Conceptualizing the Bio-Safety Level 4 Location and Management

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Abstract- **In the event of an outbreak of a high risk pathogen, such as hemorrhagic fever or smallpox, it is essential to start treating the patients and controlling infection immediately. It is a real possibility that these most dangerous pathogens be brought into Japan via well developed transportation system or terrorist attacks using biological agents, and they can be dealt with only by special BSL-4 (Bio-Safety Level 4) laboratories that satisfy BSL-4 specified by the WHO [1]. As there are no BSL-4 laboratories in operation in Japan as of 2012, it is an immediate requirement to develop a suitable environment for the operation of laboratories of this kind, in order to maintain effective health risk management for the Japanese people. In this research, we will discuss the necessary conditions for BSL-4 laboratories' operation in Japan.**

Keywords- BSL-4; Location; Management; Biosafety; Biorisk; National Security

I BACKGROUND

It often takes time to identify the pathogen, either artificial or spontaneous, during the outbreak of an infectious disease, such as the 2001 anthrax attacks in the United States or the 2003 SARS outbreak. Anthrax is a pathogen discovered in the mid nineteenth century. It took seven hours after the patient complain to be identified as the pathogen [2]. SARS was new and previously unknown, and it took more than one month to fully investigate the pathogen's characteristics [3]. Fortunately, it was found that these pathogens could be dealt with at research laboratories with the safety levels lower, BSL-2 than BSL-4 [4], and through the application of appropriate infection controls, the spread of the diseases were stopped. Although those outbreaks occurred outside Japan, due to the development of transportation systems and to the risk of terrorist attack, the possible danger of BSL-4 pathogens such as plague or smallpox being brought into the country causing the outbreak of infectious diseases, has been discussed, and need for BSL-4 laboratories has been reported by specialists [5]. In Japan, research laboratories that satisfy BSL-4 were built in Musashimurayama City in 1981 and Tsukuba City in 1984, but neither of them was put into operation, due to either protests by neighbouring residents or pre-construction agreements with them. If a pathogen that requires BSL-4 (BSL-4 pathogen) appears in the country, presently we have to request foreign research institutes to identify the sample, which would require more time than if carried out in the same country. During that extra time period, it would be difficult to carry out an effective infection control, because the characteristics of the pathogen would not be understood. In addition, if we rely on a particular country for the identification, it could affect the bilateral relationship, damaging national interests.

With regard to overseas BSL-4 laboratories, as of March 2012, 33 laboratories in 19 countries are in operation, if buildings and units are also counted. In the 1980s, the constructions of BSL-4 laboratories or the introductions of cabinets that satisfy BSL-4 were started in North America, the EU, and Australia. Laboratories in the EU are the Seventh Framework Programme for research and technological development (FP7) [6] for larger ones, as the construction plan of more comprehensive BSL-4 institutions has been announced. Also, Switzerland, yet to join the FP, has already constructed a BSL-4 site towards the yearend of 2011, and has been conducting joint exercises with NATO and the US 773rd Civil Support Team. In late 1990s, a BSL-4 cabinet was put into operation in Taiwan, while in other Asian countries, triggered by the 2003 SARS outbreak, BSL-4 laboratories or cabinets have been built or installed and put into operation since 2004. There are more currently under construction. In comparison with those countries and regions, in Japan only BSL-3 laboratories are in operation, not having been further developed since the early 1980s. The main reason for the opposition against BSL-4 laboratories is the concern about the effect on environment caused by possible leakage of pathogens [7, 8]. However, it is clear that it is not only in Japan where the BSL-4 laboratories are difficult to put into operation, since attempts to establishing or relocate BSL-4 laboratories, there have resulted in protests by neighbouring residents for the same reasons in other countries as well.

II AIM OF THIS RESEARCH

In this research, in order to put BSL-4 laboratories in operation in Japan, we will propose to utilize those laboratories not only in emergencies but also during normal times, through clarifying what environmental factors for the operation there are in each of different types of candidate locations, viz., inland areas, isolated islands, and on the sea.

