Audit Report for Laboratories of Biosafety Level 3 and Higher in Taiwan, 2007

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Abstract

SARS infection occurred in staff of a biosafety level 4 laboratory in middle December 2003, prompting Taiwan's Centers for Disease Control (Taiwan CDC) to initiate routine on-site inspection of laboratories of biosafety level 3 and higher in Taiwan in 2005. The Guidelines for Management of Infectious Biomaterials and Sampling of Specimens from Patients of Infectious Disease clearly defined that competent authorities in the central government can perform inspection of laboratories of these levels whenever necessary. In 2007, therefore, Taiwan CDC implemented an audit of one biosafety level 4 and twelve biosafety level 3 laboratories that were in operation. This audit included activities such as pre-audit planning, on-site inspection, compiling audit reports, and deficiency re-audits, with an emphasis on the operation of both the Institutional Biosafety Committees (IBCs) and the laboratories. Deficiencies found in the IBCs are as follows: (1) inappropriate administration framework and position level, (2) failing to thoroughly implement annual internal audits of all laboratories within its institution, and (3) failing to establish procedures specific for adjustment of biosafety level of infectious

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biomaterials. Deficiencies found in laboratory management are as follows: (1) failing to thoroughly implement qualification reviews of authorized personnel, (2) failing to follow the regulations in handling the adjustment of biosafety level of infectious biomaterials, (3) failing to establish inventories of infectious biomaterials higher than biosafety level 2, held in their laboratories, (4) failing to thoroughly conduct yearly routine safety tests of laboratory equipment. These findings indicated that there are still some room for improvement in the management of biosafety level 3 or higher laboratories by the IBCs at various institutions. Thus, it is necessary to continually supervise and improve the implementation of laboratory safety management.

Keywords: Biosafety Level 3 laboratory, audit, Institutional Biosafety Committee, infectious biomaterial

Introduction

The Severe Acute Respiratory Syndrome (SARS) outbreak devastating Taiwan during February to June 2003 highlighted the problems of an insufficient number of biosafety level 3 (BSL-3) laboratories in health care facilities in this country. In consideration of the possibility of another SARS outbreak and in preparation for fighting possible attack by various emerging infectious diseases, Taiwan's Centers for Disease Control (Taiwan CDC) appropriated budgets earmarked for SARS control during 2004 for nine medical centers to construct biosafety level 3 laboratories, including National Taiwan University Hospital, Chang Gung Memorial Hospital, Tri-Service General Hospital, Taichung Veterans General Hospital, China Medical University Hospital, National Cheng Kung University Hospital, Kaohsiung. Veterans General Hospital, Chung-Ho Memorial Hospital of Kaohsiung Medical University, and Buddhist Tzu Chi General

Hospital. SARS infection of staff working in a biosafety level 4 laboratory due to errors in cleaning that led to leakage from crevices of the connection between transport chamber and Biological Safety Cabinet (BSC) drew Taiwan CDC's attention to biosafety management in domestic laboratories, especially in BSL-3 and higher laboratories, although no secondary infection happened from this incident.

At the time when the fear of SARS was widespread globally, Taiwan CDC had prudently taken relevant emergency measures in response to the incident, including the following: (1) to require the laboratory to quit all operations immediately and to organize investigation team to look into it and collect necessary specimens, (2) to inform all other laboratories doing research on SARS virus to stop all work and undergo internal laboratory disinfection by using aerosol fumigation, (3) to list the names of all personnel conducting the examination and research of SARS virus for management purpose, (4) to invite experts from US Centers for Disease Control and Prevention and from National Institute of Infectious Diseases of Japan to help evaluate and ensure the safety management of biosafety level 3 and higher laboratories in this country. In January 2004, World Health Organization (WHO) also sent a three-member group to here for an overall investigation to this incident.[1] The implicated laboratory was allowed to reopen when all the deficiencies and recommendations proposed by Taiwan CDC and WHO investigation group have been implemented, and after concerns about safety were cleared by Taiwan CDC through an on-site recheck.

