

A Three-Year Experience to Implement Laboratory Biosafety Regulations in Taiwan

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Abstract

In 2003, Taiwan experienced a laboratory-acquired infection (LAI) of Severe Acute Respiratory Syndrome (SARS). To prevent similar LAIs from happening again, the Centers for Disease Control of Taiwan (Taiwan CDC) established a set of regulations for laboratory biological safety. The "Regulations Governing Management of Infectious Biological Materials and Collection of Specimens from Patients of Communicable Diseases" was promulgated in September 2005 to provide a legal basis for the control of infectious biological materials and management of related laboratory biosafety issues. This set of regulations has three core principles: (1) self-management, (2) autonomous notification, and (3) periodic assessment. With nearly three years since its implementation, this set of regulations has been duly modified to become easier for laboratories to follow. As long as industry, government, and academia continue their efforts and cooperate to design, build, and maintain safe biological laboratories, as well as instill a culture of safe laboratory practices, the laboratory-acquired infection rates in Taiwan will be minimized or even eliminated.

A Retrospective View of Laboratory-acquired Infections in Taiwan after the SARS Outbreak in 2003

1. Laboratory-associated Infection of Dengue Fever: In April 2004, a graduate student at a university in central Taiwan, who was performing research on genes responsible for anti-bacterial proteins in the mosquito species *Armigeres subalbatus*, suddenly became infected with the local Type 1 Dengue Fever. The Taiwan CDC determined that the mosquito-rearing area in his laboratory was not properly designed to effect a complete separation of the infected, virus-bearing mosquitoes from the healthy ones. The entrance to the mosquito-handling room was also not equipped with double screening in order to prevent any Dengue virus-borne mosquitoes from escaping from the room. This made it possible for the mosquitoes to transmit Dengue Fever to the laboratory personnel. After this incident was revealed, not only did the Taiwan CDC instruct this laboratory to immediately halt all related empirical studies, but it also developed and disseminated the publication, *Guidelines for*

Laboratory Management and Operations on Invertebrate Animals, to all similar laboratories in Taiwan.

2. Laboratory-associated Infection of Shigellosis: In August 2006, a graduate student in a university in central Taiwan who was working with *Shigella* in his research fell victim to Shigellosis. An inspection of the incident by the health authority suggested that it may have resulted from two possibilities. First, the student may have had little knowledge of the hazards associated with his work or how to minimize the risks incurred by these hazards by using good laboratory practice. Second, the design of the engineering controls in the laboratory may have been inappropriate. The Taiwan CDC thus provided the following list of recommendations to improve laboratory safety in this laboratory:

- All operations and cultivation of *Shigella* should be conducted in a specific area of the laboratory.
- The manual sliding door inside the laboratory should be automated.
- The hand-washing basin in the working area should be foot operated.
- The laboratory workers should be trained to practice good microbiological procedures.

After the laboratory complied and implemented the necessary improvements and training as recommended, the Biosafety Committee of this university in a documented report to the Taiwan CDC, reassessed this laboratory and granted it permission to resume its work.

The Legislation for Laboratory Biosafety

Long before the occurrence of the laboratory infection of SARS, the Taiwan CDC had already recognized the importance of instituting proper management practices for the use of infectious materials, as well as prudent laboratory and biological safety principles. The laboratory-acquired SARS incident highlighted the necessity of regulating research performed with infectious materials; therefore, an entirely new set of regulations entitled "Regulations Governing Management of Infectious Biological Materials and Collection of Specimens from Patients of Communicable Diseases," was developed and introduced on September 26, 2005. This law came into effect six months later on March 26, 2006. These Regulations contain 19 Articles whose core principles are self-management, autonomous notification, and regular assessment of laboratory activities.

Self-management

Any installation unit using or storing Risk Group (RG) 2 and above infectious biomaterials shall have an authorized person or committee responsible (such as a biosafety committee or biosafety officer) for managing and supervising the laboratory biological safety issues.

Autonomous Notification

In the event of laboratory incidents involving infectious agents, the installation units shall immediately report this event to the Taiwan CDC. Any modifications (new laboratory additions to the agent inventory, changes in experimental protocol, destruction of organisms, or sharing with collaborators) of RG3 and above infectious biological materials may be made only after they are approved in advance by the Taiwan CDC.

Regular Laboratory Assessments

The Taiwan CDC shall have an annual inspection of each BSL-3 laboratory and above in operation so as to review the ongoing operations and management of each laboratory.

