Moonshot R&D MILLENNIA* Program
*Multifaceted investigation challenge for new normal initiatives program

「Research for constructing next generation risk management system to control unknown infectious diseases derived from wild animals」

Initiative Report

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I. Concept

1. Proposed MS Goal

1.1 Proposed MS Goal title

“Realization of a society resilient to infectious diseases by 2050 through the creation of a management system for unknown infectious diseases derived from animals”

1.2 Vision for 2050 society

This report sets out a future vision of society in 2050 in which humankind is freed from the fears and constraints imposed by infectious diseases, and in which humans, animals, and the environment coexist and prosper in harmony. This society is able to rapidly develop therapeutic and preventive measures against emerging infectious diseases, and also to identify the environmental and ecological factors that contribute the spread of pathogens in the natural environment to human populations, which may cause pandemics. In doing so, the risk of infectious disease outbreaks can be appropriately managed before pathogens cross over to the human population.

It has been reported that 75% of all emerging infectious diseases are of animal origin (Taylor et al., 2001); hence, the occurrence of emerging infectious diseases is closely related to animals. The recent increase in infectious diseases caused by pathogens originating from wildlife is believed to be related to the rapid destruction of the environment (ecosystem) by human social activities and the resulting degradation of biodiversity. In addition, livestock animals such as cattle, pigs, or chickens can act as intermediaries in transmitting pathogens from wild animals to humans, and raising livestock in large numbers at close proximities to humans is also seen as a factor that can increase the risk of zoonoses. It can therefore be seen that a radical solution to the problem of zoonoses cannot be achieved through improvements to human medical technology alone; rather, solutions are required for multi-faceted problems including the health of both wildlife carrying as yet unknown pathogens and livestock animals transmitting pathogens, and the conservations of the natural environment and ecosystems for wildlife.

The future set out in this report envisages a society that embodies the concept of “One Health,” in which the health of all humans, animals and the environment is balanced and maintained through the resolution of these related issues (Figure 1).

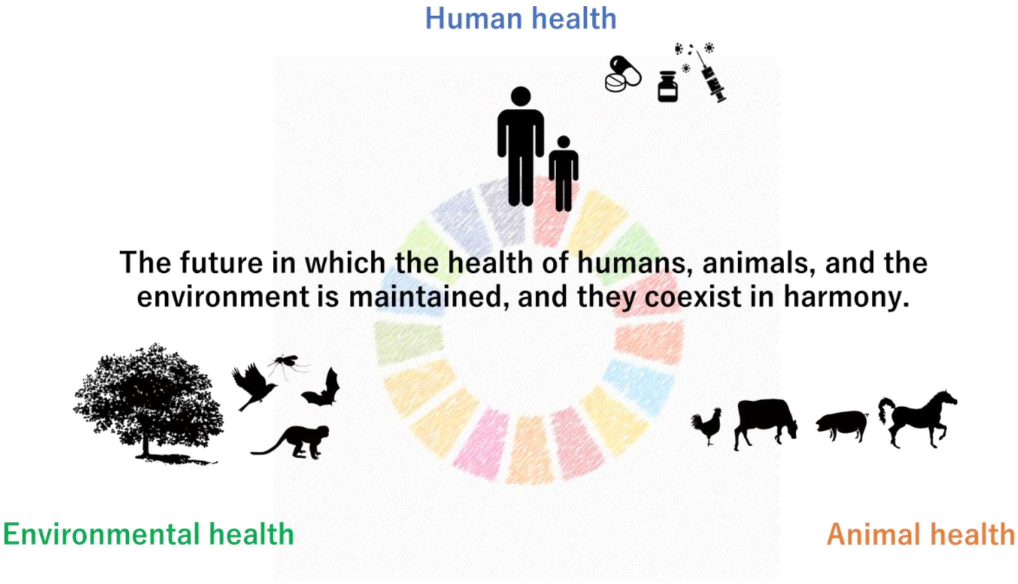


Figure 1. A vision of the future in which the health of humans, animals, and the environment is maintained, and they coexist in harmony. Realizing this ideal society is closely related to achieving the United Nations Sustainable Development Goals.

2. Targets

Realizing the ideal society set out in this report will mark the advent of a future in which humankind is freed from the fear and the constraints of unknown infectious diseases, and in which people are mindful of the impact of their own activities and actions on the natural environment and are able to live in health and in harmony with the Earth. This future embodies the concept of "One Health," in which there is a deep understanding that humans are a part of the whole ecosystem, and not only human health, but also the health of the environment and animals is balanced and maintained. This can be expected to bring about a more just and sustainable social system with less disparity between rich and poor.

On the basis of this concept, the following achievement scenario is envisaged by 2050:

- Systems will be in place to rapidly develop therapeutic and preventive measures against outbreaks of unknown emerging infectious diseases.
- Systems will be in place for monitoring unknown pathogens carried by wild animals, and the mechanism for interspecies transmission will be identified.

- Environmental and ecological factors that increase the risk of pandemics will be identified, and social activities will be carried out with due consideration of these factors

3. Background

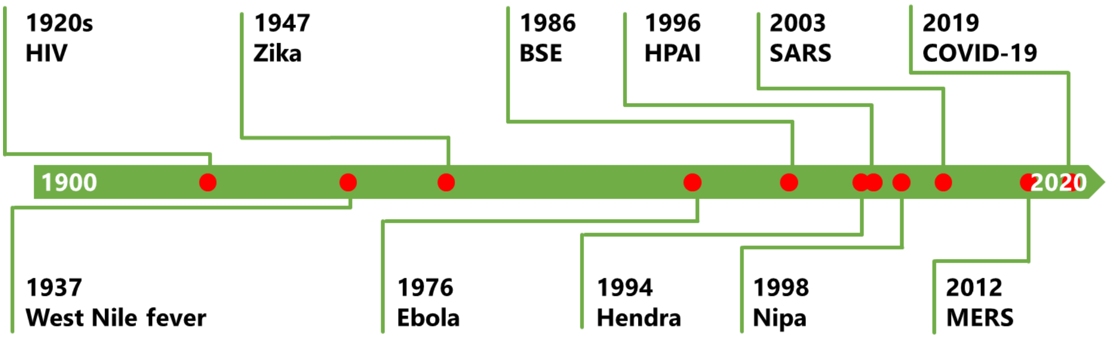
3.1 Why now?

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has caused tremendous damage to human health and economies, and as of July 2021, no end to the pandemic is in sight. The outbreak of this disease has brought home to us once again that under the present social system, it is extremely difficult to predict the occurrence of unknown infectious diseases, to develop therapeutic and preventive medicines rapidly, and to identify and implement public health measures that balance health and the economy. The development of COVID-19 vaccines was faster than expected because of previous experiences with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which were caused by coronaviruses that are genetically closely related to the causative agent of COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, it would be extremely difficult to develop countermeasures against an emerging infectious disease caused by a completely new strain of pathogen. Therefore, to ensure the continued development of humankind, we need to overcome urgently our vulnerability to infectious diseases and construct systems to manage the risk of future pandemics caused by unknown pathogens.

Recent zoonotic disease outbreaks

Outbreaks of emerging infectious diseases are caused by the transmission of pathogens through contact between wild animals and humans, and because of this, epidemics of such diseases in the past were often limited to developing countries, where there is likely to be a greater concentration of hot spots with a high risk of outbreak. However, the risk of global outbreak has increased dramatically in recent years, in part because of the greater movement of people internationally. In fact, humans have been exposed to the risk of zoonotic disease numerous times over the past 100 years (Figure 2). The majority of pathogens causing these zoonotic diseases are viruses, meaning that there is an extremely high risk of pandemics in the future caused by viruses carried by wild animals.



UNEP report (2020) "PREVENTING THE NEXT PANDEMIC"を改編

Figure 2.The main zoonotic diseases that have broken out over the past 100 years (adapted from the United Nations Environment Programme report). In the majority of these diseases, the pathogen was a virus originating from wild animals.

One Health measures for zoonotic diseases

The increase in infectious diseases caused by pathogens originating in wild animals has occurred in response to biodiversity degradation due to the rapid destruction of the environment (ecosystem) by human social activity. In addition, livestock animals, which act as intermediaries for pathogens between wild animals and humans, are likely to be a factor contributing to the risk (Johnson et al., 2020). For this reason, a radical solution to the problem of zoonoses cannot be achieved through improvements to human medical technology alone. Managing the risk of future outbreaks of zoonotic diseases requires measures that transcend the disciplines of medicine, veterinary medicine, environmental studies, etc., and are based on the One Health concept that not just humans, but also animals and the environment, must all be maintained in a state of health.

The relationship between the destruction of the natural environment and infectious diseases

There is a complex interplay of factors behind the spillover of zoonotic diseases from wild animals to humans. The United Nations Environment Programme report (2020) states that various social activities of humans are a major factor in spillover, and in particular, food issues such as increased consumption of animal protein, the expansion of unsustainable agriculture, increased trapping and use of wild animals, and changes in the food supply chain are pressing issues for developing countries as well as factors believed to increase the risk of zoonotic disease. In addition to food issues, zoonotic diseases are also associated with a wide variety of social, economic, and environmental problems, such as climate change, natural resource issues, and increased international human movement. A simulation study that combined data on infectious diseases with environmental factors such as world population distribution, urbanization, vegetation, changes in land use, biodiversity, and climate change showed that areas with broadleaf evergreen forests, mammalian species richness, and significant changes in land use were predicted to be hot spots associated with higher risk of zoonotic disease emergence. That study found that all these environmental factors increase the opportunities for contact between humans and wild animals, with the risk of greater possibility of spillover of unknown pathogens into human populations (Allen et al., 2017; Figure 3). An approach that seeks to resolve environmental problems in addition to medical issues is therefore needed to reduce the risk of future outbreaks of zoonotic diseases.

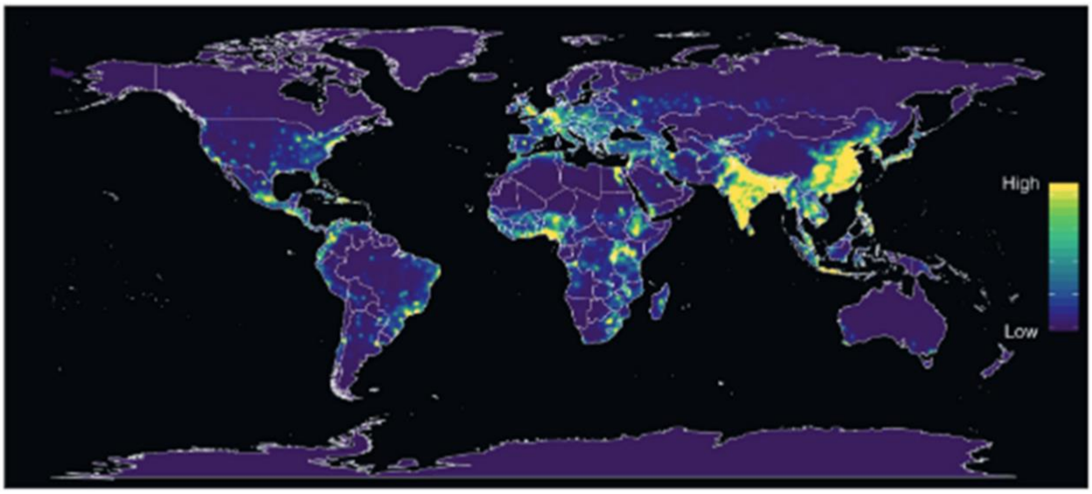


Figure 3. Zoonotic disease risk hot spots (from Allen et al., 2017). The results of a study estimating the risk of zoonotic disease that included factors such as population distribution, urbanization, vegetation, changes in land use, biodiversity, and climate change show that Southeast Asia and Japan are regions at particularly high risk.

The role of livestock animals in the transmission of infectious diseases

In relation to the transmission of pathogens through livestock animals, Johnson et al. (2020) showed that livestock animals harbor more zoonotic viruses than wild animals (Figure 4). This suggests that livestock animals are likely to be important intermediaries for the transmission of viruses between wild animals and human populations, as viruses may acquire infectiousness and pathogenesis to humans more easily under environments in which livestock are intensively raised or different livestock species are raised together. The close proximities between humans and livestock also facilitate reverse zoonotic transmissions, where humans pass pathogens to livestock. It is well known, for example, that avian influenza viruses from wild birds are not naturally capable of infecting humans, but can acquire the ability to do so as a result of genetic mutation and genetic reassortment that may occur in pigs. The influenza virus that caused a global outbreak in 2009 contained gene segments derived from humans, pigs, and birds through genetic reassortment. It is therefore essential for the risk management of zoonotic disease to implement appropriate zoning for humans, livestock animals, and wild animals, and to construct systems for monitoring pathogens.

