of surveillance in preparation for the risk of infection coming into Okinawa during international exchange and large-scale event, 2) establishment of a Communicable Diseases Diagnosis Center (tentative name) and enhancement of the infection control function of Okinawa by collaboration with main research institutions in Japan, 3) epidemiological studies by using the characteristics of islands and organic collaboration with bio-banks, 4) improvement of clinical abilities of medical institutions in the prefecture and construction of an appropriate diagnosis/treatment system concerning emerging infectious diseases, 5) progression from 'research base' to 'research and countermeasure base' in order to contribute to improvement of health and medical care of residents of the prefecture and worldwide infection research and countermeasures. Examing these ideas in detail is necessary in the future.

Subcommittee meeting B-1 (Shionogi & Co., Ltd.)
"Current status and issues of influenza virus infection control"

Diverse viral types are detected in seasonal influenza every year including resistant strains. In other countries, highly pathogenic avian influenza including H5N1 and H7N9 has emerged. Fatal cases have been reported and occurrence of pandemic is of concern. For these issues, the following items are needed: (1) Collection and sharing of surveillance information, (2) prevention of infection and expansion of infection by highly effective vaccines against seasonal/pre-pandemic/pandemic influenza, (3) development and providing of a high-sensitive rapid diagnostic drug and an anti-influenza agent with a novel action mechanism.

Subcommittee meeting B-2 (Daiichi-Sankyo)
"Needs for preventive and therapeutic drugs against infectious diseases in Asia and contribution by companies"

In Asia, needs for vaccines and therapeutic drugs against various infections are still not satisfied. Some countries try to develop and manufacture vaccines in their own country, but there are many problems, such as inability to perform preclinical studies or construct a production system. For these problems, pharmaceutical and health care industries in Japan as an Asian country may be able to contribute by supporting preclinical studies, providing manufacturing techniques, and developing therapeutic drugs. To overcome problems in Asia, devising to increase incentive of Japanese companies is also needed, such as strengthening of public funds widely promoting from research and development to manufacturing and preparation of a system to use vaccines and therapeutic drugs at a low price in Asia. Global Antibiotic Research & Development Partnership (GARDP) proposed De-Risk (division of research and development expenditure by 3rd-party fund and company) and De-Link (separation between the drug price and reward received by company) and introduction of concrete examples of episodes provoking incentive of companies to develop preventive and therapeutic drugs against infectious diseases.

Subcommittee meeting C-1 (SYSMEX)
"Malaria elimination aimed by WHO: Contribution by new diagnostic technique"

The numbers of patients with malaria and deaths from malaria have decreased since 2000, but the decreases became stagnated in the 2010s. Based on these results, WHO clarified their concern that elimination of malaria is standing at a crossroads". Japan is able to contribute in 3 fields: diagnosis, new drug development, and vector control.

Especially, the high-sensitivity DNA test capable of amplifying specific DNA under a fixed temperature condition and multichannel automated blood cell analysis capable of detecting infection before disease onset and distinguishing highly malignant falciparum malaria from the other malaria types are very sensitive testing techniques, and these are expected to exert strong power in picking up asymptomatic parasite carriers. Regarding the significance of detecting pre-disease carriers, close verification is desired.

Subcommittee meeting C-2 (Sumitomo Chemical)
"Current status and issues of vector control in Asia and Africa"

At present, vector control most strongly contributes to malaria elimination. Long-lasting insecticidal mosquito nets, long-lasting indoor sprays, and mosquito larvae anthelmintic have been introduced and made achievements. However, to overcome problems, such as drug-resistant mosquitoes, and emergence of a new vector (infection-mediating pests) active outdoors during daytime from nocturnal mosquito species, it is important to continue introduction of a new drug. It is also necessary to establish a method to monitor the effect of vector control in parallel to vector control. To constantly advance vector control techniques, stable fundraising is also important and construction of a network with international institutions, such as WHO, UNITAID, and GHIT Fund, is essential for developers, for which Japanese industry-government-academia collaboration is necessary.

End