We will also discuss the distinctive conditions for the operation in the social environment of contemporary Japan.

III Methodology

By literature research, we will identify and examine conditions expected to exist for the operation of BSL-4 laboratories in each type of locations. Adding to this, we will investigate possible ways to utilize BSL-4 laboratories in normal times.

BSL-4 laboratories considered and examined in this research are comprehensive laboratories equipped with infrastructures such as the facilities to retain people who have had close contact with infected patients; facilities to treat carriers and infected patients; those to perform autopsies and treat the bodies of the deceased; an emergency power source that enables the laboratory to operate during unforeseen events; a water supply and water treatment system able to deal with contaminated water; the facilities for medical waste disposal, and; the headquarters to manage these functions accurately and efficiently.

IV Result

A. Locations

Considering the present difficulties in establishing BSL-4 laboratories on land, we examined the option of having them operate at sea area within Japan’s territorial waters. In the following, we will explain the results of our comparison between the operations of BSL-4 laboratories in inland areas, on isolated islands, and at sea, based on the different conditions for operations of BSL-4 laboratories according to the types of locations shown in Table Ⅰ.

TABLE Ⅰ CONDITIONS AND FOR OPERATIONS OF BSL-4 LABORATORIES ACCORDING TO THE TYPES OF LOCATIONS

Location / **Condition**		On land			At the sea (within territorial waters)
		Island area	Isolated island		
Residence		Yes	Yes	No	No
Land acquisition		Required (excluding state-owned lands)			Not required
Stakeholder		Neighbouring municipalities and residents		People working in surrounding area	People living in Japan (especially those who residing in costal areas and working in the sea areas)
Consensus development		Required			Not required
Means of transportation to the site		Auto-mobile Airplane	Ship Airplane (Automobile)		Ship Airplane
Relocation of laboratory		Not possible			Possible
Time of disaster	**Earth-quake**	Directly affected by ground movement			Not directly affected by ground movement
	Leakage of patho-gens and terrorist attack	Possibility of contamination of surrounding areas with pathogens that may remain until the areas are dis-contaminated			Although surrounding waters are contaminat-ed with pathogens, they defuse in the water thereby decreasing their concentration

Comparing the operations in inland areas or in isolated islands with those at sea, since land acquisition is not required in the case of sea operations, not only would there be no acquisition cost, but also the time before construction work starts can be shortened, since we would not have to spend time in acquiring land. In addition, in the event of an earthquake, while laboratories on land would be affected by ground movement directly, thereby requiring that they meet legal earthquake resistance standards, those on the sea are less reactive to ground movement, and so their structure could be simpler than those on land. For these reasons, we think that sea-based BSL-4 laboratories can reduce construction costs and shorten the time for construction, while having high earthquake safety.

In establishing and operating a BSL-4 laboratory, it is necessary to develop consensus with stakeholders such as neighbouring municipalities and residents if it is to be built in an inland area or on an inhabited isolated island. If it were to be built on an uninhabited isolated island, the subject of consensus development would probably be those who are doing business in surrounding waters, such as persons engaging in fishery. In the case of a laboratory on a floating body at sea, if it is moored at a certain place then the subject of consensus would be the same as in the case of an uninhabited isolated island, while if it moves around within Japanese territorial waters, e.g. if it is built on a ship, we should consider the people living in Japan, especially those who reside in coastal areas, the subject of consensus.

If a BSL-4 laboratory was in an inland area, the means of transportation would be automobiles and airplanes. In the case of an isolated island, they would be ships and airplanes. Automobiles are also a possibility if the island is connected with land by a bridge. To a sea laboratory, ships and airplanes would be the only means of transportation.

With a sea laboratory, since it is possible to relocate the laboratory itself, we would be able to choose the location of operation according to the situation, such as weather/sea conditions and the location of outbreaks. In addition, the probability of a terrorist attack may be lowered by changing the laboratory's location at irregular intervals.

