Chapter 4 Response to COVID-19

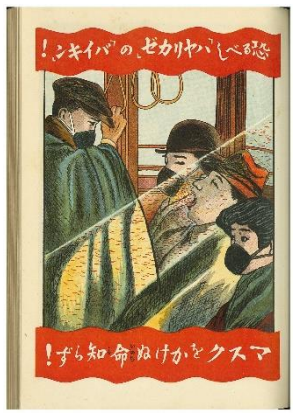
This chapter looks back over the history of infections and humankind and overviews the response to COVID-19, its impact on actual research sites, and the prospect of S&T development in the light of the COVID-19 pandemic.

Section 1 History of Infections and Response to COVID-19

❶ History of Infection and Humankind and Lessons to learn from the History

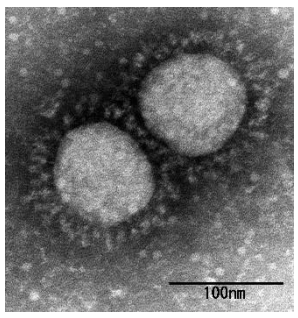
Infections can be confirmed in human history from old times. For example, smallpox had been feared as a highly contagious and deadly disease since before the Common Era, and marks of smallpox infection were confirmed in Egyptian mummies. There were large outbreaks of plague in medieval Europe. It is said that one out of three people died of the disease. Because patients died with darkened skin, the plague was feared as the "black death." In 1918, the 1918 influenza pandemic (Spanish flu) that was a new influenza became prevalent around the world. It is estimated that 600 million people of the 1,800 million population of the world contracted the disease and the death toll rose to 20 to 40 million. It is recorded that about 390,000 people died in Japan. In 1919, the Hygienic Bureau of the Ministry of Home Affairs released "Instructions for Prevention of Influenza" which include "refrain from being in large crowds of people" and "always wear a respirator or gauze mask in a crowd, electric train or railway train, or cover your nose and mouth lightly with a handkerchief or facecloth."

However, development of vaccines and antibiotics drastically improved prevention and treatment of infectious diseases. Japanese researchers greatly contributed to the development of infection study. For example, KITASATO Shibasaburo discovered the toxin and antibody of tetanus and identified bacillus pestis. His discovery of serotherapy of tetanus, in particular, is highly evaluated as leading to the discovery of serotherapy of diphtheria by Behring who won the first Nobel Prize in Physiology or Medicine. In recent years, OMURA Satoshi discovered Avermectin, which is an ingredient of a specific medicine of parasite infection, and he received Nobel Prize in Physiology or Medicine (See Chapter 3, Column 1-6).



Poster recommending mask in the Taisho Period
Influenza, Hygiene Bureau, Ministry of Home Affairs, March 1922
Housed in the National Institute of Public Health

Instructions for Prevention of Influenza
Website of the National Institute for Defense Studies
(http://www.nids.mod.go.jp/military_archives/digital_siryo/index.html)



Separated COVID-19 variants
Provided on the website of the National Institute of Infectious Diseases (NIID)
(https://www.niid.go.jp/niid/ja/basic-science/virology/10097-virology-2021-1.html)

For smallpox, a vaccine was developed in the 18th century. As a result of systematic vaccination, the WHO could declare the eradication of smallpox in 1980.

This way, the development of science and technologies gave humankind strong weapons including vaccines and antibiotics. However, infectious diseases that are called emerging infectious diseases including human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS), Ebola hemorrhagic fever, severe acute respiratory syndrome (SARS), highly pathogenic avian influenza and novel coronavirus disease (COVID-19[1]) and re-emerging infectious diseases including tuberculosis, malaria, dengue hemorrhagic fever, rabies and antimicrobial resistant bacteria still cause deaths of a large number of people even today and continue to be threats to mankind.

Many of the emerging infectious diseases are caused by viruses that were not known to us, and these viruses did not come into existence on Earth but had coexisted in the bodies of other animals. Humans are infected with emerging infectious diseases as a result of contact with these viruses in one way or another.