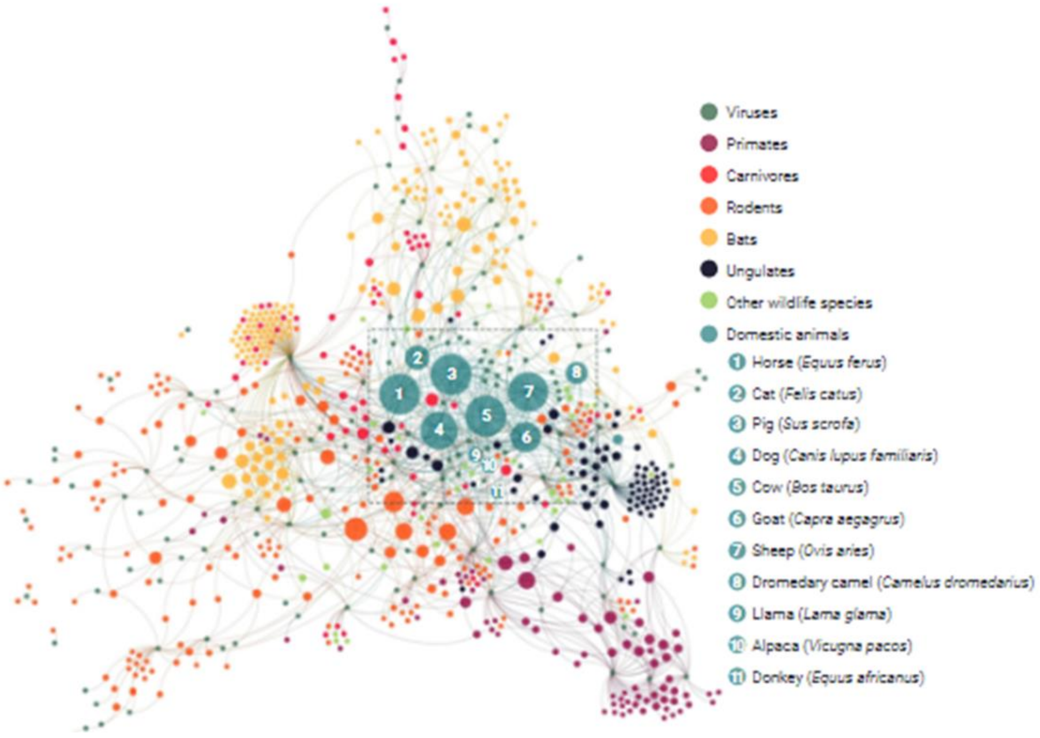


Figure 4. The bipartite network of zoonotic viruses shared by wild and domestic animals (from Johnson et al., 2020). The size of the circle indicates the number of viruses, and the network indicates shared viruses. It can be seen that captive animals share a variety of virus strains with wild animals, indicating that they act as intermediaries between wild animals and human populations.

With the issues mentioned above, there are a great many cases in which radical solutions cannot be found through scientific and technical research and development (R&D) alone—instead, long-term, sustainable policies and support within an international framework are essential. The Moonshot Research and Development Program is working on initiatives to achieve the ideal society by 2050 by combining scientific and technical solutions to challenges with solutions to the social issues that have been discussed.

Recent research trends in related fields

In Japan, various infectious disease research projects are being carried out under the auspices of the Japan Agency for Medical Research and Development (AMED). These include not only basic research carried out within Japan, but also the creation of international collaboration centers for joint research with foreign countries, with the aim of promoting international research into infectious diseases. Numerous other projects are being carried out in anticipation of future outbreaks of zoonotic diseases, including a project to collect and preserve human pathogenic viruses and zoonotic viruses as a national bioresource that will be launched in 2021. Other measures for as yet unknown infectious diseases steadily being implemented in the field of medical research in Japan include the recent formation of the Life Intelligence Consortium, which promotes artificial intelligence (AI)-based drug discovery through interdisciplinary with the field of information technology (IT).

Related Moonshot projects

Goal #2 of the Moonshot Research and Development Program is “Realization of ultra-early disease prediction and intervention by 2050.” One of the challenges being addressed to achieve this goal is understanding and controlling networks of virus–human interaction, and collaboration with the present project may be expected to accelerate further research in the field of human medicine for the development of therapeutic and preventive methods against unknown pathogens. In addition, Moonshot Goals #4, “Realization of sustainable resource circulation to recover the global environment by 2050,” and #5, “Creation of the industry that enables sustainable global food supply by exploiting unused biological resources by 2050,” will provide solutions to problems of food and resources in developing countries and contribute greatly to realizing a society with a reduced risk of zoonotic disease outbreak, which is the aim of the present project. Furthermore, the Millenia Program, set up to create new Moonshot Goals, has selected projects for elucidating biodiversity and systems of symbiosis with nature, aiming at autonomous food procurement using plants, achieving harmony among humans, and proposing a regionally decentralized society. Each of these leads—albeit indirectly—toward future solutions to the various issues that increase the risk of outbreak of unknown infectious diseases and toward realizing international collaboration. Tie-ups with these projects will allow a multi-faceted approach for ensuring the achievement of the goals of the present project.

Current issues

As mentioned above, R&D relating to human medicine and environmental issues is commencing among the existing Moonshot Goals. However, in the case of research into pathogens in wild animals, while unknown pathogens carried by wild animals are being collected and analyzed in Japan and overseas, it can be difficult to demonstrate the merits of investment in R&D for monitoring future risks and it is not always possible to secure continuous budgets. Due to this problem, the information that has been collected so far has not yet been systematically accumulated and utilized in the same way as information in the field of human medicine. To bring about an ideal society, we must promote R&D focusing on wild animals, the environment, and ecosystems, and bring the technology at least up to the same level as that of related fields. At the same time, we must establish systems for accumulating and coordinating the results obtained from various projects and build a framework for utilizing the information.

Summary

To establish a system to prepare for the risk of outbreak of zoonotic diseases in the future, it is essential to be able to perform a risk assessment by integrating various information pertaining to the risk of unknown infectious diseases. To achieve this, it is necessary not only to promote independent R&D in various fields, but also to integrate the results of each field, such as R&D in human medicine, the collection of information on unknown pathogens carried by livestock and wild animals, and the accumulation of information on biodiversity, soil, and vegetation in the environmental field. Thus, there is a growing need for basic research to promote interdisciplinaryresearch in related fields with the aim of bringing about multi-faceted zoonotic disease measures based on the One Health concept. Advanced R&D that contributes to the field of human medicine and environmental areas such as food and resource issues is already underway within the other Moonshot Goals. To promote measures for zoonotic disease more effectively, there is a need now to promote research assessing the risk of infectious disease in wild animals in parallel with these existing projects, and to develop basic technologies for efficient collaboration among various fields.

The present research project mainly focuses on R&D to control the risk of spillover of pathogens from wild animals to human populations as one of the necessary elements for realizing an ideal society, while at the same time, the R&D plan has been conceived on the supposition that the creation of basic technologies for bridging research in various fields at the boundaries of human medicine, animals, and the environment, which are the components comprising the One Health concept, is an essential element for achieving the goal (Figure 5).

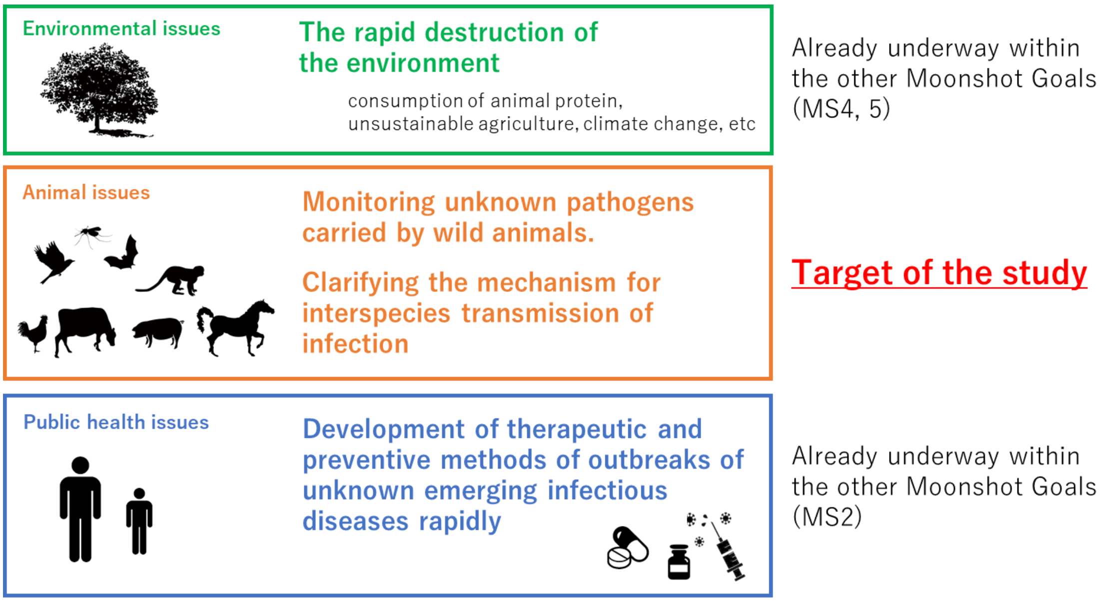


Figure 5. Overview of the existing Moonshot Goals and the target area of the proposed research project

3.2 Social significance

Measures to control zoonoses are a realistic proposition that must be addressed as a matter of urgency, and now that the threat of unknown infectious diseases has become a common understanding shared worldwide owing to the COVID-19 pandemic, there is no room for doubt about the need to act. In addition, the transmission of pathogens from wild animals via livestock animals not only causes health hazards to humans, but also has a significant impact on the production base of the livestock industry and the international trade of products, which is a major problem from the perspective of food security. In addition, problems relating to the natural environment all need to be addressed by initiatives that treat them as international issues. The problems relating to infectious disease are major ones that need to be resolved individually, and managing the risk of unknown infectious diseases by addressing these problems is an essential task so that humans, animals, and the environment can coexist and prosper in harmony.

In a society that has achieved this goal, information on all the pathogens existing in the natural environment, which is currently not fully understood by humankind, will be visualized to the greatest extent possible, and systems will be established to manage and accumulate this information appropriately, thereby liberating us from the fear of unknown diseases. It is impossible to eradicate all pathogens that exist in the natural environment; hence, it will probably be extremely difficult to reduce the risk of a pandemic to zero. Nonetheless, we aim to achieve the goal by identifying, as far as possible, the pathogens that could become a risk, and developing systems for monitoring and managing spillover.

In addition, along with information related to infectious diseases, a variety of ecological and environmental data can be obtained in the scenario. By utilizing these data, we can provide infectious disease management expertise for policy-making aimed at solutions to the human social activities that influence the risk of pandemics from unknown zoonotic diseases, and to the environmental problems arising from these activities. Thus, achievement of the proposed Moonshot Goal will not only solve the problem of infectious diseases, but also have a ripple effect for solutions to issues in peripheral fields.

The society that we aim to achieve in 2050 will contribute to achieving the United Nations Sustainable Development Goals (SDGs), which are the current common international goals, by building a system for management of the risk of infectious disease. This society can be expected to realize harmonious coexistence that embodies the concept of One Health, protecting the health of humankind by keeping humans, animals, and the environment in a mutually beneficial state, and we therefore believe this project to be of enormous significance.

3.3 Action outline

As already noted, the issues relating to control of zoonotic disease are extremely diverse, including not only problems in the field of human medicine, but also international environmental issues, and issues of food, ecosystem conservation, and livestock health. Therefore, as well as basic research and cross-sectoral, interdisciplinary research carried out by researchers in related fields, policies for Japan to formulate a national action plan within an international framework, assistance in the form of capacity-building for developing countries that could become pandemic hot spots, and international collaboration for different countries to share information and create cooperative systems are also absolutely essential. In conjunction with this, the development of relevant laws and regulations to efficiently promote cooperation in different fields must also be considered.

To implement the above measures continuously, it is necessary to demonstrate the industrial, commercial, and social benefits of the control of zoonotic diseases in a way that will be acceptable to the public. Preparation for crises in the future tends to be neglected if there are no problems in the present, but the COVID-19 pandemic has made us all aware that it is essential for humanity. To build a consensus of society as a whole that activities for such preparedness are an essential investment, the government, industry, and academia need to work together on systematic initiatives for open science and science communication.

There are a great number of issues that will have to be addressed, such as the incompatibility between the need for rapid disclosure for crisis management and the priorities of researchers when handling information such as the genetic sequences of pathogens, or the possibility of diversion of technology to biological weapons (the “dual-use” problem). New methods of data management and legal regulations may have to be developed to solve these issues.

It is also extremely important in infectious disease research that facilities are operated with appropriate biosafety management. Establishing advanced, biosafety facilities across Japan and developing human resources specializing in infectious diseases is thus an important task to carry out extensive R&D at domestic research institutions.

To achieve the goal of the proposed research project, it will be necessary to create a system that involves not only researchers, but also politicians, public officials, industry, and other members of society as a whole, and in parallel with R&D, to develop forward-looking human resources and establish and equip specialized organizations and facilities systematically. Resolving these societal issues will require strong leadership in the political area.

4. Benefits for industry and society

Achieving the goal that this research study aims for may be expected to provide guidelines for solving not only the problem of infectious diseases, but also the environmental and food problems that are the root causes of such diseases. The findings will provoke a ripple effect across the government, industry, and academia in all related fields, further increasing the momentum toward achieving the SDGs.