In the case of pathogen leakage or smuggling caused by humans, such as operational errors or terrorist act, if it occurs on an inland laboratory, the pathogen may remain until the leakage area is decontaminated, or it may remain even after decontamination, according to the characteristics of the pathogen. On the other hand, if the pathogen leaks into the sea, it would diffuse in the water, thereby decreasing the amount of pathogen per volume, reducing the likelihood of infections. However, as the amount of pathogen per volume necessary to cause infection differs according to the characteristics of pathogens, smaller numbers of a pathogen per volume do not necessarily mean lower infection rates.

When constructing a BSL-4 laboratory on the sea, it can be built on a ship, or on a floating body without a self-propelling function.

While ships can easily stay at one particular location, it must be stationed by mariners, as stipulated by the Mariners Act/Ship Act. As BSL-4 laboratories deal with the most dangerous pathogens, it is desirable to reduce the number of personnel involved in the laboratory operation as much as possible. In addition, we have to take into account labor costs for the mariners and the running cost of internal combustion engines.

In order to move a floating body in the manner of a ship, there is an option of towing a BSL-4 laboratory by tugboat. Since there are many 3,000 ps to 4,000 ps tugboats in Japan, with the largest one being 10,000 ps, we think that, with prior consultations with the owners of those boats, it is possible to prepare conditions for moving floating bodies.

To have a ship or a floating body stay at a certain location, the options appear to be twofold: 1. anchoring with fixed ropes, and 2. keeping the location by operating screws according to information from GPS. For anchoring, the anchor point and fixed ropes must be strong enough for the whip/floating body to anchor with everywhere the BSL-4 laboratory goes. We also have to think about the maintenance cost of those points and equipment. When we tow floating bodies, we also have to consider sea conditions. We calculated the probability of sea conditions being good enough for towing in each of five sea areas we posited: the Seto Inland Sea; Pacific offshore Shikoku; Pacific to the east of Shionomisaki Cape; Western Kyushu; the Japan Sea from Akita to Tottori Prefecture. The result was that, except for the Japan Sea in winter time when wave conditions are most severe with the probability of towing condition less than 30%, in all the sea areas (including the Japan Sea in seasons other than winter) towing is possible throughout the year with the success probabilities as high as over 90 % [9]. Among those areas, the Seto Inland Sea has the calmest sea conditions throughout the year, so with that aspect it is most suitable for establishing a BSL-4 laboratory. However, when we want the laboratory to be moved from one place to another, the Seto Inland Sea may not be so appropriate for operation, because it contains many islands and some important sea routes, and there are environmental laws, most notably the Seto Inland Sea Act.

With regards to the sea area of Western Kyushu, since the distances from neighbouring countries (the Eurasia continent) are shorter than those to the Pacific-side sea areas, it would become the target of attack, such as a terrorist attack, more easily than those areas.

Assuming BSL-4 laboratories are to be operated according to Japanese laws, laboratories on ship or on floating bodies must be situated within the territorial waters, which is within 12 nautical miles (22.224km) from the base line. Adding to this, we should take into account that the operation area has to be outside harbour areas, which are specified so in Ports and Harbours Act (Section 3 in Article 2), since there are harbour facilities, including sea routes, in those areas.

B. Examination on Management

1) Function of BSL-4 Laboratory:

Upon the outbreak of infectious disease, the spread of infection can be controlled by isolating patients and the people who had contact with them, and in the case of some pathogens, by vaccination. In order to perform infection control appropriately, we expect BSL-4 laboratories discussed in this research to have the following functions and structure.

In addition to experimental facilities to identify the pathogen, the laboratory needs to have retaining facilities, treatment facilities, and those to perform autopsies and treat the bodies if there are fatal cases. We have to be aware that each function should have two or more sets of facilities, because, in order to meet the BSL-4 standard, those facilities have to be well maintained, and have to keep functioning even during maintenance. Each facility should have an independent power source and water supply, as well as infrastructures for water treatment and waste disposal. Also, second sets of or independent infrastructures should be considered for the case of emergencies. Adding to these, it is necessary to have a headquarters to manage these facilities in an organized manner. We must develop a system that can function in any situation.