Re-emerging infectious diseases are infections against which prophylaxis and therapy including vaccines and antibiotics were established and that were thought to become overcome in the near future, but they started to become epidemic again. There are various causes of resurgence of infectious diseases that were thought to be brought under human control. Many of the resurgences are attributed to human behavior including inadequate use of antibiotics leading to the appearance of resistant strains and vitalization of the movement of people as a result of globalization.

Research on prophylaxis and treatment of emerging and re-emerging infectious diseases are advancing. Regarding HIV infection that was feared as a deadly illness since its discovery, in particular, if its onset is prevented by early detection and treatment, patients can live a healthy life as long as those of people without the infection. MITSUYA Hiroaki made a great contribution to R&D into HIV infection and treatment of AIDS by developing azidothymidine (AZT) which was the world's first AIDS remedy.

Today, response to COVID-19 is a pressing issue and many countries are developing vaccines and remedies. Because it is very likely that new infectious diseases will emerge, we need to build a system in preparation for the next unknown infectious disease. In this process, examination of the response to COVID-19 and history of past infections and humankind may become valuable lessons for response to new infectious diseases.

Column 1-8 Setting up BSL-4 Facilities at Nagasaki University to Enhance Research on Infectious Diseases

During the long national isolation that started in the 17th century, Nagasaki was the only international trade port in Japan and a special place where Western culture came in. Furthermore, opening of "Narutaki-juku" by Siebold who was a physician of a trading house in Dejima made Nagasaki the birthplace of Western medicine in Japan. On the other hand, because trade ships brought in unknown infectious diseases together with Western culture, Nagasaki experienced frequent epidemics of foreign infectious diseases including smallpox and cholera. In addition to

[1] Coronavirus disease of 2019

overseas trade, there was a geographical factor for infectious diseases in Nagasaki. Nagasaki has a large number of big and small islands, where filariasis and other parasitic diseases were prevalent and there have been many cases of viral diseases including adult T cell leukemia even in recent years. Infectious diseases were a significant challenge for medical scientists of universities and community physicians in Nagasaki, and they have been overcome with treatments and prophylaxis learned from Western medicine and with efforts of researchers.

The origin of Nagasaki University is "Igaku-Denshujo" which was the first medical school in Japan opened by the Dutch army surgeon Pompe in 1857. Following the spirit of Pompe, many researchers and physicians from home and abroad worked on infectious disease research and treatment and developed the school to the university of today. Later, the East Asia Research Institute of Endemics (current Institute of Tropical Medicine) was established in 1942. Today, the institute has local branches in Africa and Southeast Asia to tackle research of infectious diseases. In response to COVID-19, Nagasaki University early developed a rapid test system using a fluorescent LAMP[1] method to improve examination capability, which was demanded by society. To address the mass infection on an international cruise ship in the port of Nagasaki, the university made various contributions including playing a major role in controlling the situation without a single fatality by handling health management of the crew and accepting patients.

Research of infectious diseases requires research facilities that satisfy the international safety standard. Nagasaki University with a long history of infectious disease research started construction of the second BSL-4[2] facilities in Japan, which can handle pathogens of the highest risk level, to be completed in 2021. The facilities are planned as research facilities for safe management of pathogens with high pathogenicity in order to develop remedies and vaccines against them. With their completion, a system for "constant research from basics to application" covering every infectious disease will be established in Japan. At the same time, the facilities will be the first BSL-4 facilities where infectious disease researchers will be trained. It is expected that handling of the latest research equipment in the facilities will drastically advance infectious disease research in Japan and contribute to control of infectious diseases that bring threats not only to Japan but also to the world.

Figure 1 Rapid Test System using Fluorescent LAMP Method
Provided by Canon Medical Systems

Figure 2 Appearance of BSL-4 Facilities
Provided by Nagasaki University

[1] Loop-mediated isothermal amplification
[2] BSL (Bio Safety Level) is grading of laboratories/facilities handling microorganisms, pathogens, etc. Handling level is set according to the risk of the pathogen handled in the laboratories/facilities. The COVID-19 virus (SARS-CoV-2) is to be handled at BSL-3 facilities.