Specifically, the analysis methods that integrate information on ecosystems, the environment, and pathogens accumulated in this proposed research can become an important decision-making tool for formulating urban development and land-use plans. Recently, the industrial and economic worlds have come to a major transition phase, with a proposal made to introduce into economics the ideas of “biodiversity offsets,” which are activities to compensate for the impact of human social activities on ecosystems by establishing diverse ecosystems in different areas from where the impact occurred, and “natural capital,” which is acquired from the services performed by ecosystems such as food and water supply, climate control, resource security, and disaster preparedness (the Dasgupta Review). Corporate activities that are mindful not only of traditional commercial value in terms of money, but also of environmental impact and sustainable development will thus have new value, which may well give rise to industrial structures and forms of evaluation with different values from the present. In this new phase of major change in society’s values, the project implemented by the proposed research study will serve as basis for evaluation of the asset value brought about by conservation of biodiversity, which in turn reduces the adverse effects imposed by zoonotic diseases.

The COVID-19 pandemic has highlighted once again that research investment in infectious diseases is an extremely important security issue. Dobson et al. (2020) calculated that the cost of 10 years of pandemic prevention measures would amount to around just 2% of the economic losses through the novel coronavirus. Thus, continued investment in preventive R&D is wholly rational in the long term. The top priority for the future is therefore to resolve the issue of how to strengthen research and basic technologies related to infectious diseases as a national security policy so that Japan will be able to cope with the national crisis of a future pandemic, and the importance of infectious disease preparedness is accepted by the public. To resolve these issues, it is hoped that the government will exercise strong leadership and have the foresight to continue to develop and improve the technologies that form the basis of countermeasures against infectious diseases. It is likely that the process of establishing systems to coordinate information from related fields will lead to reform of the vertical structure of the government, which is a hurdle for research into infectious diseases, bringing about a society that is able to respond quickly and flexibly.

II. Analysis

1. Essential scientific/social components

As mentioned in section I above, multi-faceted initiatives in diverse fields are needed to realize the ideal society proposed in the present report. This report has focused its analysis on R&D to control the risk of spillover of viruses from wild animals to human populations.

To manage the risk of unknown zoonotic diseases, it is necessary to establish systems of close collaboration among related fields based on the concept of One Health and to identify the potential risks present in animals and the environment through interdisciplinary research. This will require the creation of systems that can appropriately assess and monitor the risk of spillover of pathogens into human populations by continuously monitoring and collecting all relevant information in the environment, including wild and livestock animals and pathogen-carrying arthropods, understanding the coexistence of pathogens and their natural hosts, and researching modes of transmission among different animal species and the mechanisms by which pathogens cross the species barrier.

To address these issues, it will be necessary to develop technologies to search for unknown pathogens carried by wild animals efficiently and to promote basic research to understand the detailed molecular mechanisms of pathogen transmission across the species barrier. There will also be a need for research on methods to control contact between humans and environmental risk factors (wild animals and vectors) which may facilitate the transmission of pathogens to humans. In addition, fieldwork such as wild animal capture surveys will be essential for efficient implementation of this R&D, and at the same time, it will be necessary to establish cross-disciplinary cooperative frameworks among researchers to facilitate the work and research methods that minimize the impact of fieldwork on researchers and the natural environment, and even to reform laws and regulations.

To bring about risk analysis and management that combine information on the natural environment and ecosystems with information on pathogens in the future, information on areas other than pathogens will also have to be accumulated by improving the quality and quantity of this information and linking it to information on the environment, ecosystems, and pathogens obtained through investigations. This will require the development of technology to collect information efficiently and precisely, as well as the establishment of technological systems that enable the appropriate storage and linkage of the accumulated data.

As a sociological issue, when putting measures in place, it is necessary to bear in mind that the social behavior of people that brings them into contact with environmental factors (hazards), which is a primary risk factor for pathogen transmission, will change over time. Environmental factors in this context would be, for example, animal species that are highly likely to harbor pathogens or vectors such as arthropods or blood-sucking insects. These factors may be avoided through zoning measures that reduce the opportunities for contact between humans and animals or eradication of pathogen transmitting vectors. An example is severe fever with thrombocytopenia syndrome (SFTS), an infectious disease spread via ticks; to prevent infection from ticks, people are encouraged to dress appropriately when entering grassy areas. Another example is dengue fever, a mosquito-borne infectious disease that broke out in Japan in 2014. In this case, measures included cordoning off public parks for spraying with insecticide. Thus, in addition to the scientific issues, due consideration is required for anthropogenic factors (e.g. changes in people's habitat and behaviors) for an effective disease control. In this respect, it is necessary to utilize the information on risks obtained through R&D and verify the changes in social behavior that are made to deal with this risk.

Also, since the risk of emergence of pathogens that may cause pandemics is closely related to environmental and food issues, the worldwide hot spots are concentrated in developing countries. The R&D already mentioned will therefore need to take place not only in Japan, but also within an international framework, and cooperation with international organizations will be essential. In Japan, it is anticipated that a domestic organization equivalent to the specialized organizations for infectious disease control in other countries (such as the Centers for Disease Control and Prevention [CDC] in the USA) will need to be established, and that a national action plan within an international framework will need to be formulated.

The common issues that emerge throughout are therefore the further development of experimental methods to increase the resolution of the information that is collected, the creation of cooperative frameworks and infrastructure for the future development of interdisciplinary research, and the development of technology to link information accumulated in databases, as well as the development of related laws and regulations for the efficient operation of the results of these developments, changes in social behavior, and international collaboration.

To address these issues, the following efforts will be necessary.

(1) Increasing the resolution of information collected through research in the environmental and animal health fields

a) The need to increase the resolution of information from research into pathogens and wild animal ecology

To monitor the risk of pandemics due to unknown pathogens hidden in wild animals, we need to gain an understanding of the kinds of pathogens that wild animals carry, which requires capturing wild animals and taking samples from them to conduct virological or molecular epidemiological analysis and putting systems in place to carry out such research continuously. In particular, the scale of field sampling needs to be expanded so that the risk can be better monitored through data analyses using information with a greater scale and higher resolution.

Bats and rodents have received particular attention as natural hosts of unknown pathogens. Since many of the pathogens that have caused pandemics in the past have originated in bats, research on pathogens harbored by bats has been conducted worldwide (USAID PREDICT). However, pathogen spillover from wild animals to humans depends greatly on the involvement of unknown animals other than the natural bat hosts that act as transmission vectors. For example, although the pangolin is assumed to have acted as an intermediary in the spread of the SARS-CoV-2, a survey report by the World Health Organization (WHO) released in March 2021 suggests this as only a possibility, and the true route of transmission has yet to be determined (WHO report). Thus, to assess the risk of spillover of unknown pathogens, it is desirable to accumulate knowledge on the ecology, living area, and behavioral habits of not only the main natural hosts of pathogens, such as bats, but also other animal vectors that transmit these pathogens. If information on the habitat area of a particular species and the other species that share this behavioral range can be identified, transmission route of unknown pathogens might rapidly be identified.

The surveillance of livestock animals is also important because these act as intermediaries in the process of transmission of pathogens from wild animals to humans. It is sufficiently possible that a seroprevalence of unknown pathogens in the livestock animals raise before pandemic in human society. Therefore, in parallel with the accumulation of information on wild animals, surveillance of livestock animals should be conducted. These surveillance will provide useful information for managing the risk of unknown zoonoses, suggesting the importance to create systems enabling surveys of the status of livestock animals. Creation of these information collection systems is essential for detecting signs of pathogen spillover, and is an important issue for assessing the impact of pathogens on human populations.

A cooperative framework between infectious disease and wild animal researchers is extremely important in the investigation of pathogens in wild animals. Searching for and capturing wild animals requires highly specialized knowledge, and the expertise of infectious disease researchers is indispensable for carrying out the work of searching for pathogens in wild animals safely. Frameworks enabling researchers belonging to both fields to collaborate therefore need to be constructed.

b) Development of analysis techniques to comprehensively obtain information on wild

animal habitats and co-existing species

As noted in **a)** above, a comprehensive understanding of the ecological information of wild animals in the natural world is essential for the development of measures to control zoonotic diseases. An example of the importance of this is SFTS, which has recently attracted attention in Japan as an emerging zoonotic disease. SFTS is a viral disease that was first reported in China in 2010. The first outbreak in Japan was reported in 2013, and cases have continued to be reported. The disease-causing pathogen is the SFTS virus (SFTSV), which is maintained and circulating among ticks and wild animals such as deer, wild boar, raccoon dogs, and raccoons. In particular, it has been reported in Japan that the SFTSV antibody prevalence exceeds 40% in deer (Maeda et al., 2016). Also, a recent study has shown that the seroprevalence of SFTSV antibodies in raccoon dogs and raccoons has increased greatly over the course of a few years (Maeda et al., 2019); therefore, the infection status of wild animals has changed in recent years. SFTS cases in Japan have mainly been reported in western regions, although surveillance of SFTSV in ticks have shown that SFTSV is widely distributed across Japan, including regions where no cases of SFTS have been reported. At the same time, it has been reported that there may be an association between the antibody prevalence rate in deer and the number of human cases in a region. The apparent disparity between the regions where cases have occurred and the distribution of the virus suggests that the opportunities for contact between humans, ticks, and deer or other wild animals may differ by region, which points to the importance of understanding the risk factors. Thus, zoonotic disease outbreak is closely influenced by various factors including in the natural environment, the presence of wild animals such as ticks or deer, and the social behavior of humans; it is therefore important to have a grasp of wild animal ecological information. In the case of SFTS, antibody surveys in wild animals appear to be a useful indicator of the risk of viral infection for humans, and therefore wildlife surveillance can inform both epidemiological status among wildlife and human infection risks. High-resolution information on the infection status of wild animals cannot be obtained in a large scale by the current mainstream methods such as manual analyses of data obtained by visual observation and fixed-point cameras. Thus, there is a need for the development of new information collection techniques using advanced technologies. For example, if multiple layers of data (e.g., video data from cameras, drones, satellite data) from a specific environment can be combined to analyze and monitor the effects of environmental changes on the habitats of wild animals continuously, it will be possible to detect new types of contact between wild animals and humans at an early stage and intervene to prevent such encounters from taking place.

Analysis that makes use of environmental DNA technology has recently been reported as a method for obtaining information from the environment in which organisms live (Leempoel et al., 2020). Environmental DNA is DNA derived from tissue fragments, feces, etc., that have been dropped from organisms living in habitats such as lakes, marshes, or rivers. Analysis of environmental DNA makes it possible to infer the habitat distribution, number of individuals, or biomass of organisms. At present, environmental DNA technology is a very powerful tool in the analysis of fish and other aquatic organisms, and while a number of cases of research using this technology with terrestrial animals have been reported, further technological advances are needed for full-scale application. If ecological surveys of terrestrial animals can be conducted using environmental DNA detection technology, it will be possible to obtain large quantities of information on wild animal habitats and coexisting organisms with relative ease.

At the same time, there are various issues—for example, it is difficult to determine the precise animal species on the basis of genetic information alone, and experts still need to make decisions based on anatomical characteristics. Also, even if the animal species can be determined by genetic information, the genetic sequence alone is insufficient to determine the age, sex, and blood relationship of the animal, and interpretation is difficult in cases where the habitat and behavioral range of the adult and juvenile are completely different. Future developments to resolve this issue will be needed, such as identification of individuals using image recognition technology, the development of age estimation technology using completely new methodologies, and the development of technology to estimate age, etc., from epigenetic data of DNA.

c) Development of technology for detecting trace amounts of pathogen genes

The technology for comprehensively obtaining and analyzing the genetic information of unknown pathogens has undergone dramatic improvements as a result of the development of a new generation of genetic analysis technologies, such as next-generation sequencing (NGS). However, the extremely small size of the virus genome in comparison to the host genome and diversity of virus genomes—they may be RNA or DNA, single strand or double strand—make it very difficult to detect. While the gene amplification technology using polymerase chain reaction improves the sensitivity of detection, it has the problem that only partial gene sequences can be obtained and only pathogens with known sequences can be detected, which reduces the resolution of the information. To obtain genetic information derived from pathogens more efficiently and with greater precision, further technological development of both devices and techniques will be needed.

In addition, while the cost of NGS equipment is decreasing every year as a result of rapid technological innovation, the technology is still expensive for research sites, and it is difficult to operate without a properly equipped laboratory. To solve this problem, it would be useful to develop technology to prevent the degradation of samples collected in the field, or to develop devices capable of performing genome analysis simply and cheaply in the field. It is often difficult to transport pathogens from sampling sites (or from developing countries that are hot spots) because of problems related to biosafety or genetic resources, and there will continue to be a need for technology that can perform analysis in the field.