According to the degree of infection, patients are taken into retaining or treatment facilities or facilities. If a person had contact with infected people, that person would be taken into the retaining facility. Since the maximum latent period of Class 1 infectious diseases specified in the Infectious Diseases Act is 21 days, we should consider what to prepare in the environment with 21-days stay in the closed area. For example, communication infrastructures by which people can contact the outside, and recreation facilities could be offered. If a person in the retaining facility were diagnosed as having no sign of the infectious disease, that person would go back to the normal environment. If disease symptoms appear, the person would be accommodated into the treatment facility.

Because of this, retaining facilities have to have a depressurized room where individuals can wait before moving out.

In the treatment facilities, the environment should enable the following criteria: to keep a certain distance between patients, to make the pathogen move in one direction without stagnating by air-conditioning, to purify the air by layers of filters before exhausted to outside, to pressurize and heat-treat drain water, and to incinerate waste. All medical personnel are to wear a special suit when contacting patients, and the air pressure in patient rooms is to be kept low in order to prevent the pathogen from spreading to other areas. These are the conditions required for any BSL-4 laboratories and must be met without question. Adding to these conditions required for BSL-4 laboratories, there must be a greater number of medical instruments such as artificial respirators than other types of laboratories. A patient in the treatment facility would go back to the normal environment when fully cured. If one passes away, he/she would be taken into an autopsy and corpse disposal facility.

With autopsy and corpse disposal facilities, like the treatment facilities, the autopsy facilities must meet the BSL-4 standard in order to prevent the medical staff from becoming infected. In addition to performing autopsies, they must be able to isolate and temporarily store pathogens. As for body disposal facilities, they can prevent the leakage of pathogens by incinerating the corpses and bringing them outside. As there may be cases that the body of the deceased is incinerated without the family seeing it, a contact system with patients' families needs to be established, especially taking into account Japanese traditional values.

Experimental facilities are also required to meet the BSL-4 standard. They identify samples retrieved from the points of disease outbreak, retaining facilities, or treatment facilities. Pathogens are stored or incinerated. As the number of samples would increase as infections spread, the workloads for medical staff would surely become substantial. Since medical staff have to work in special suits, their bodily movements are highly limited, and they would be under a lot of mental stress. For these reasons, their work hours should be limited to a few hours per day, and we need to be able to increase the number of medical staff according to the situation. Since medical staff would have to stay at the BSL-4 laboratory without going out, it is highly important for the laboratory to have refreshing facilities and communication infrastructures to keep in contact with the outside world.

If the power supply stops, all of the facilities with the functions described above could not remain safe against pathogens. Needless to say, each facility must have an emergency power source. Adding to that, we would consider providing each facility with an independent electric generator. Likewise, water supply, water treatment, and waste disposal should have back-up facilities for the times when workloads are beyond their capacities. Infrastructure facilities with those functions should have back-up system that can operate independently.

In order to make the BSL-4 laboratory with multiple functions explained above operate efficiently in controlling infections, we would put the headquarters with risk-management-hub function. The headquarters must maintain its functions without halt under any circumstances.

2) Training of Specialists and Work in Practice:

Specific trainings are required for those who have contact with pathogens at BSL-4 laboratories, such as doctors, nurses, pharmacists and laboratory technicians. If a BSL-4 laboratory functions in normal times as a place for training of medical staff, in emergency both trainers and trainees can deal with real situations there. This is a realistic idea because, we think that, in real emergency situations it is not necessary that all the staff who work in them have all the relevant knowledge and skills, since what we need in dealing with those situations are the person in command who have the high level of knowledge and skills, and staff who have knowledge and skills sufficient for performing the tasks they request. In order to realize such a training environment, it is necessary to implement a well planned program that is ready for emergency even in training sessions in normal times, while taking into account the numbers and the levels of trainers and trainees at the BSL-4 laboratory.