❷ The Government's Response to COVID-19

<Establishing Government Headquarters>

On March 26, 2020, Japan established the Novel Coronavirus Response Headquarters under Article 15, paragraph 1 of the Act on Special Measures for Pandemic Influenza and New Infectious Diseases Preparedness and Response (Act No.31 of 2012). The Headquarters decided (later amended) the "Basic Policies for Novel Coronavirus Disease Control by the Government of Japan" on the 28th of the same month. The government is steadily implementing COVID-19 control measures to protect people's lives.

<Promoting R&D>

Using a total of 193 billion yen up to FY2020, the government supported R&D related to COVID-19, which includes development of therapies, vaccines and medical equipment.

■ Figure 1-4-1/Example of Medical Equipment Development Supported by the Government ■

[Prevention]

■ **Empirical research of SpO2 measurement and monitoring system using smartphone application for COVID-19 infected people at home or in hotel in cooperation with LINE**

-Noncontact automatic measurement of vital data including blood pressure and SpO2 with camera by using smartphone application
-Remote monitoring using smartphone

Aggravation alert for patients

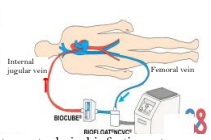
General infection screening

Project name: Technology development to control viral infection, etc.
Research representative: Allm Inc.
Research period: June 2020 to March 2021

[Treatment]

■ **Clinical study on effectiveness and safety of new high-performance ECMO system for COVID-19 pneumonia**

-Examination of usefulness of "ECMO system with excellent antithrombotic property, which can be used safely for a long period of time" for COVID-19 pneumonia patients



Project name: Technology development to control viral infection, etc.
Research representative: National Cerebral and Cardiovascular Center
Research period: May 2020 to March 2021

From Material 4-1 of the 26th Expert Panel on Healthcare Policy

For medicine development, the government is supporting examination of the effects and safety of existing medicines including Favipiravir which is an anti-influenza virus agent and Ivermectin which is an antiparasitic agent as well as development of new medicine.

The government also supports development of new vaccines including vaccines using methods different from existing methods (e.g., the recombinant protein vaccine by Shionogi, UMN Pharma and the National Institute of Infectious Diseases; the DNA[1] vaccine by Osaka University/AnGes and Takara Bio; the mRNA[2] vaccine by Daiichi Sankyo and the Institute of Medical Science, the University of Tokyo). The three vaccines above are currently under clinical trial.

In addition, the government supported medical equipment development including clinical research on the effectiveness and safety of the new high performance ECMO System for COVID-19 pneumonia and empirical research on a system for remote monitoring of patients through automatic measurement of vital data including blood pressure, oxygen saturation and respiration rate by using smartphone applications.

[1] Deoxyribonucleic acid
[2] Messenger ribonucleic acid

Column 1-9 Development of Quick Test of COVID-19 by Using Smart Amplification Process (SmartAmp)

In order to prevent the proliferation of COVID-19, it is important to prevent the spread from infected people to others. For this purpose, it is necessary to establish a system to perform a rapid test for diagnosis of the novel coronavirus.

An R&D program in the Kanagawa area supported by the government is tackling the development and dissemination of a quick test for the novel coronavirus by using SmartAmp assay[1]. The PCR[2] method, which is a standard virus detection method, amplifies nucleic acids[3] specific to the virus and makes judgment based on the results. Nucleic acid amplification requires repeated changes in temperature, which takes about 2 hours to get the results. On the other hand, the SmartAmp method takes only 10 to 30 minutes because it amplifies nucleic acids at a constant temperature. Furthermore, packaging of the whole process enables testing of 24 specimens in about one hour.