Finally, with regard to the technology for analyzing the gene sequences collected in these studies, it will also be necessary to develop software for identifying gene sequences derived from unknown viruses. The present method is to search for virus genes based on their similarity to information registered in databases, but this involves the problem that detection is difficult in the case of a virus with a gene sequence that is markedly different from known sequences. Technological developments in terms of software are therefore needed for the discovery of unknown pathogen genes. For example, there is a need to develop programs that can expand the current method of searching for pathogen genes based on sequence similarity and find new, previously unrecognized similarities, or to develop completely new methodologies.

d) Development of technologies that contribute to virus isolation

Infectious pathogens need to be obtained to analyze in detail the pathogenicity and *in vivo* dynamics, but it is likely that only a very small proportion of the microorganisms in nature can be cultured artificially with the current technology. To investigate pathogens harbored by wild animals comprehensively, it will be essential to develop basic technologies for the highly efficient isolation and culture of unknown pathogens. On the other hand, if it were possible to establish a technology to create infectious viruses from genetic sequences for every type of pathogen artificially (a reverse genetics system), this method could perhaps become an alternative to virus isolation. If the isolation and cultivation of pathogens derived from wild animals did indeed become possible, this would solve the problems described above associated with deciphering the full-length genome. At the same time, there would be exponential increases in the amount of data that could be obtained in areas such as screening for effective drugs against the pathogen, the development of vaccine seeds, and research using experimental animals, seamlessly linking this research to the field of human medicine.

However, with acquiring and banking infectious pathogens in this way, there is a risk of dual use—diversion for use as biological weapons. Great care will therefore be needed with the use of infectious pathogens.

(2) Construction of information collaboration infrastructure to accelerate interdisciplinary research

a) Development of genome information for all wild animal species

Information on the genome of wild animals that are the natural hosts of pathogens is essential basic information for the development of environmental DNA technology . However, the number of wild animal species for which the complete genome has been sequenced is extremely limited. For example, bats are currently the focus of considerable attention as natural hosts of viruses that could cause zoonotic diseases. Yet, while there are about 1,100 species of bat, up until 2018, the genome of just 13 species had been sequenced. Even though there has been rapid progress with the genome sequencing of around 30 species since 2019, the vast majority of species have yet to be sequenced and the work is only just beginning (Table 1). For this reason, basic information needs to be put in place in parallel with the introduction of the advanced technologies discussed in (1) above.

If the available information on wild animal genomes became more extensive, it would be possible to obtain information on the host range of pathogens through laboratory experiments by, for example, using molecular biological techniques with genetically engineered cells. Reverse genetics technologies that manipulate viral genes together with improvements in the technologies that utilize host genome information may be expected to lead to the accumulation of knowledge about the molecular mechanisms when pathogens cross the species barrier.

Information on the whole genome of wild animals is of tremendous academic significance, but insufficient analysis has been done in this area to date because there has been little need for it for the purpose of commercialization or practical implementation. The importance of wild animals has now been reaffirmed as a result of the COVID-19 pandemic, and collecting and expanding information on wild animal genomes will provide a good opportunity to accumulate basic information that will advance research on not only infectious diseases, but also zoology and ecology. The accumulation of this information will contribute to the clarification of the mechanism by which the relationship of coexistence between an pathogen and its natural host is established, providing valuable insights for both comparative biology and the study of evolution.

Table 1. Bat species for which information on the whole genome is publicly available, and the year of publication (partially revised from Scheben et al., 2020)

Species name	Year published	Species name	Year published
Myotis lucifugus	2010	*Macrotus californicus*	2019
Eptesicus fuscus	2012	*Megaderma lyra*	2019
Myotis davidii	2012	*Micronycteris hirsuta*	2019
Eidolon helvum	2013	*Miniopteru schreibersii*	2019
Myotis brandtii	2013	*Mormoops blainvillei*	2019
Pteronotus pamellii	2013	*Murina aurata feae*	2019
Pteropus alecto	2013	*Noctilio leporinus*	2019
Pteropus vampyrus	2014	*Nycticeius humeralis*	2019
Rhinolophus sinicus	2016	*Phyllostomus discolor*	2019
Hipposideros armiger	2016	*Pipistrellus pipistrellus*	2019
Miniopterus natalensis	2016	*Rhinolophus ferrumequinum*	2019
Desmodus rotundus	2016	*Tadarida brasiliensis*	2019
Eonycteris spelaea	2018	*Tonatia saurophila*	2019
Anoura caudifer	2019	*Aeorestes cinereus*	2020
Antrozous pallidus	2019	*Molossus molossus*	2020
Artibeus jamaicensis	2019	*Myotis myotis*	2020
Carollia perspicillata	2019	*Pipistrellus kuhlii*	2020
Craseonycteris thonglongyai	2019	*Pteropus giganteus*	2020
Cynopterus brachyotis	2019	*Rousettus aegyptiacus*	2020
Hipposideros galeritus	2019	*Pteronotus mesoamericanus*	2020
Lasiurus borealis	2019	*Rousettus leschenaultia*	2020
Macroglossus sobrinus	2019		

b) Construction of basic technology to link information between databases

There are currently numerous databases covering diverse areas in the field of life science. There are also the GenBank of genetic information and the Protein Data Bank (PDB) of protein structures, and in the field of pathogens alone, there are GISAID and NEXTSTRAIN, which are widely used for gene analysis of influenza viruses and SARS-CoV-2, as well as the Global Virome Project, which aims to amass a comprehensive collection of virus genomes from around the world. In the field of ecosystem research, there is a database provided by the Global Biodiversity Information Facility (GBIF), and the International Barcode of Life Project (iBOL) is building a DNA barcode library for investigating species from short DNA sequences. Each field alone thus has a huge range of databases, and as zoonotic disease control is a multidisciplinary issue, the information is scattered across multiple databases. In addition, the information from related fields includes data based on descriptive documents and literary information such as research papers. Thus, there is a need to create new information-related infrastructure and develop new technologies for operating it to align this information efficiently.

Movement toward collaboration among databases, such as the promotion of Resource Description Frameworks (RDFs) for data to link information in different web-based databases in a cross-sectoral manner, has gathered speed in recent years. In addition, development of output technologies that use information from complex and diverse databases, such as the development of AI capable of explaining the reasoning for output results by learning from not only pure big data, but also descriptive information (e.g., knowledge graphs), is advancing. Creating the collaboration infrastructure to merge information from related fields while combining it with AI and other analysis technologies capable of interpreting complex data will undoubtedly create new value.

c) Development of programs and AI to simulate and analyze pathogen mutations

Simulations have been developed to predict viral gene mutations in pathogens such as influenza viruses, human immunodeficiency viruses, and SARS-CoV-2, for which a wealth of genetic information has been accumulated. In the case of influenza viruses, work is carried out every year to select vaccine strains based on the huge amount of genetic data on hemagglutinin, a surface protein, and the analysis of virus antigenicity; predictions are made of which amino acid sites in the hemagglutinin gene are likely to undergo mutation, which sites will be involved in antigenicity, and how the influenza virus population will change as a result of the vaccine (Huddleston et al., 2020). This research is only possible because highly precise information has been accumulated over many years, and it is extremely difficult to predict mutations that acquire infectivity to humans in unknown pathogens for which no prior information has been accumulated. To resolve this problem, systems need to be developed for making highly precise predictions in unknown pathogens, which will require collecting as many closely related species as possible from the environment and analyzing them to accumulate information, while at the same time, using existing information on closely related species to build theoretical models that can search for pathogen-derived proteins involved in human infectivity and to infer by analogy the mutations that are responsible for pathogenicity and infectivity. Realizing such technology will call for the handling of exceptionally multilayered information, and one hopes there will be breakthroughs in the use of AI, for example. There have been tremendous advances in machine learning methods in recent years, including the development of technologies that do not require huge amounts of learning data, and these methods have the potential for predictions with a level of precision that humans could never achieve. The development of AI that can explain the reasoning behind the analysis results is one of the topics in this field, and the creation of collaborative frameworks for information relating to zoonotic diseases in parallel with the development of methods to use this information fully is desirable in the future.

(3) Related social issues

a) The nature of international collaboration

Preparedness for unknown zoonotic diseases is an issue that needs to be addressed by the international community working in alignment. In the present research project, we focus mainly on scientific and technical issues within Japan; however, establishing research systems and putting in place systems of international cooperation and information coordination in developing countries, where pandemic hot spots are thought to be concentrated, is a major social issue for the future. This will require far-reaching administrative reforms, including the establishment of research institutes specializing in zoonotic disease control and the formulation of national action plans, and we will need to reconsider how Japan is positioned within international society.

b) Legislation of the related laws and regulations

When researching the pathogens harbored by wild and livestock animals, the ministries and agencies that have jurisdiction differ depending on the animal species involved, and the related laws and regulations of the various ministries and agencies are not the same. As a result, the laws and regulations that serve as the basis for conducting research and implementing countermeasures related to infectious diseases in the various fields are often unclear, which is a major challenge for smooth collaboration between researchers and local administrative departments. In parallel with the construction of collaborative frameworks between researchers, there is also a need for reform of administrative systems, and the laws and regulations that create hurdles for the collection of samples also need to be reconsidered.

An example of need of legal and regulatory reform is the surveillance of SFTS. In China and the Republic of Korea, SFTS infection was demonstrated in cows, pigs, sheep, goats, and horses; however, Japan’s domestic surveillance mainly targets wild animals such as deer and wild boar, and does not include livestock animals. A probable reason for livestock animals not being part of the surveillance is the difficulty in achieving collaboration between different government agencies. Zoonotic diseases occur through the relationships between the natural environment, wild animals, livestock animals, and humans, and cooperation among relevant ministries and agencies equipped to deal with issues that span multiple fields will be essential for dealing with zoonotic diseases in the future.

c) The importance of open science and science communication

While preventive research to prepare for infectious disease pandemics is an area of research that attracts attention when an unforeseen pandemic strikes, it can be difficult to demonstrate the benefits of this research because the results are not returned to the public in times of peace. Therefore, R&D aimed at preparedness is often subject to budget cuts, making continued operations extremely difficult. This is a common problem not only in Japan, but also worldwide, and it can be a challenge to evaluate properly the social benefits of basic research aimed at preparing for unknown diseases and explain these benefits to the public and funding providers. Thus, there is a need to review the current methods for evaluation of policies and to develop methods that evaluate secondary effects appropriately through the creation of evaluation axes focused on sustainable social development, corporate activity public relations, and risk management.

In addition, the prompt release and sharing of the genetic information of pathogens is desirable in terms of risk management, but from the perspective of the priorities of the researcher, publishing the sequence leads to the loss of novelty. It is therefore necessary to establish a shared awareness of new methods for evaluating results to resolve these conflicting issues.

There are also the social risks that research on pathogens may harm the reputation of the region where the research is carried out and may cause an increase in health concerns. A system needs to be put in place whereby appropriate communication to the general public of the risks is carried out concurrently with research to look for unknown pathogens; this issue has become a challenge when conducting epidemiological studies of livestock animals. As already stated in section II.1, surveys on the status of infiltration of pathogens in livestock animals can serve as an indicator for assessing the risk of spillover to human populations; however, there are also negative views of these surveys because of concerns that they may damage the reputation of the region. For example, as noted in **b)**, hardly any surveys on the status of infiltration of SFTSV in livestock animals have been carried out. It would be desirable to discuss the methods needed for communicating risk to ensure that there is a proper understanding of the results and that risk management is implemented.

2. Science and technology map

The present research project focuses on research based on biotechnology and research in the field of IT for methods to analyze the information that is collected, with the aim of resolving the problems set out in section II.1.

The Integrated Innovation Strategy 2020 (decided at the Cabinet meeting of 17 July 2020) identifies AI technology and biotechnology as basic technologies to be strategically addressed in the future, and similarly identifies comfort and security from the guarantee of safety against natural disasters and infectious diseases as an applied field to be strategically addressed. These scientific and technical fields have seen rapid development in recent years.

The following is an overview of the related technologies in each field.

(1) Next-generation sequencing technology

There have been remarkable technological developments in the field of genetic analysis in recent years, and in particular, the development of NGS technology has steadily brought down the cost of genetic analysis (Figure 6). With this decrease in cost, there has been a corresponding rapid increase in the amount of genome information from different animals, microorganism genome sequences, and metagenome information that has been accumulated in databases (Figure 7). The decrease in the cost of experiments using NGS and the acceleration of information accumulation are predicted to continue in the future.