In case of an emergency, it is evident that well trained medical staff would be necessary, but also of necessity would be logistics. Without being able to refill food and clothing for both the medical staff and the medical detainees and to provide medication and medical instruments for medical practices, emergency operations would be impossible. Therefore, during normal times, it is crucial to have trainings under various scenarios simulating cooperation between BSL-4 sites and the outside agencies and to have operation manuals constantly revised for best use.

3) Standard of Facility Management:

As mentioned earlier, Japan has a full-fledged program for developing scientists who can operate in BSL-4 sites. One possible enhancement to this would be management of scientists handling BSL-4 pathogens and personnel surrounding the scientists.

In order to establish a management standard for biorisk safety, EU's European Committee for Standardization (CEN) has openly asked for public comments concerning the Laboratory Biorisks Management Standard (CWA:15793: 2008) in 2009. The agreed standard is not based on specific pathogens as categorized by the WHO. Rather, the standard focuses on inherent risks according to environmental changes, e.g., when introducing new pathogens to a laboratory, when altering the layout design of a laboratory, when switching staff members or inviting over visitors, when drastically changing existing security management standards, etc.[10] The standard gives weight to human factors, and before any public involvement, it calls for the organization to have its executive board understand the responsibilities pertaining to the installment of the standard, to simultaneously establish a management standard for biorisks specific for the organization, and to continuously implement educational activities. As the CEN's standard is the first ISO-approved standard specific to biorisks, chances are very high that it would permeate internationally.

C. Use of BSL-4 Laboratories in Normal Times

4) Estimated Cost for a BLS-4 Laboratory:

According to Ministry of Health, Labour and Welfare, the cost for establishing a BSL-4 laboratory of a certain scale is estimated to be 12.7 billion Japanese yen [11]. This includes the construction cost and design management fees of facilities of laboratory, and cost for research instruments such as positive-pressure suits, experiment cabinets, and electron microscopes. The following costs are not included: land acquisition cost; cost for construction and process-management of primary infrastructure facilities; cost for various procedures; consumption taxes and so on. Adding to that amount of cost, once the laboratory starts to operate, there is running cost that is estimated to be approximately 550 million Japanese yen a year. The amounts is this much due to factors such as: experiment instruments are to be order-made; gloves can last just about one year; microscopes will be corroded because of fumigated formalin gas and will have to be replaced; it takes as long as two months to clean air-conditioning facilities; maintenance of doors and sealing requires significant amount of work, and so on and so forth.

5) Necessity of Use in Normal Times:

It is not a realistic political option to deal with the risk of outbreak of infectious diseases that require BSL-4 laboratories only by hardware measures. If hardware measures alone are taken against the risk of disasters caused by infectious diseases with highly dangerous pathogens, since when they occur is uncertain, such investment in Japan could become a target of criticism as of no use insofar as they do not occur. Thus, it is desirable to propose a plan that has a positive use of BSL-4 for society even in normal times as well, while being able to reduce the damage of disaster caused by outbreak of infectious disease with a highly dangerous pathogen.

6) Training Specialists:

As of 2011, Japanese government offers two specialist training programs at a national-level: one is run by National Institute of Infectious Diseases and National Institute of Public Health, both of which are affiliated to Ministry of Health, Labor and Welfare; the other is run by Ministry of Education, Culture, Sports, Science and Technology.