Video explaining SmartAmp Assay
Created by K.K. DNAFORM
https://www.youtube.com/watch?v=CzY9bIDlgLQ

SmartAmp test system (simplified package)
Provided by K.K. DNAFORM

Novel coronavirus detection using SmartAmp assay can be used for administrative testing and its use for diagnosis, etc. is covered by health insurance.

Section 2 Impact of COVID-19 on Research Sites and Countermeasures

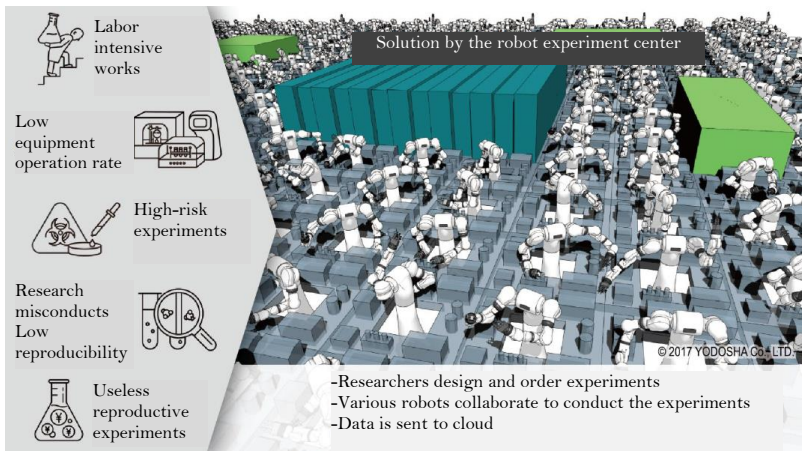
1 Impact on Research Sites and Initiatives to Establish New Research Styles

Spread of COVID-19 has made a great impact on society and research sites are no exception. Because research project related to COVID-19 are implemented as an exception in universities where entry is restricted and the government is actively expanding investments in these fields, their research results are expected to increase. However, in other fields, especially where experiments and field survey are important, various restrictions including moving of researchers caused reduction or suspension of research activities[4]. According to a survey conducted by National Institute of Science and Technology Policy (NISTEP)[5], 85% of doctoral course students and 79% of doctoral course graduates answered they were "already affected" as of May 2020. Many respondents answered that there were problems especially regarding access control to the building, laboratory or facilities (laboratory equipment) used for research activities and suspension/postponing of data collection and outdoor surveys.

[1] Implemented under the Regional Innovation Ecosystem Program
[2] Polymerase Chain Reaction
[3] Refers to DNA or RNA (Ribonucleic acid), which are the genome (genetic information) of the virus. Genome of coronavirus is RNA.
[4] Center for Research and Development Strategy (CRDS), Japan Science and Technology Agency (JST) "Research Transformation (RX)" – Toward Future R&D Coexisting with COVID-19, January 2021
[5] NISTEP, Survey on the impact of the COVID-19 on research activities-Web Questionnaire Survey on Japan Graduates Database (JGRAD), Research Material-298, September 2020

On the other hand, social expectations are rising for science, technology and innovation to address various social challenges including the spread of COVID-19. In order to continue research activities free of distance/time constraints under the circumstances, it is necessary to establish new research styles including remote research activities, automated experiments by robots and virtual experiments in virtual spaces based on a rich store of experiment data. For example, RIKEN, the National Institute of Advanced Industrial Science and Technology (AIST) and other entities are working to construct a robot experiment center where various robots cooperate to conduct automated life science experiments. A research group of Osaka University is automating observation of molecule kinetics in cells by replacing manual operations with robot operations and replacing human cognitive functions including search for cells with machine learning.

■ Figure 1-4-2/Conceptual Drawing of Automated Robot Experiment Center ■



From JST Website
(https://www.jst.go.jp/mirai/jp/program/core/JPMJMI20G7.html)

In response to the urgent international challenge of the spread of COVID-19, there is an increase in preprint [1] (papers before review, which are scheduled for contribution to an academic journal) publications relating to the novel coronavirus especially in the biomedicine field. As preprint, research results are swiftly shared without review that takes several months to one year[2]. Because preprints are published without review by a third person, careful assessment is required. Nevertheless, there is a growing trend to share the latest knowledge on the novel coronavirus and use the knowledge for infection control under careful examination by researchers.