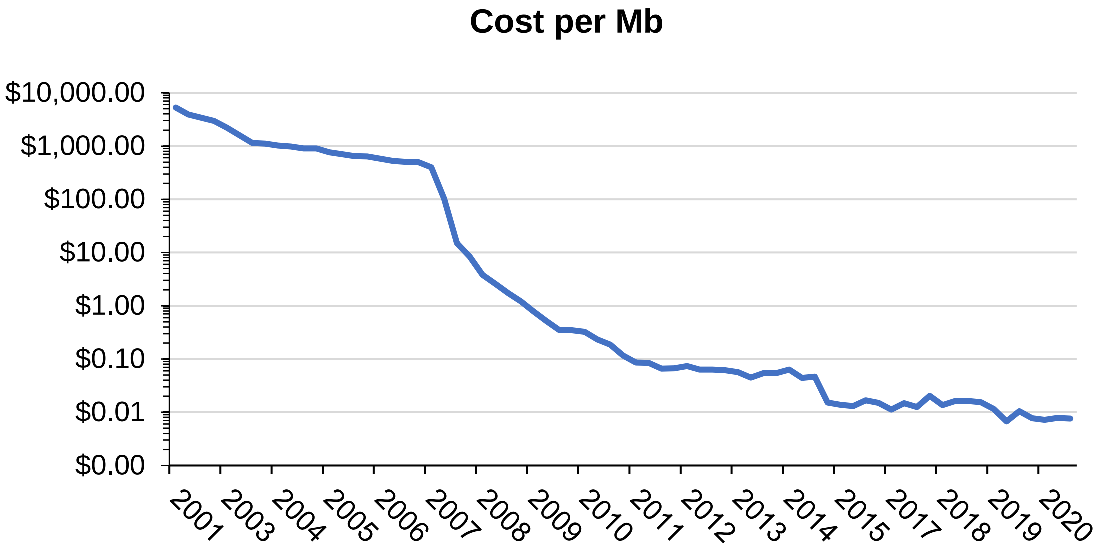


Figure 6. Changes in the cost of sequencing. From https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data

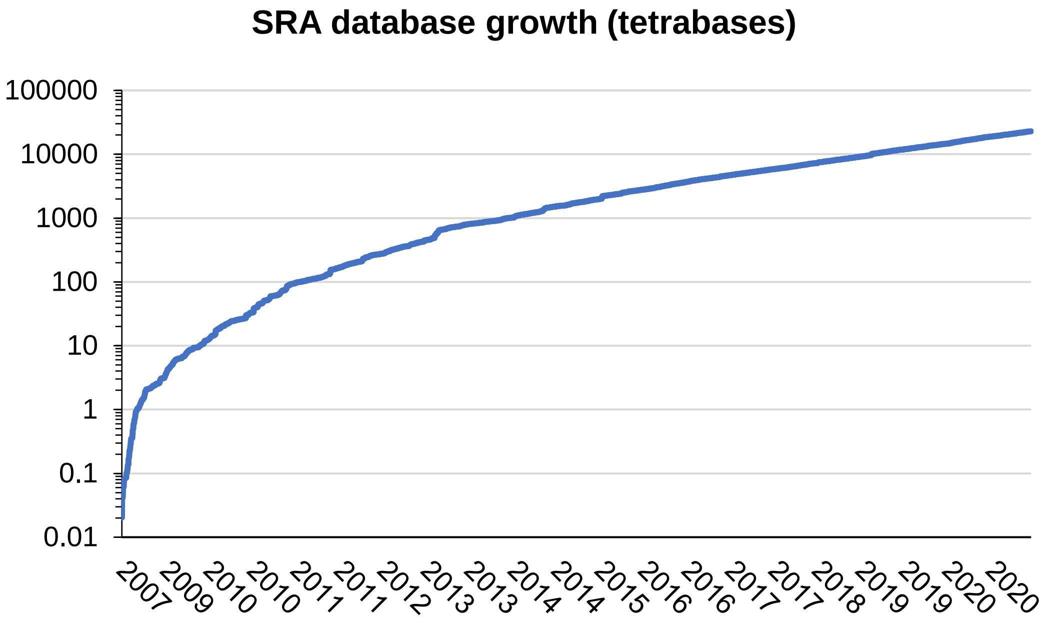


Figure 7. Changes in the length of sequences stored in databases. From https://www.ncbi.nlm.nih.gov/sra/docs/sragrowth/

However, as described in section II.1, obtaining complete genome information on pathogens still has challenges, and in many cases, the gene sequences deposited on databases are only partial. For example, while over 10,000 genetic sequences from viruses originating in bats are currently deposited in the National Center for Biotechnology Information database (NCBI Virus), the majority of these are partial sequences of 1,000 bp or less (Figure 8).

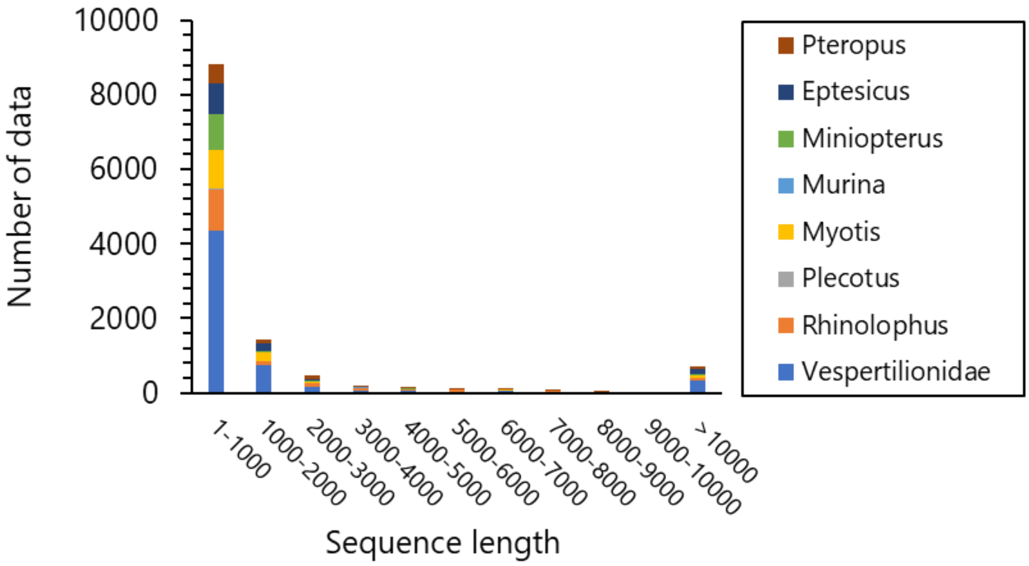


Figure 8. The number of nucleotide sequences and the sequence length of viruses originating in bats deposited in databases. Viral sequences have been detected in a variety of bat species, but most are partial sequences of 1,000 bp or less.

There is also a need for the development of portable devices that can carry out the full test process in the field, which would allow the processing of samples that cannot easily be brought back to the research institution. Issues for future NGS technology include the need to increase further the scale of genome sequencing and reduce running costs, while at the same time, making devices smaller and lighter, simplifying the library preparation process, and training researchers in developing countries to use these technologies.

Other countries have an overwhelming share of the market for NGS technology, and technological development in Japan is by no means flourishing. The current NGS technology for short-read sequencing is dominated by Illumina, and although Nanopore sequencers (Oxford Nanopore Technologies Ltd.) are gaining ground for long-read sequencing, they still have issues with accuracy. NGS technology will be an important basic technology in the present research field, and thus, there is a pressing need for domestic innovation that does not rely on other countries. Also, along with device development, there is also a need for R&D of intangibles such as technology for purification when processing samples and technology to analyze the acquired gene sequences. Since NGS technology is a vital technology for not only the present research project, but also research across the whole field of life sciences, innovations in NGS technology may be expected to act synergistically on the present research project.

(2) Bioscience technology

According to the report "Panoramic View Report of the Life Science and Clinical Research Field," which was published in 2019 by the Center for Research and Development Strategy (CRDS) of the Japan Science and Technology Agency, third- and fourth-generation sequencers, single-cell omics analysis technology, organoid technology, AI technology, and imaging technology using various types of microscopes are set to become future trends in the bioscience field (Figure 9).

Third- or fourth-generation sequencers	**Genome editing**	**Cryo-electron microscopy**
Single-cell multiomics	**Artificial intelligence**	**Super-resolution microscope**
Organoid **Body-on-a-Chip** **3D bioprinting**	**Chimeric antigen receptor (CAR)-T cell therapy**	**Optogenetics**

Figure 9. Future trends in bioscience technology according to the "Panoramic View Report of the Life Science and Clinical Research Field" published by the Center for Research and Development Strategy

Sequencers have already been discussed above, while organoid technology is extremely important for isolation and culture experiments of viruses that are difficult to culture with existing technology, and omics analysis and imaging technology are vital for analysis of virus–host interactions such as infection patterns.

In recent years, as a result of the establishment of new host cell culture systems, there have been many reports of the successful *in vitro* cultivation of bacteria and viruses that were difficult to isolate and culture in the past. For example, host cell culture technology using intestinal epithelial organoid culture has been used for the successful *in vitro* culture of norovirus and rotavirus, which have been difficult to cultivate in the past (CRDS Panoramic View Report). In addition, there have also been reports of the establishment of systems of infection of Zika virus in human induced pluripotent stem (iPS) cell-derived brain organoids and influenza virus in human adult-derived lung organoids (CRDS Panoramic View Report). The application of the cutting-edge cell culture technology to the field of infectious disease research in this way is expected to be of great use in the search for unknown pathogens.

Omics and imaging technologies play an important role in the existing Moonshot Goal 2 project “Understanding and Control of Virus–Human Interaction Networks” (Project Manager: Dr. Matsuura), which is related to the present research study. Although the present report will not describe these technologies in detail, the development of this technological field is important in, for example, the construction of experimental systems using model animals that can evaluate the pathogenicity of newly collected pathogens, and is expected to have a significant ripple effect on the analysis of pathogens collected in the present research project.

(3) Research fields that require fieldwork, such as sampling from animals and the environment

Fieldwork research, which mainly involves sampling from wild animals and the environment, requires greater budgets, time and more personnel than other research fields, which can become hurdles so that the rate of development is inevitably slower than in the fields described in (1) and (2). In addition, zoonotic diseases that have the potential to cause pandemics are highly likely to appear in hot spots such as developing countries, and securing continuous human resources and budgets can be a major challenge for research that requires sampling of such pathogens in the field.

Under the Japan Initiative for Global Research Network on Infectious Diseases (J-GRID) (now integrated into AMED), Japan has been working for many years on improving international collaboration centers to promote infectious disease research in Thailand, Vietnam, China, Zambia, India, Indonesia, the Philippines, Ghana, and Myanmar. It is hoped that international fieldwork can be continued and developed by maintaining the cooperative frameworks for research in these centers. The cooperation of the administration and research institutions of the host country is essential for sampling research in the field, and from this perspective, it is important to build relationships of trust over a long period of time to create global cooperative networks.

There is undeniably a possibility that in the future, new pathogens may be found in wild animals that live in Japan. The results of wild animal surveillance in Japan have shown that diverse wild animal species, including deer, wild boar, raccoon dogs, and raccoons, have been infected with SFTSV. At the same time, genetic analysis of SFTSV has shown that the virus was present in Japan for many years before the outbreak of the disease in humans, indicating that further unrecognized pathogen may be circulating in wild animals in japan . Research on pathogens in wild animals is therefore a major issue for Japan as well as for other countries, and it is extremely important to conduct continuous surveillance.

These fieldwork studies involve a number of issues not related to science and technology, such as securing personnel and budgets for continuous research as mentioned above, as well as the various procedures for capturing wild animals and the thorough implementation of biosafety and research ethics to protect the people and values of the host country. Nonetheless, there is growing momentum internationally to accumulate information on pathogens carried by wild animals, and this is an area of research in which Japan must continue to expand its efforts. It is hoped that in combination with the technological innovations in related fields described above, fieldwork research will become even more vigorous.

Systems for managing the samples collected in the fieldwork mentioned above were started in 2021 by AMED under the National BioResource Project (Core facility upgrading program: Human pathogenic virus and zoonotic virus resource facility), and systems are being put in place for banking the pathogens that are collected. Pathogens collected in the future will not only be used for risk management of infectious diseases, but will also have the potential to become new bioresources. Fieldwork to search for unknown pathogens is thus an important field that is expected to grow.

In the Introduction, we mentioned the use of livestock animals for risk surveillance. To date, there is no system in place for banking samples from livestock animals raised in Japan, and the storage of such samples is left up to local governments. Thus, there is a need to establish systems and initiatives for appropriate banking of samples from livestock animals so that when a pathogen is discovered in the course of wild animal surveillance within Japan, a retrospective survey of the infiltration status of livestock animals in the same area can be carried out.

(4) Information technology (AI research, etc.)

As shown in Figure 9, AI technology is of great interest as a major trend in the field of life sciences, and has become indispensable to current life science research. AI research within the field of life science has recently become an area of vigorous research in Japan, and the AI Japan R&D Network was established on the basis of the Integrated Innovation Strategy 2019 (decided at the Cabinet meeting of 21 June 2019) and the AI Strategy 2019 (decided by the Council for Integrated Innovation Strategy on 11 June 2019). In addition, the Life Intelligence Consortium (https://linc-ai.jp/) was established to develop AI and big data technologies for life science fields such as pharmaceuticals, chemistry, food, medicine, and health care, and as of April 2021, 55 life science companies, 44 IT companies, and 12 research institutes have joined the consortium and are actively engaged in promoting a variety of research projects.

The development of AI technology requires vast quantities of high-quality data as training data; hence, it is naturally suited to research areas with active database construction or technological developments relating to information collection. For this reason, fields with abundant, high-quality data are inevitably bound to be prioritized for the spread of AI technology, while its application to research fields such as wild animals—the target of the present research project—that include complex and diverse phenomena and have extremely small amounts of accumulated data is still developing. The quality and quantity of information collection in the field of the present research study is expected to become a hurdle for the future diffusion of AI technology, and the development of information collection discussed in (1) to (3) above is an urgent task to remove this predicted hurdle.