In addition to the emergency response to this laboratory-associated SARS infection, equally important to CDC was the establishment of a management program for BSL-3 and higher laboratories[2, 3]. Therefore, Taiwan CDC has required all BSL-3 laboratories constructed after 2004 to undergo an on-site

check and audit before they can operate. Furthermore, Taiwan CDC promulgated the Guidelines for Management of Infectious Biomaterials and Sampling of Specimens from Patients of Infectious Disease (shortly termed as the Guidelines) [4] on September 26, 2005, which came into effect on March 26, 2006. Article 11 of the Guidelines explicitly describes the relevant procedures of audit for BSL-3 and higher laboratories that are currently under operation or newly established. In Taiwan, the number of BSL-3 and higher laboratories in operation increased from three before 2003 to sixteen in 2007, as listed in Table 1. To ensure the safety of BSL-3 and higher laboratories in operation, Taiwan CDC had conducted annual audit activities for all of them since 2005, and starting from 2007, these activities were entrusted to Taiwan Biological Safety Association (TBSA).

Table 1. List of Biosafety Level 3 (BSL-3) and Higher Laboratories in Taiwan

No.	Title of Institute	BSL	Date to Start its Operation
1	School of Preventive Medicine, National Defense University	4	Before 2003
2	Division of Virology, Taiwan Centers for Disease Control	3	Before 2003
3	College of Medicine, National Taiwan University	3	Before 2003
4	Division of Mycobacteria, Taiwan Centers for Disease Control	3	Mar. 15, 2004
5	National Yang-Ming University	3	Nov. 29, 2004
6	Chang Gung Memorial Hospital	3	June 20, 2005
7	Chung-Ho Memorial Hospital of Kaohsiung Medical University	3	June 20, 2005
8	Kaohsiung. Veterans General Hospital	3	June 20, 2005
9	National Taiwan University Hospital	3	Aug. 10, 2005
10	School of Preventive Medicine, National Defense University	3	Aug. 10, 2005
11	Animal Health Research Institute, Council of Agriculture	3	Jan. 9, 2006
12	Buddhist Tzu Chi General Hospital	3	Feb. 15, 2006
13	Bureau of Food and Drug Analysis, Department of Health	3	Mar. 23, 2006
14	China Medical University Hospital	3	Jan. 18, 2007
15	Tri-Service General Hospital	3	Jan. 26, 2007
16	Taichung Veterans General Hospital	3	Feb. 15, 2007

Materials and Methods

A. Laboratories to be audited

One BSL-4 and twelve BSL-3 laboratories nationwide, currently under

operation, were included in the audit list, with the exclusion of three units of BSL-3 laboratories just approved by Taiwan CDC in 2007.

B. Planning of audit activities

i. Audit training: TBSA organized “a training course for auditors in charge of the audits of BSL-3 and higher laboratories” in November 2006, inviting scholars and experts experienced in management and auditing of BSL-3 laboratories to speak about audit skills and share experiences. [5]

ii. Creating a checklist: TBSA convened a meeting to make “checklist for audits of BSL-3 and higher laboratories” together with auditors to define the criteria and standards for on-site audits. Some of the core issues in this checklist include verification of technical documents and records, on-site observation, spot checks of software and hardware management, and interviews of laboratory personnel, etc. [5]

iii. Schedule arrangements: TBSA must first make an appointment on the date of audit with a laboratory to be audited one month before it is scheduled, and then Taiwan CDC will issue an official notice to the laboratory to confirm the date scheduled. A maximum of two laboratories can be scheduled for audit on the same day, with three hours and three to four auditors arranged for each of them.