❷ Initiatives to Spread Correct Understanding of COVID-19

At first, many things about COVID-19 were not known including the infection path and symptoms, which caused vague anxiety in many people and disorder in the world. Later, however, research results showed that COVID-19 spread through contagion and droplets and that it is effective to take measures such as wearing a mask and avoiding the three Cs (closed spaces, crowded places, and close-contact settings) to prevent infection. In order to control infection, it is necessary for each and every citizen to correctly understand COVID-19 and take control measures in a coordinated manner. Not limited to COVID-19 but generally, the science and technology community is required to disseminate scientific and objective information in a suitable expression and manner for the receivers. This part introduces a few

[1] Refers to papers before review (by editors and experts of the field to check for errors and suitability to appear in the journal), which are scheduled for contribution to an academic journal later. Preprint servers to publish preprints appeared in the fields of physics and social sciences in the 1990s. The use has been gradually spreading to other fields since the mid-2010s to take advantages of quick information provision and securing of priority of the research.
[2] NISTEP, Survey on Utilization and Perception of Preprints, Research Material-301, February 2021

initiatives to disseminate information on COVID-19 correctly and in an easy to understand way for people.

・Miraikan -The National Museum of Emerging Science and Innovation: COVID-19-related information

To Miraikan belong science communicators who have diverse backgrounds and can convey science and technology in easy to understand ways. Miraikan set up a special page of "COVID-19-related information" titled "Facts about Coronavirus Disease 2019, COVID-19 and the Novel Virus" in March 2020. The page answers questions about how to respond to COVID-19 in a way easy to understand even for children by using illustrations.

How to confront new infectious diseases
Novel coronavirus is mystifying, isn't it?
https://www.miraikan.jst.go.jp/resources/COVID-19/

・Science Portal

Science Portal is a comprehensive website operated by JST to provide up-to-date science/technology information. A feature page, "Novel Coronavirus Infection – COVID-19 and Us", was launched on Science Portal in July 2020. The page provides not only COVID-19 news but also articles suggesting how we should respond to and overcome COVID-19 in addition to expert explanations on COVID-19 and knowledge obtained by the latest research.

Novel Coronavirus Infection – Novel Coronavirus and Us
https://scienceportal.jst.go.jp/featured/sp_covid-19.html

Section 3 Prospect of Science and Technology Development based on the Impact of COVID-19

The 2020 White Paper on Science and Technology depicted a future society in 2040, which will be brought about by science and technology development, based on S&T Foresight 2019[1] (published in November 2019) that is a foresight conducted by NISTEP. Later, however, the spread of COVID-19 made society recognize the need for digitalization and move towards an era of change. How will the impact of COVID-19 change the relationship between S&T and society? This section introduces the direction of science and technology based on the impact of the COVID-19 pandemic.

S&T Foresight Survey
https://www.nistep.go.jp/research/science-and-technology-foresight-and-science-and-technology-trends

[1] https://www.nistep.go.jp/research/science-and-technology-foresight-and-science-and-technology-trends
A survey conducted about every five years from FY1971 to predict S&T and the relationship between S&T and future society, and in order to contribute to the formulation of the Science and Technology Basic Plan.

❶ Science and Technology that Support Future Society

S&T Foresight 2019, which was cited in the 2020 White Paper on Science and Technology, was implemented before the spread of COVID-19, but includes remote medicine and education and other subjects that are expected to play a major role after social changes following the spread of COVID-19 (Figure 1-4-3).