The course by National Institute of Infectious Diseases and National Institute of Public Health is called FETP (Field Epidemiology Training Program), aiming for training specialists in field epidemiology. Similar programs have been implemented in 48 countries. Upon the prevalence or the mass outbreak of an infectious disease, specialists of field epidemiology grasp the facts and investigate the cause quickly and accurately. FETP started in 1999, aimed mainly at doctors who had a degree in pathology, and since then has trained 41 specialists by March 2010. Adding to doctors, trainees have been with occupations including pharmacist, nurse, veterinarian, and clinical technologist. At present, it trains mainly doctors. The content of the program includes epidemiological learning such as study on and learning epidemiology of infectious diseases, analyses and evaluations of surveillances of infectious diseases, and practical training. It also includes training on risk communication skills such as how to announce information about infectious diseases. A number of other countries also have FETP, so there is a program offered in cooperation with the FETPs in those countries as well. One reason that FETP was started in Japan can be the fact that Japanese medical education system focuses rather on pathology and there is no university department specialized in the epidemiology of infectious diseases.

The program by Ministry of Education, Culture, Sports, Science and Technology started in fiscal year 2005 as the Program of Founding Research Centers for Emerging and Re-emerging Infectious Diseases. Twelve research centers in six Asian countries and two African countries, and eight universities in Japan cooperated in that program and completed its five-year plan achieving the goals such as accumulating basic knowledge about emerging and re-emerging infectious diseases and sharing research equipment and resources. Since fiscal year 2010, J-GRID: Japan Initiative for Global Research Network on Infectious Diseases has been running as phase 2 [12]. It is also a five-year program, ending in fiscal year 2014. As of March 2012, 8 universities and 2 laboratories from Japan have joined the program at 12 sites in 7 Asian countries and 3 sites in 3 African countries. As research institutes in the twelve overseas centers have BSL-4 laboratories, Japanese researchers are deepening their knowledge by studying infectious diseases not seen in Japan directly at all of those centers.

Before those national-level programs, domestic research institutes also had been cooperating with overseas research institutions and organizations independently in order to gain knowledge of infectious diseases, and at individual level there are quite a few doctors and medical workers who are studying overseas. Specialists who learned overseas are actively engaging in the activities of teaching younger people in Japan, chiefly in scientific societies and voluntary organizations. The needs for knowledge of infectious disease has increased in the country, especially after the 2003 SARS outbreak, and there have been active information exchanges between nurses, pharmacists, and laboratory technicians, who are most needed in outbreaks of infectious diseases. It seems that a foundation of ways to deal with infectious diseases in Japan is being formed among non-doctor medical workers as well.

Practical training at BSL-4 laboratories is still not possible in Japan, and so we are depending on foreign countries to have one. If BSL-4 laboratories are put into operation, surely we can train specialists there in normal times to develop more effective measures to deal with infectious diseases than what we have at present, whereas in emergencies we can have an improved infection control by the trained specialists.

V CLOSING OBSERVATIONS

In 1981, a globe box that satisfied the BSL-4 standard was installed in the National Institute of Infectious Diseases in Musashimurayama City. Since then, the neighboring residents have been protesting against the BSL-4 facility operation in the institute around which public facilities including hospitals, educational institutions, and parks are scattered. The National Institute of Infectious Diseases was established in 1961 in Musashimurayama, before the instalment of the BSL-4 facility, and since then has been functioning as a research laboratory for viruses. Given the level of science and technology back in 1961 the emergences of high-level viruses, which surprise even us today, would have been impossible to predict. In the social environment back then, it might have been thought to be natural to have a new state-owned organization, viz., the research institute of infectious diseases, in the area surrounded by public facilities. The time changed after that: pathogens of BSL-4 level emerged inducing establishment of BSL-4 laboratories, and in 1981, a BSL-4 facility was installed in the National Institute of Infectious Diseases that was a virus research laboratory. Although the importance of consensus development and effectiveness of BSL-4 concerning public utilities are acknowledged today, we suspect that in 1981 there may not have been social environment in which consensus for installing a BSL-4 cabinet in an existing institute could be developed. In the same year, a BSL-4 cabinet was installed in the Institute of Physical and Chemical Research (a public corporation at that time, an independent administrative institution today) in today's Tsukuba City, as a bio-resource center was set up at the institute. However, since an agreement had been made with neighbouring residents before the BSL-4 cabinet managed to start operating, it has not yet been put into operation as of March 2012 as a BSL-4 site, likewise to the National Institute of Infectious Diseases.