Status Quo of Laboratory Biosafety in Taiwan

From experiences acquired during the resolution of the above-mentioned laboratory infection incidents, the Taiwan CDC realized that either the involved laboratories were not operating at the proper biosafety level, or that the workers were not properly trained to work with the organisms in the laboratory. Before 2006, there was no compulsory requirement for laboratories storing and/or using RG2 and above infectious biological materials to establish any biosafety-managing programs; however, the new "Regulations Governing Management of Infectious Biological Materials and Collection of Specimens from Patients of Communicable Diseases" clearly state that all laboratories storing or utilizing RG2 and above infectious biomaterials must have a biosafety committee or a biosafety officer, depending on the size of the affiliated laboratory (i.e., if the operating staff has five or more members, a committee shall be established; but if the number is less than five, then a designated biosafety officer shall be responsible for managing the laboratory biosafety program). By the end of 2007, 291 laboratory units had established their biosafety committees, another 62 units had appointed their biosafety officers, and all of them had completed the required registration with the Taiwan CDC.

Ever since the implementation of this set of regulations, whenever a laboratory unit introduces or changes an experimental protocol for a BSL-2 laboratory or higher, or renovates or constructs a new laboratory, it must first get approval from the unit's biosafety committee or biosafety officer. If the laboratory intends to col-

laborate with another laboratory on a research project involving RG2 or higher organisms, then prior approval has to be granted by the biosafety committee or officer of both laboratories. For any status change or modification of RG3 and above infectious biomaterials, a report and approval by the Taiwan CDC are required in addition to approval by the biosafety committees. In 2007, the CDC received notification of 57 cases of status changes for RG3 and above infectious biomaterials. Through this piece of legislation, the managing of RG2 and above infectious biomaterials in Taiwan, including the transfer of biological materials, is now a much safer established practice.

The fact that the SARS laboratory-acquired infection incident took place in Taiwan had cast much doubt as to the effectiveness of the Taiwan CDC to oversee the safe management of laboratories in general and that of laboratories designated as BSL-3 and above in particular. Before the year 2003, Taiwan had only three BSL-3 laboratories and one BSL-4 laboratory; however, at the end of 2007, there were 21 BSL-3 and above laboratories in Taiwan, and 16 of them had passed inspection by the Taiwan CDC and begun operation. After each laboratory opening, the Taiwan CDC would conduct an annual on-site inspection. Any deficiencies spotted during the inspection would be corrected or improved by the unit within two months, and those deficiencies would then be reevaluated at the next inspection. By implementing this continuous inspection process, the laboratory would be reviewed and improved continuously with regard to biosafety issues.

Revision of Regulations Under the New Act of 2007

Although the original "Regulations Governing Management of Infectious Biological Materials and Collection of Specimens from Patients of Communicable Diseases" came into force less than two years ago, industry, government, and academic professionals in various related fields have already voiced different views and opinions. A new amended version of its parent law, the "Communicable Disease Control Act," was promulgated on July 18, 2007, so a revision of this subsidiary law, scheduled to take effect by the end 2008, has also been worked on at the Taiwan CDC with the following intended changes:

1. The title of the Regulations will be revised and changed to "Regulations Governing Management of Infectious Biomaterials and Laboratories."
2. The original biosafety management regulations combined the risk group of a biological agent with the appropriate laboratory biosafety level (i.e., an RG2 disease-causing pathogen shall be operated in a BSL-2 laboratory and a RG3 disease-causing pathogen shall be operated in a BSL-3 laboratory). However, the risk group of

an infectious biomaterial does **NOT** always necessitate assignment to a specific biosafety protection level. Rather, the risk group should relate to the specific risks of the operation being performed (such as large-scale cultivation, PCR, or microscopic diagnosis) and whether these manipulations of the organism present sufficient risk of exposure to warrant assignment to a given biosafety level. Thus, the context is to be revised to reflect this management change (Table 1).

3. Over the past decade, Taiwan has focused much of its energy on learning about and creating innovative business ventures in order to establish an intellectual type of entrepreneurial society. One major approach to this grand scheme was to promote the operation of incubation centers for various technologies and skills. Currently, the majority of such centers are located on university campuses. Since such biological/technology research and development projects carried out at those on-campus centers may be entirely or partly financed and co-sponsored by outside constituents and may often use agents in RG2 and above, an amendment of the Regulations was added to address these outside partners in a given laboratory unit. The amendment states that should non-facility members work with infectious materials within the facility, those users and their operations are strictly subject to the management jurisdiction of the laboratory unit.

Based on the requirement for biosecurity, the original text of the Regulations will now include that the inventory of all RG2 and above infectious biomaterials at the laboratory should be accounted for periodically. Any discrepancies found during the inventory process should be reported to the unit's biosafety committee or design-

nated biosafety officer. Discrepancies involving RG3 and above infectious biomaterials must be reported immediately to the Taiwan CDC as well as to the local health department.