In addition to big data-driven research and image recognition, a trend in AI research for the future is the wealth of research into explainable AI, fusion AI capable of acquiring and expanding knowledge without being taught, and fusion AI capable of reasoning and acting appropriately to the context. For example, Fujitsu’s Deep Tensor technology allows AI to explain the basis of the inferences it draws by capturing the meaning of connections between concepts using a knowledge graph. In infectious disease research, the ability to explain the data that are used as the basis for judging the risk of outbreak of a pandemic due to unknown pathogens or making inferences based on literature or other documents are extremely important topics, and the development of AI research in these areas will have benefits for measures to control zoonotic diseases.

AI research in the field of life science is therefore expected to develop greatly in Japan in the future. However, this trend cannot have really been spread beyond the priority areas of medicine, health, and food to fields such as zoonotic disease, which is the target of the present research project, or the related field of agriculture, forestry, and fisheries or fields related to the environment. Building the foundation to promote the spread of this technology to peripheral fields is therefore a pressing task that must first be addressed.

(5) Research fields involved in database construction

Data-driven research has become an extremely vigorous part of life science R&D. The databases managing the big data that are important for carrying out the AI and data-driven research described in (4) are operated by the National Bioscience Database Center (NBDC) and the Database Center for Life Science (DBCLS), which are domestic institutions specializing in maintaining and operating various life science databases. The trend toward database integration has accelerated in recent years, with the CRDS issuing a strategic proposal relating to data integration in the field of human life sciences (CRDS Strategic Proposal “Integration of Bio-Medical Things,” published in 2018). However, when viewed from an international perspective, the scale of the budget and personnel invested in fields relating to databases in Japan is small (Table 2), and the personnel and budget in these fields will have to be expanded to accelerate data-driven R&D in Japan in the future.

Table 2. Comparison of institutions operating databases in different countries (as of 2015) (From National Bioscience Database Center. 2016. https://biosciencedbc.jp/gadget/unei/jigyou_houkoku.pdf.)

Center (Region)	Databases	Budget (2015)	Personnel
NCBI (USA)	Genome, GenBank, GEO, dbGaP, SRA, OMIM, PubChem, Pubmed	$175.8 million.	287
EBI (EU)	Ensembl,ENA, EGA, ArrayExpress, ChEMBL, UniProt	€67.2 million	513
NBDC/DBCLS (Japan)	NBDC human database, NBDC RDF portal	1.41 billion yen	64
DDBJ (Japan)	JGA, DDBJ	1.46 billion yen	39

As a recent trend, there is increasing momentum toward building integrated infrastructure for databases across fields, and the technological development for this is being implemented (Figure 10). An example of this is the launch of the NBDC RDF portal (https://integbio.jp/rdf/), a website that integrates multiple databases. However, this trend is limited to a few highly versatile life science fields, and it has not yet spread to the field related to zoonotic diseases targeted by the present research project. It is necessary for this trend for database integration to spread to the field related to zoonotic diseases as quickly as possible.

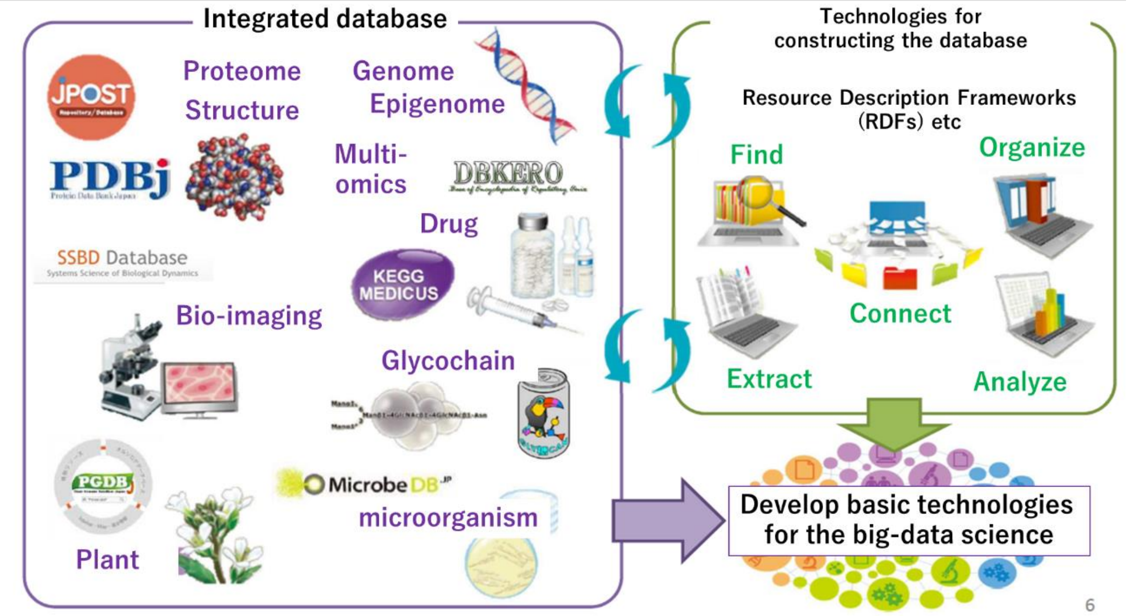


Figure 10. Overview of initiatives in Japan toward database integration from https://www.lifescience.mext.go.jp/files/pdf/n1934_04-2.pdf

(6) Summary

The 6th Science, Technology and Innovation Basic Plan (decided at the Cabinet meeting of 26 March 2021) states, “In response to new biological threats, the government will promote research and development related to early detection of outbreaks, understanding and forecasting of epidemics, prevention and control, and risk communication with the public.” Measures for unknown zoonotic diseases, the target of the present research study, are therefore an issue to be addressed strategically in the future.

Thus far, we have outlined the science and technology related to the issues for achieving the goal of the present research study; all of which is in line with future trends in science and technology and conforms to Japan’s next innovation strategy (the Integrated Innovation Strategy 2020, decided at the Cabinet meeting of 17 July 2020). Research in these fields is therefore expected to accelerate dramatically in the future, and there is every likelihood that the innovations needed to achieve the goals of this research project will be realized.

3. Japan’s position in overseas trends

(1) International trends in zoonotic disease surveillance research

Large-scale projects in preparation for unknown zoonotic diseases have been implemented in the USA and Europe since 2009 (Integrated Control of Neglected Zoonoses [ICONZ], Zoonoses and Emerging Livestock Systems [ZELS], USAID PREDICT). USAID PREDICT in particular conducted virus searches in hot spots for pandemic outbreaks in developing countries over the 10-year period from 2009 to 2019, discovering many viruses while contributing to capacity-building in developing countries, such as human resource development and the establishment of testing systems. In addition to this search for pathogens, research is also being conducted to analyze the genomic information of bats, which have attracted particular attention as a natural host for unknown pathogens (BAT1K project). Thus, there is far greater surveillance of both pathogens and wild animals overseas than in Japan. In Australia, a large number of research projects into wild animals and zoonotic diseases are being carried out with funding from the government and industry. There is no detailed information on China, but there is likely to be considerable field surveillance, as shown by the fact that most of the analysis information on viruses derived from bats registered in GenBank is from Chinese research teams. Therefore, large-scale surveillance research has been consecutively carried out overseas with abundant funding and human resources.

In parallel with these surveillance studies, a number of papers assessing the risk of spillover of unknown pathogens have been published in other countries in recent years (e.g., Grange et al., 2021; PNAS). In particular, the paper by Grange et al. reports the creation of a website that serves as a framework for risk assessment (SpillOver: Viral Risk Ranking https://spillover.global), which ranks pathogens with high spillover risk on the basis of risk assessment by a group of international experts. However, with the recent rapid progress in virus discovery, the accuracy of these traditional risk analyses has been questioned because of the excessive number of registered pathogens, and papers have been published evaluating the accuracy of various risk assessment reports (Wille et al., 2021). Thus, the development of methods for assessing spillover from wild animals still appears to be in the formative stage.

Japan has also implemented international research projects related to zoonotic diseases under various program names, including the Science and Technology Research Partnership for Sustainable Development (SATREPS), J-GRID, and AMED. While these projects have been on a smaller scale than those carried out by other countries, the foundation for international collaboration has been established. In particular, J-GRID (now AMED) has been promoting important research such as the identification of large numbers of unknown novel viruses in infectious disease research at overseas collaboration centers (Achievement reports from J-GRID: https://www.amed.go.jp/program/houkoku_h28/0106jgrid.html).

As stated earlier, Africa, Central and South America, Southeast Asia, and other regions are attracting attention as hot spots with a high risk of zoonotic disease outbreak. Section I.3.1 noted that the occurrence of zoonotic diseases is closely related to rapid environmental change resulting from human social activities and food problems, and many of these hot spots are developing countries. Capacity-building in developing countries to enable continuous surveillance is therefore important for global zoonotic disease control, and developed countries need to cooperate with various regions to address this issue. From a geographical perspective, Japan should take a leading role in Southeast Asia, and it is extremely important for Japan as a country to tackle this issue.

To deal with unknown pathogens from an international perspective, specialized biosafe research facilities are essential. The USA built new biosafety level 4 (BSL-4) facilities in the 2000s, and currently has approximately 10 BSL-4 facilities in operation. Since 2015, further BSL-4 facilities have been constructed in Germany, France, and China, with systems for clinical examination and research put in place. Research at BSL-4 facilities is essential for collecting and analyzing the scientific information on pathogens that is needed for infectious disease measures through experiments and other procedures, as well as for the R&D of specific technologies for the diagnosis, treatment, and prevention of infectious diseases. In Japan, however, for societal reasons, the operation of BSL-4 facilities is limited to clinical examination during emergencies, and their use for research purposes is restricted. With BSL-3 facilities, apart from the public testing laboratories in each prefecture, there are only a dozen or so research facilities operated by universities, companies, and national research institutes, and the number of the facilities is by no means sufficient. These facilities need to be improved and expanded if Japan is to demonstrate international leadership in infectious disease measures in the future.

(2) Japan’s strengths in related technological fields

NGS was discussed in section II.2 as a basic technology to support sampling in the field, but Japan lags behind other countries in the development of the devices needed for NGS analysis. European and American manufacturers have a virtual monopoly in NGS devices, and technological development of NGS in Japan has lacked vigor. Nonetheless, Japan is moving forward with technological development in fields such as sample purification and library preparation, which are the preliminary steps for NGS analysis, as well as the development of programs to analyze data obtained from NGS devices. It was mentioned earlier that the development of NGS devices has undergone a series of dramatic technological transformations because of breakthrough innovations. If Japan were to concentrate on the development of new devices based on new innovations while at the same time developing software and other intangible technologies for use with these devices, it could perhaps become a world leader in NGS technology.

Environmental DNA is one of the analyses that use NGS technology, and Japan is a world leader in its approach to the environmental DNA field, having established the world's first scientific organization specializing in environmental DNA (The eDNA society). The eDNA society has been carrying out activities aimed at standardizing data for analysis, such as publishing methods with international standards for collecting and processing environmental DNA from aquatic systems, from an early stage, and possesses extremely significant knowledge of the research field of the present research project. In the application of environmental DNA technology to terrestrial mammals, Japan was the first to develop common primers for mammals (Ushio et al., 2015). Japan may well be able to demonstrate its strength by promoting the fusion of conventional infectious disease research and environmental DNA research for putting in place measures against zoonotic diseases. In particular, in the analysis of environmental DNA of wild animals envisioned in the present research project, Japan can be expected to lead the international standardization of sampling methods.

A study by Leempoel et al. (2020) found that environmental DNA in soil samples succeeded in detecting equal to or more species than camera traps (Figure 11), and the application of environmental DNA methods to the present research project is highly feasible. However, problems due to the inadequacy of databases that do not cover the genome information of wild animals have been identified, and as already mentioned, enhancing the genome information of wild animals will be essential for future research. Research into wild animal genome information is proceeding at a furious pace, and it includes the Genome 10K project, which aims to acquire genome information on all animals. By participating in this international effort, Japan will be able to cooperate in the efficient accumulation of wild animal genomes that will serve as basic information for zoonotic disease control. Japan is one of the world's biodiversity hot spots, and among the mammals alone, there are 50 species endemic to Japan, including 16 species of bat. It is therefore significant for Japan to take an active role in the acquisition of genome information from a wide range of wild animals.