In 1981, the situations were not like today with regards to the method of consensus development, the amount of information about dangerous facilities the people in Japan had, their awareness of them, and the financial situations of local governments. In 2010, background social environments are quite different. Experience has been built up with regards to consensus development concerning public utilities, mainly through the cases of nuclear related facilities and other unwanted facilities, thereby Japan's own know-how has been accumulated. Also, by the development of communication technology, the environment for the people to gain relevant knowledge about infectious diseases and laboratories has improved, causing the change of their awareness from that in 1981. Meanwhile, because of the aging problem and other factors, it is clear that the financial difficulties of local governments will remain to be a significant issue. There can be some cases where local governments agree to have an operating BSL-4 laboratory, after considering well the merits and demerits resulting from inviting the laboratory and discussing thoroughly with the laboratory side.

The necessity of BSL-4 laboratory operation has been well discussed by specialists. Clearly, an important factor in order to put BSL-4 laboratories into operation as soon as possible is to obtain consensus of the people of the country. BSL-4 laboratories require vast investment on hard infrastructure. Because of that, we think that it is important to consider a consensus-development model that takes the structure of beneficiaries into account, elucidating BSL-4 laboratories' positive use in normal times and effectiveness in reducing the damages of disasters.

On the backdrop of such social conditions, Nagasaki University in May 2010 has expressed its intention to establish a BSL-4 site. The Nagasaki prefecture is unique in that it has been permitted to actively maintain contact with overseas countries since the 17th century despite the seclusion policy of the then government, and as a consequence, has been a region where infectious diseases often spread around. By the 19th century, the region has become a center for research on infectious diseases and a port for the most innovative medical knowledge and technologies. Also, Nagasaki has suffered from an endemic disease in the island areas. As such, Nagasaki University has commenced its research on infectious diseases in 1942 and has greatly contributed to the prefecture, as well as to the entire nation, in terms of countermeasures against infectious diseases. The university has also been engaging in consensus building activities for operation of BSL-4 site, annually holding about 10 lectures customized for local residents on infectious diseases. It is clear that Nagasaki University's move to establish a BSL-4 site is based on experience and achievements developed over many years.

BSL-4 sites cannot be operated merely by specialized scientists. Cooperation with outside organization in areas such as logistics, as well as support from the general public, is necessary. Moreover, safe and smooth management requires establishment of a standard, and only when trainings and revisions of manuals are conducted during normal times would BSL-4 sites exert its full capabilities during emergency times. Discussions concerning BSL-4 have largely changed since the 1980s, and many see BSL-4 sites not just as countermeasures against epidemics, but as countermeasures for terrorist attacks, in other words, as national defense sites. It is now time for Japan to serious consider operating BSL-4 sites domestically, involving multiple organizations, such as Ministry of Health, Labour and Welfare, Ministry of Defense, National Police Agency, Japan Coast Guard, Fire and Disaster Management Agency, etc., upgrading Japan's unique framework and management standard, and bringing into view international contribution in the East Asia region.

VI CONCLUSION

The most important point in BSL-4 laboratories' operation is that discussions should not be restricted to the domestic scope but take place across the borders, chiefly involving liaisons with organizations in Asia, Europe, and America, as well as the WHO. Currently, Japan is discussing the establishment of BSL-4 laboratories in the context of pathogenic research, and both MEXT and MHLW are conducting such researches primarily in the field of pathology. As MEXT is also conducting research in the field of bio-security, it is crucial for future management of BSL-4 laboratories that MEXT liaises with Ministry of Defense in such research and that all relevant ministries prepare to collaborate together once laboratories' operation commences. Our future research will focus on the bio-security aspects of the necessary conditions for BSL-4 laboratories' operation in Japan

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