Conclusion

Along with continuous biosafety education as well as experiences dealing with laboratory infection incidents, Taiwanese laboratory workers have gradually become more conscious of and cognizant about laboratory biosafety. Some of the positive changes that have occurred as a consequence include:

1. Negligence of individual vs. responsibility of the laboratory unit: After the 2003 SARS laboratory infection incident, the news media appeared to focus on the individual involved in the incident. Little attention was given to whether there was any negligence in the management of the laboratory or the institution, or if either should be held responsible. Similarly, in the 2004 Dengue Fever laboratory infection case, only the laboratory Principal Investigator was interviewed by the Taiwan CDC. It was interesting that the university already had a biosafety committee, but the committee did not investigate the exposure. Now, however, the Regulations implemented in 2006 stipulate that the biosafety organization of an installation unit should bear the burden of managing and supervising all the biosafety concerns at the laboratory. Therefore, when the Shigellosis laboratory infection occurred later that year, the biosafety committee of that university actively participated in the investigation and discussion, demonstrating that the biosafety committee of this unit organization had begun to operate effectively.

Table 1

A comparison of laboratories of various biosafety levels needed to operate with Level 2 and above infectious biomaterials.

Operation Risk Level	Infectious Biological Materials			Inactivated Biomaterial ^(b)	Noninfectious Biomaterial ^(c)
	Cultivation ^(a)		Non-cultivation Process		
	≥ 20 L	< 20 L			
RG2	BSL2 ⁺ or above	BSL2 or above	BSL2 or above	BSL1 or above	BSL1 or above
RG3	BSL3 or above	BSL2 ⁺ or above	BSL2 or above	BSL2 or above	BSL1 or above
RG4	BSL4	BSL4	BSL3 or above	BSL2 ⁺ or above	BSL2 or above

(a) Cultivation: When HIV or HTLV is propagated or cultivated *in-vitro* in a BSL-2⁺ laboratory, the total volume has to be kept under 200 ml, and the total number of individual virus should not exceed 1×10^9 . As to the cultivation of SARS virus or new H₅N₁ type influenza virus, no matter how big or small the volume will be, it must be done in a BSL-3 laboratory.

(b) Inactivated biomaterials: This means that the originally pathogenic biomaterial has gone through certain inactivation processes, but is short of being verified by some reliable methods (such as culture method) to assure that it's indeed inactivated.

(c) Noninfectious biomaterials: This means that the biomaterial has gone through certain inactivation processes and has also been verified by some reliable methods (such as culture method) to assure that it's indeed inactivated.

2. Passive vs. active effort to coordinate the attitude of the laboratory workers and the installation unit: During the two investigations of laboratory infection incidents before 2006, laboratory personnel were not willing to cooperate with the investigation. The laboratory personnel assumed that investigators from the health authorities were accusatory and looking for excuses to have them penalized; therefore, they were uncooperative at the interview sessions. However, with proactive and sustained laboratory biosafety education and training and the outreach campaign launched by the Taiwan CDC over the past few years, laboratory workforces have gradually realized that whenever a laboratory infection occurs, the purpose of the investigation that follows is to find the root cause and provide solutions to rectify the problems that caused the incident. Once this was realized, the involved unit's biosafety committee actively cooperated with the investigation and did its best to correct the deficiencies based on the investigation findings and to follow the recommendations provided by the outside investigators.

3. Passive investigation vs. active notification: The Taiwan CDC learned about the three aforementioned laboratory infection incidents from physicians who report all suspected cases of communicable diseases. This is followed by onsite epidemiology investigations and confirmed by laboratory assays. None of the laboratory infection incidents were voluntarily reported to the Taiwan CDC by the laboratory. Then in January 2007, a research institute located in Northern Taiwan detected a suspected laboratory infection outbreak of influenza vaccine strain H5N1, and instead of covering up the incident, it immediately reported the finding to the Taiwan CDC. Although this incident later turned out to be false, it did demonstrate that Taiwan laboratories have evolved into

becoming more responsible and proactive with regard to the biosafety of their own laboratory.

4. The Taiwan CDC will continue its efforts to reinforce: The functioning of all laboratory units' biosafety organizations, whether a committee or a designated individual, to campaign and aid their laboratory personnel's internal educational training program and to carry out emergency response drills related to laboratory biosafety incidents. Hopefully, all these efforts will further promote a sound laboratory biosafety management system, elevate the importance of the Taiwan laboratory biosafety standards, and advance Taiwan towards the target of a zero incident rate for laboratory-acquired infections.

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