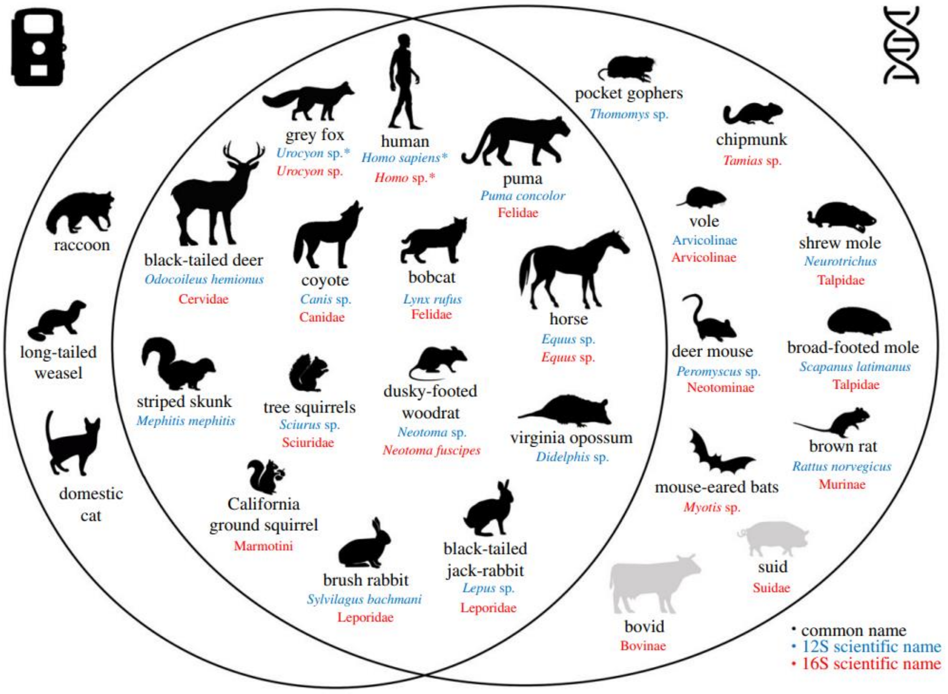


Figure 11. Comparison of detection ability of environmental DNA (from Leempoel et al., 2020). Many of the animals detected by camera trap were also detected by environmental DNA technology, and some animals could only be detected by environmental DNA technology.

The USA and China presently have an extremely strong presence in AI, big data-driven research, and other IT fields. Nonetheless, attempts in Japan aimed at development in these fields have begun, and the 6th Basic Plan for Science, Technology and Innovation (decided at the Cabinet meeting of 26 March 2021) includes further development of AI technology, while the Ministry of Education, Culture, Sports, Science and Technology has set digital transformation in the bioscience research field as a strategic goal of its Strategic Research Promotion Project for FY2021. Recent technological development in the AI field has been dramatic, and the status may change drastically depending on future technological innovations—it is possible for Japan to rise to the top internationally by developing the next generation of technology through future innovation. Cutting-edge research into technological development in the IT field is taking place under the other Moonshot Goals, and these technological developments can be expected to have a ripple effect on the present research project.

III. Plan for realization

1. Area and field of challenging research and development, research subject for realization of the Goals

The technological fields necessary for resolving issues to achieve the goal of this research project are as described in section II.2: (1) the field of information collection technology, including NGS and other biotechnology and field surveys for sampling, and (2) the IT fields of AI research and database integration technology. Infrastructure creation and challenging technical development need to be promoted in these and all other related fields.

The R&D scenarios for resolving the various issues are as follows.

(1) Increasing the resolution of information collected in research in the environmental and animal health fields

a) Developmental research to apply environmental DNA techniques to research into terrestrial animals

Environmental DNA can be a very powerful tool as a technology to collect high-resolution ecosystem information on wild animals on a large scale. However, since the current environmental DNA technology mainly uses water as the analysis target, there are many hurdles to be overcome to be able to conduct research on terrestrial animals.

For example, to interpret information obtained from environmental DNA analysis, the spatiotemporal scales that the information obtained at the sampling location can cover must be clarified. There has been an accumulation of data with which to display or calculate the spatiotemporal dynamics of environmental DNA in terms of diffusion, degradation, and other behaviors in aquatic systems, but there has been little such information accumulation for environmental DNA on land. To apply environmental DNA technology to wild animal research, it is therefore necessary to start with research that accumulates basic information. For the target of environmental DNA sampling, technology needs to be developed to analyze environmental DNA from samples from all types of situations, such as soil and air, in addition to sampling from water bodies such as springs, which has already been studied.

To clarify the dynamics of unknown pathogens in wild animals, in addition to data on the animal species inhabiting a given area, quantitative information such as the population densities and numbers of individuals of these animals is needed. For the data collected using environmental DNA technology to be made quantitative, problems such as amplification bias and optimization of primer sequences during gene amplification and international standardization of sample processing methods must be resolved. Technological development with the aim of resolving these issues will therefore be needed.

In addition to information on species and the numbers of individuals, it will also be desirable to obtain information on individuals themselves, such as age, blood relationship, and sex, since these factors have a direct bearing on the behavioral range of individuals and the behaviors that can transmit pathogens. To obtain such detailed individual identification data from environmental DNA research, which deals with comprehensive metadata, innovative technological development unconstrained by existing methods is required. It might be possible to resolve these issues if technology can be realized to estimate the age of individuals based on epigenetic data from the obtained environmental DNA.

An important issue when commencing research using environmental DNA is the need to confirm the precision of the information obtained. To achieve this, quantitative measurements using existing visual observations and fixed-point cameras must be conducted in parallel with environmental DNA analysis, and the consistency of the two data sets must then be verified. Traditional observation research using visual data is extremely difficult to carry out on a large scale because of the cost and personnel expenses, and a breakthrough is essential to solve this problem. There have been considerable developments in recent years in data collection technologies that combine sensing devices with AI and video analysis technologies that utilize AI image recognition technology. Application of these technologies to field studies of wild animals in combination with environmental DNA analysis techniques is expected to make it possible to obtain information more efficiently and at higher resolution.

The issues relating to environmental DNA are thus very diverse, and setting topics for the medium to long term is necessary to resolve these problems.

b) Technological development related to pathogen research using NGS

Various technologies have been developed for the detection of viral genomes, which is difficult because of the minute amounts involved. The such technology to be reported in Japan was Fragmented and primer Ligated dsRNA Sequencing (FLDS), which focuses on the fact that only viruses form double-stranded RNA during the replication process; this method extracts and purifies only virus-derived double-stranded RNA (Urayama et al., 2016). Thus, there are emerging technologies capable of efficient isolation of viruses as a preparatory stage for NGS analysis. Development of these technologies may allow viral genomic information to be collected with far greater efficiency than is currently possible.

With regard to software that enables searching unknown virus sequences, new technologies to search for virus-derived sequences will need to be developed from a different perspective compared with existing technologies. The construction of new gene sequence analysis models or the development of completely new algorithms that use machine learning or other technologies to search for virus-like characteristics among gene sequences may be the breakthrough needed to resolve this problem. A technique to analyze viral genes by considering the virus gene sequence to be a language and interpreting the grammar and meaning using AI natural language processing was recently reported (Hie et al., 2021). Thus, there is the potential for completely new discoveries in viral gene analysis technology through the application of AI technology. In addition, a huge ripple effect can be expected in the future from the development of new viral gene analysis technology if application of the technology to predict mutations of the viral gene and other factors that are important for evaluating vaccines efficacy and pathogenicity are kept in mind.

The above issues need to be addressed by developing and verifying technologies through the use of sequence data accumulated in the past and samples that have been stored, while setting research topics with a view to application of these technologies to samples that will be collected in the future.

R&D to meet the needs of researchers in the field by making smaller, portable NGS devices is being carried out at the level of practical application, such as the use of MinION (Oxford Nanopore Technologies Ltd.) for testing during the Ebola virus pandemic in developing countries. However, this technology also has the drawback that there are many errors during gene sequencing, so there are still issues to be resolved.

It has been pointed out that a problem with many viral metagenomic studies currently being carried out is that they investigate a single host species at a single location, with little work to screen large cohorts for new viruses, particularly if the virus does not show disease symptoms in livestock animals (Wille et al., 2021). With virus metagenome surveillance using NGS, it is important to conduct virus metagenome studies that sample multiple host species continuously and to include meta-information such as the age and location of the individual host animals. Collecting and releasing genome information in conjunction with meta-information that includes details of the host individual and the sampling site allows researchers in the fields of mathematical science and IT to use the information for research that couples together metagenome analysis and individual information. To gain an understanding in advance of novel infectious viruses, surveillance research that searches for unknown viral genomes must be promoted along with the collection and publication of information on host individuals and sampling sites.

Looking at the overall experimental process, the bottleneck at present is manual gene extraction and sample preparation, and there are many cases of surveillance research in developing countries where it is difficult to secure the facilities (e.g., laboratory equipment, power supply) for conducting experiments. The development of technologies that can skip these processes may be expected to accelerate surveillance research dramatically in hot spots of unknown infectious diseases.

c) Development of technologies that contribute to virus isolation

The number of discoveries of new viral sequences has increased rapidly in recent years because of the development of NGS technology, and the number of registrations is increasing every year. At the same time, it is still difficult to isolate an infectious virus; this is because virus isolation and culture techniques are greatly affected by factors such as the freshness of the sample and the culture substrate used in the experiment, so it is much more difficult to obtain high throughput compared with genetic analysis techniques. Innovations in virus isolation and culture technology will be important since experiments using isolated viruses in combination with predictions from genetic data are essential for evaluating the pathogenicity and the properties of viruses. To overcome this problem, technology has been developed to produce cells derived from wild animals. As described in section II.2, virus isolation techniques that apply technology to produce organoids or iPS cells have also been reported. However, while technology systems have been established for humans and mice, there are a great many technical and cost issues to be resolved before the technology for producing and maintaining organoids or iPS cells can be expanded to all wild and livestock animals. Therefore, to apply these technologies to wild animal research, basic information on gene expression in wild animals will have to be accumulated, while technological developments will be needed to make it possible to use these technologies more cheaply. At present, costly cutting-edge technologies are developed in order of priority on the basis of risk, and thus, are limited to animals with a high probability of harboring potential pandemic pathogens, such as bats, rodents, and primates. In the future, new technological innovations that reduce the technical and cost hurdles to producing specialized cells such as organoids or iPS cells are likely to permit this technology to be disseminated more widely.

(2) Creation of information collaboration infrastructure to accelerate interdisciplinary research

a) Project to upgrade wild animal genome information

To conduct research such as environmental DNA analysis and the search for viral genes described in (1) above, complete genome information is needed for the wild animals to be targeted. For example, to conduct environmental DNA analysis, universal primers to amplify the genes of all animals have to be designed. However, it is difficult to design primer sequences that are common to all animal species if the wild animal genome information is incomplete. It is also difficult to identify the animal species from sequences that have been detected if the complete genome information is not available. It is therefore essential that the information relating to wild animal genomes be upgraded as a major prerequisite for the present research study. At present, gene sequences derived mainly from mitochondrial DNA are used as the target for environmental DNA analysis—it is therefore necessary to create a comprehensive database of, at the very least, the mitochondrial DNA sequences of different animal species. Also, considering that it will be desirable in the future to collect detailed individual information such as blood relationships and age, and it is hoped that the decoding of host DNA that includes epigenetic characteristics will eventually be possible.

In the field of plant research, complete genome analysis is being conducted to search for useful traits in plants in the wild environment and introduce them into cultivated species; wild animal genome analysis may therefore bring unexpected benefits. Whole-genome analysis of bats has shown that genes related to immunity have evolved in special ways, which is a factor that has allowed bats to coexist with a wide variety of viruses (Pavlovich et al., 2018). Analysis of wild animal genomes is therefore an important topic for the future as it can yield findings that are important for not only measures against infectious diseases, but also comparative biology and evolution. As mentioned earlier, efforts are being made internationally for wild animal genome projects, and it is therefore important to put in place research frameworks for collaboration with existing projects.

b) Creation of basic technology to link information in different databases

The use of RDFs to link information between different databases, such as in the NBDC RDF portal, will allow seamless compatibility with future data analysis using AI. Using this RDF technology to integrate the databases containing information related to zoonotic disease collected in this research project, such as databases of information on ecosystems, soil, vegetation, and climate, with other databases will further accelerate research in related fields aiming for the construction of future zoonotic disease management systems.

Together with this development of integrated databases, methods will be required for analyzing and interpreting multilayered information. Huge amounts of information will be collected during the course of the present research project, and this information is expected to include not only numerical data, but also descriptive data based on documents and multiomics information. In the society we aim to achieve by 2050, systems can be expected to be in place for the risk of unknown infectious diseases to be evaluated through comprehensive analysis of this information, and for the results and their interpretation to be communicated and explained to the public and policy-makers. Considerable time is still needed before this vision can be realized, and research aimed at constructing new theoretical models and AI-based research will need to be carried out in parallel with the collection and accumulation of data. Research of this type is expected to use AI equipped with the functionality capable of explanation of the basis for analysis and AI capable of reasoning to find the appropriate results from complex contexts. This may be possible by, for example, combining pattern recognition based on deep learning with systems using knowledge graphs.

It is hoped that the ultimate goal of this research project, a risk management system capable of integrating and interpreting all kinds of information, will become a technology that can be used not only in Japan, but also internationally. For this, Japan will be expected to take the initiative in aiming to resolve the technical issues described above, and at the same time, to exhibit strong leadership in sharing this vision with other countries to create a framework that transcends national and regional boundaries. First, collecting information within Japan and proving the concept for realizing this goal is important. Providing the hardware technology and expertise amassed through this process will allow the collection of information on the situation in all regions around the world, as well as the construction of optimal models for each region. Ultimately, it may be possible to set a future goal integrating the results from each region to identify a general measure of the conditions under which unknown pathogens with a high potential to cause a pandemic will emerge and spill over to humans.