■ Figure 1-4-3 Examples of Science and Technologies Related to the Impact of COVID-19■

❷ Future of Science and Technology in the Light of the Impact of COVID-19

How will the future science and technology change after the spread of COVID-19? S&T Foresight 2019 set up 702 S&T topics that were expected to be realized by 2050 (“the topics”) and conducted a web-based questionnaire about the importance[1] of different topics and prospects for their realization to collect subjective knowledge of a wide range of experts including a network of about 2,000 experts, researchmap (a researcher database run by JST), academic societies and economic organizations (from February to June 2019). Later, in response to the spread of COVID-19, another web-based questionnaire was conducted covering a network of about 2,000 experts out of the respondents above (from September to October 2020).

As a result, S&T related to work and working styles (e.g., achievement of unmanned factories and unmanned shops, process control of construction work using AI, high-level VR system regarding telework) and technologies related to health crisis management (e.g., ultralight sensors that can quickly detect infection with specific pathogens, epidemic prediction and alarming system) were predicted to be realized

[1] Indices were calculated as follows: in order to realize a desirable society 30 years from now, importance for Japan is very high (+2), high (+1), neither high nor low (0), low (-1), very low (-2)

earlier[1]. This is a prediction of a future society where emerging and reemerging infectious diseases are controlled and people are working in flexible working patterns. The direction agrees with the vision aimed at by Society 5.0. On the other hand, realization of S&T concerning exploration and development of frontier fields including outer space and the deep sea and S&T concerning energy conversion, which had been thought to be realized relatively late, were predicted to come even later. Efforts are required to minimize the impact of COVID-19 on research sites.

■ Table 1-4-4 S&T Topics Expected to Have Earlier Social Realization Following the COVID-19 Pandemic ■

Category	○ Before the sentence indicates the top 10 S&T topics expected to have earlier social realization following the COVID-19 pandemic.	Results of S&T Foresight 2019 (Year)	Change caused by COVID-19 (year)
Work and working styles	○ Advanced and integrated worker productivity monitoring technology to improve the health and comfort of office workers, and promote work efficiency improvement and reformation of working style	2030	-2.7
	Transition to a highly productive society with highly free employment configurations, premised on not requiring to go into the office, and having multiple jobs	2030	-2.4
	High-level VR system (conference, manufacturing management) and a supporting high-speed information distribution system	2027	-2.0
	Achievement of unmanned factories, unmanned shops, unmanned logistics warehouses, unmanned home deliveries by extensive spread of work robots to the three-product (food, cosmetics and pharmaceuticals) industry, service industry and logistics industry	2029	-2.1
	Technology to constantly ascertain and analyze the status of work progress at the construction site using AI, which properly manages and automatically optimizes and modifies processes	2030	-2.1
Health crisis management	○Advanced indoor environmental health monitoring and control technology that suppresses indoor "health disorders" and "outbreaks of infectious disease"	2030	-2.6
	○Ultralight sensors that can be used in contaminated areas and aircraft, that can quickly detect infection with specific pathogens, infectivity to other persons, and susceptibility of uninfected people	2031	-2.4
	○A rapid and accurate detection system for minute amounts of pathogenic microorganisms in public and customer facilities as well as transportation facilities such as airports, harbors and railways	2032	-2.1
	○Epidemic prediction and alert system based on an electronic health record system and comprehensive infection surveillance system using test/prescription and other medical data and various web data.	2029	-2.1
	○A system that quantitatively predicts and evaluates the effects of emerging infectious diseases on humans, including the pathogenicity and the potentiality of causing global epidemics, with comprehensive consideration of factors such as the environment, pathogens, and hosts.	2031	-2.1

*Years were calculated as follows: Much earlier (−5.0 years), earlier (−3.5 years), somewhat earlier (− 1.5 years), no change (0.0 years), somewhat later (+1.5 years), later (+3.5 years), and much later (+5.0 years)

Source: Prepared by MEXT based on NISTEP, Perspective of Science and Technology in the post COVID-19 era, Research Material-309

[1] NISTEP, Perspectives of Science and Technology in the post COVID-19 era, Research Material-309, April 2021