2. Direction of R&D for realization of goals

Up until 2030, the present research project will concentrate on the development of basic technology and the creation of collaborative frameworks to put in place the preparations for efficiently conducting subsequent research, while at the same time, continuing the collection of field samples to expand the samples available for the analysis of unknown pathogens (Figure 12). Over the 10-year period until 2030, we will work to create a cooperative framework and research environment within Japan by focusing on basic research and technological development, as well as domestic information collection and sampling, and build theoretical and empirical models by studying known pathogens to clarify how the risk of pathogen spillover relates to environmental and ecological information and the pathogen infiltration status of livestock animals.

With regard to surveillance and building cooperative frameworks overseas, initiatives will be implemented to tackle the social issues of capacity-building and the formulation of action plans with a view to building cooperative frameworks for the future.

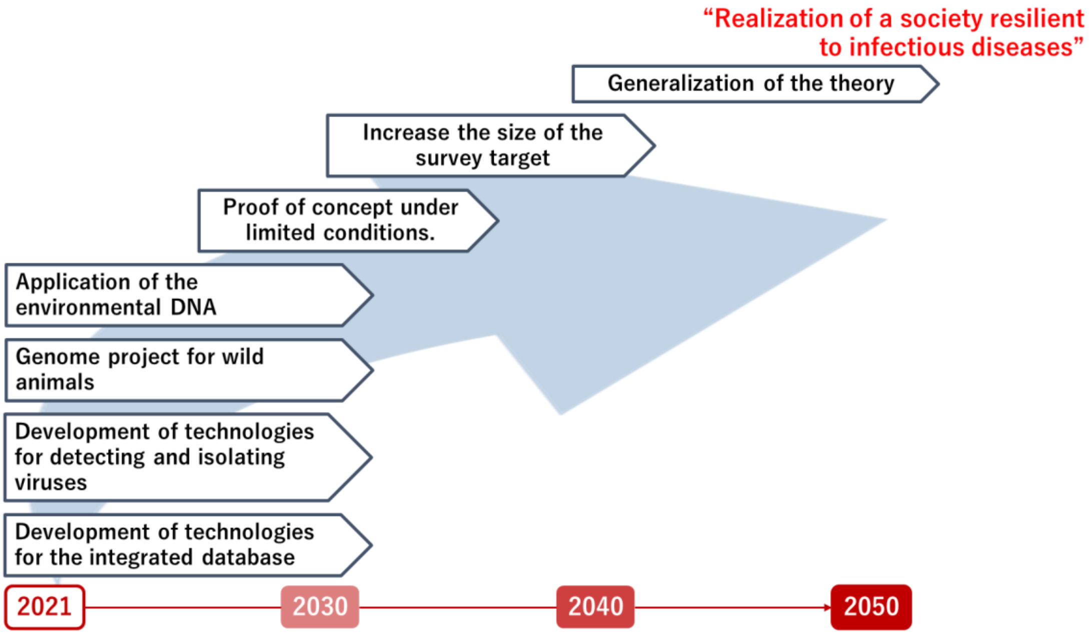


Figure 12. Scenario aimed at achieving the goal of the present project. Basic research and development will be carried out and information collection will start by 2030, after which, large-scale information collection will be carried out and technology to analyze and use the data will be developed.

The specific scenarios for the period until 2030 are as follows:

(1) Technology for the collection of samples and information

Basic knowledge relating to verification of the usefulness of samples other than water, such as soil and air, and the spatiotemporal scales that can be covered by the obtained data, will be collected to make environmental DNA technology applicable to terrestrial animals. In parallel, the project aims to decode the wild animal genome information necessary for designing common primers for gene amplification and identification of animal species from collected gene sequences, thereby putting in place the basic technology for full-scale information collection.

As a means for confirming the precision of information obtained by environmental DNA technology, refinements will also be made to observation methods using conventional technologies such as fixed cameras and image analysis, and both data sets will be used to accumulate information.

The expertise and cooperative frameworks that have been accumulated to date at various research institutions will be used to continue research looking for unknown pathogens in wild animals. To ensure that the research is implemented continuously, the cooperation of the relevant administrative agencies will be encouraged to enable the work to be carried out smoothly and with consideration given to construction of cooperative frameworks in which researchers and collaborators from various fields can benefit from each other.

For the analysis of pathogen genomes and for isolation and culture technologies, the results of technological development will be verified using known pathogens and samples collected in the past, and application will be expanded as needed to samples collected in the future.

The development of software technology will first focus on the development of new methods by using the abundant viral genome information stored in existing databases. The methods that are developed will be applied to the analysis of vast amounts of genetic information amassed from samples collected in field study.

Many technology spin-offs are predicted from the process of technology development described above. For example, environmental DNA technology is an extremely useful tool for ecological research, and is therefore expected to be used in the ecological field. Information from the analysis of wild animal genomes is also expected to be used in fields other than infectious disease research, such as species conservation, evolutionary research, and the search for useful genetic traits harbored by wild animals. Therefore, the technology developed in the present research project is expected to have a ripple effect across a wide range of different fields.

(2) Research on the construction of information collaboration infrastructure

In preparation for future initiatives, information that should be extracted from existing databases and linked will be prioritized, and sequentially stored information will be modified into formats that can be linked. Information on known pathogens such as SFTSV will be integrated to carry out theoretical verification and develop case studies using specific, known pathogens as models, with the aim of developing theories and analysis techniques that can utilize information and conditions related to the risk of pathogen spillover to humans.

(3) Establishment of cooperative frameworks for epidemiological studies

The cooperation of researchers working in areas that include infectious diseases, wild animals, and ecology will be essential for conducting the field study involved in the present research, and we will therefore form a consortium to put in place frameworks for sharing valuable information and samples. We also aim to build systems for managing and storing samples from livestock and wild animals.

For constructing a cooperative framework, taking as a model case a pathogen such as SFTSV that involves multilayered factors is expected to bring steady results. SFTSV is a significant pathogen that causes disease in humans, and it involves factors such as ticks that transmit the pathogen, wild animals that live with the ticks in the natural environment, the environment in which the wild animals live, and livestock animals that are raised in the periphery of this environment (Figure 14). Since there are regional differences in the occurrence of SFTS even within Japan, it is likely to be a useful model case for verifying how each of the above factors work together to be involved in spillover to humans, and conducting verification using a known pathogen will allow the application of the present conception to be verified.

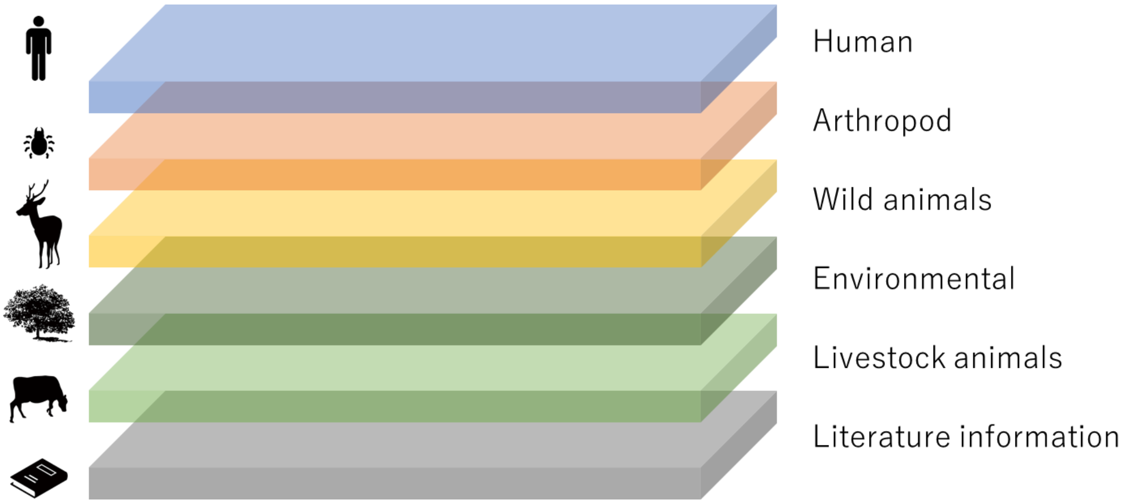


Figure 13. Multilayered factors affecting the outbreak of SFTS. Factors from a range of fields are intricately involved in outbreaks of SFTS, making it a useful model case for research and development in the present project.

While aiming to achieve the above milestones, we will use these technologies to disseminate data from the analysis of known pathogens and the results of analysis under Japanese environmental conditions globally while further expanding the scope of the research to accumulate information on hot spots and other regions around the world for emerging infectious diseases with the aim of achieving the goal for 2050.

3. International cooperation

Large-scale projects to control zoonotic diseases are now being carried out by countries and institutions around the world. However, with research that requires field surveillance or field studies, it is not possible for a single country or project to cover regions across the entire world, including the developing countries that may become pandemic hot spots, to search for unknown pathogens in each of these regions. It is therefore necessary to share roles at the international level and allocate regions of responsibility, as well as to implement the continuity of projects through systematic capacity-building. To achieve this, Japan must build cooperative international relations with individual institutions while building systems for sharing information and samples among nations as a national policy. The implementation of the R&D set out in the present concept will not only serve as a solid foundation for sharing information and results, but also, by enhancing domestic measures against zoonotic disease, be important in contributing to the reduction of pandemic risk in the region and demonstrating international leadership.

As has already been mentioned, Japan has been developing international collaboration centers for many years. As well as continuing these initiatives in the future, Japan will need to participate as a nation in international information-sharing networks such as the Global Virome Project and the Genome 10K Project, rather than simply participating through short-term funding for individual researchers, so that a framework can be built for all domestic researchers to benefit from these networks.

When sampling is carried out for infectious disease research in developing countries, it is essential that relationships of trust be built between the parties (or countries) involved because of problems such as genetic resources. It would be desirable to build a framework for international collaboration that respects and further develops the relationships of trust that have already been built up by individual research institutions.

4. Interdisciplinary cooperation

As already noted, the problem of zoonotic disease is an issue that spans a wide range of research fields and cannot be solved by researchers working alone in specific fields. This initiative will therefore require collaboration across a great many sectors, including from personnel other than researchers, for which a truly diverse, cross-disciplinary cooperative framework will need to be created.

To build a cooperative framework that can be implemented continuously, it is necessary to establish topics that all the researchers who are involved will be interested in and find exciting. There are limits to requesting voluntary cooperation based entirely on goodwill, so it would be desirable to build a framework for everyone participating in the project or consortium to be able to carry out research aimed at achieving the goal while maximizing their own benefit. To achieve this, it will be necessary to reconsider the shape of society to enable the appropriate evaluation of the results and the value of research preparing for unknown infectious diseases, as set out in section 5 below.

5. ELSI (Ethical, Legal, and Social Issues)

As an ethical and legal issue, it will be necessary to reform the vertical relationship of agencies within the administration, as well as their laws, regulations, and systems, which have become a hindrance to smooth research and information-sharing. For example, various administrative procedures have to be followed to conduct sampling from wild animals, but these onerous procedures can be a barrier to the smooth implementation of measures for zoonotic diseases. It may perhaps be necessary to attempt the construction of an administrative system that can maximize the efficiency of research results and infectious disease control. In the field of animal health, although the importance of epidemiological studies of the pathogen infiltration status of livestock animals is recognized, a nationwide system for banking samples has not yet been established because there are also many concerns of reputational damage to specific regions or farmers. Measures such as risk communication, informed consent from people, and the formulation of rules for handling samples are required to solve this problem, and as these cannot be implemented by researchers alone, administrative and political cooperation is essential to establish a complete framework in preparation for an outbreak of a zoonotic disease. Bearing in mind the above issues, it may be necessary to establish a domestic organization to act as a control center within the country, equivalent to, for example, specialist organizations in other countries that carry out infectious disease measures, such as the CDC.

While the importance of measures against outbreaks of unknown zoonotic diseases is recognized, it is difficult to evaluate the monetary value generated by such activities (their marketability and social implementation), and this has undeniably been a factor limiting the rate of R&D in the past. Thus, there is a need for a system to evaluate properly the results of infectious disease measures, not only to achieve the present goal, but also to take continuous measures in the future. In the current value system, the success of a measure against an infectious disease means that drugs or vaccines against that disease are no longer necessary, and the economic value cannot be calculated because no drug market is created. However, it has been calculated that the cost of 10 years of pandemic preventative measures amounts to just 2% of the economic loss from COVID-19, and the ecosystem conservation effects that accompany infectious disease measures bring economic benefits (the concept of the Dasgupta Review)—these are surely evidence of the fruits of measures for infectious diseases. Efforts are needed to explain these fruits to the public correctly so that they can be understood, and a change in the values of the recipients is also necessary.

IV. Conclusion

Based on the foregoing, we propose as a new Moonshot Goal for the post-COVID-19 era, “Realization of a society resilient to infectious diseases by 2050 through the creation of a management system for unknown infectious diseases derived from animals.”

This goal will not only reduce the risk of emerging infectious diseases to humanity, but also contribute to the conservation of the natural environment and ecosystems, and together with initiatives for other Moonshot Goals that address global problems of food, resource issues, and climate change, it is expected to provide insights for solving global issues.

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