C. Audit activities

i. Pre-audit meeting（20 minutes）

1. Meeting opening: Taiwan CDC personnel in charge of audit-related matters explain the regulatory basis, schedule, core issues, and scope of the audit activities.
2. Briefings by laboratories: Laboratory representatives provided briefings on facility design (including floor plan, negative pressure and

air conditioning system, and access control), documents related to security containment, maintenance and test of laboratory equipment and security devices, list of personnel receiving security training, framework and operation of IBC, and correction of deficiencies identified during previous audit, etc.

ii. On-site audit（130 minutes）

1. Management of IBC: Taiwan CDC personnel in charge of the audit-related business verified the overall situation of IBC operation and inventory management (including new additions, sharing, destruction, and deposit) of infectious biomaterials.
2. Management of laboratories: Auditors performed an on-site observation and verification of laboratory operation based on the items in the checklist.

iii. Post-audit meeting（30 minutes）

Auditors and personnel from Taiwan CDC made an explanation to and discussion with representatives of laboratories about overall findings, emphasizing on their deficiencies and giving them recommendations.

D. Audit report

TBSA collected deficiencies and recommendations from each of the auditors, compiled a draft report in ten workdays, and then sent it to auditors for confirmation. Next, the supervising institution of the laboratories is officially informed about the report via a written notice by Taiwan CDC

E. Re-audit of deficiencies

Laboratories would have to correct all deficiencies described in the audit report and update Taiwan CDC about the corrections made in two months after they were informed. On the other hand, recommendations in the audit

report were not part of the re-audit, as they were only for laboratories' reference.

Results

A. Deficiencies found in IBC management are as follows:

i. Failing to establish working procedures and record sheets for alteration of infectious biomaterials. (in four laboratories)

ii. Failing to thoroughly implement annual internal audits of all laboratories higher than BSL-2 within its institution. (in four laboratories)

iii. Unclear administration framework or inappropriate position level for IBC. (in three laboratories)

iv. Failing to cover the work described by Article 4 of the Guidelines about the mission of IBC. (in two laboratories)

v. Failing to assign certain personnel (such as biosafety officers) to take care of the supervision of internal biosafety operation of the laboratories. (in two laboratories)

vi. Failing to convene an IBC meeting by the deadline specified by IBC Constitution. (in one laboratory)

vii. Failing to report to Taiwan CDC on changes in IBC members or basic details of the laboratory. (in one laboratory)

B. Deficiencies found in laboratory management are as follows:

i. Administration management

1. Failing to thoroughly implement qualification reviews of authorized BSL-3 personnel (in two laboratories)

2. Failing to follow the regulations while handling the sharing or destruction of biosafety level 3 infectious biomaterials. (in two

laboratories)

3. Failing to thoroughly implement the registration and sign-in control for personnel accessing BSL-3 laboratory. (in one laboratory)

ii. Documents and records

1. Failing to establish an inventory for BSL-2 and higher infectious biomaterials held by laboratories. (in two laboratories)
2. Failing to thoroughly implement the process of reviewing the journal kept by laboratory staff by the supervisor. (in one laboratory)
3. Failing to thoroughly record the proceedings of laboratory equipment maintenance. (such as records of autoclave and HEPA leak testing) (in one laboratory)
4. Failing to present documents or records of Emergency Response Standard Operating Procedures for BSL-3 laboratory, rules on safe use of equipment, and records of personnel training and medical surveillance. (in one laboratory)

iii. BSC test

1. Failing to periodically conduct BSC function tests. (in one laboratory)
2. Do not evaluate the stability of negative pressure when two units of BSCs share the same ventilation system and are used in different time. (in one laboratory)
3. Ventilation system of Class II, Type A2 Biological Safety Cabinets is constructed by the method of close connection instead of air collection traps. (in one laboratory)
4. Biological indicators used to monitor the validation of fumigation in BSC disinfection are either placed in inappropriate sites or insufficient sites, making it hard to verify the thoroughness of disinfection. (in one

laboratory)

iv. Autoclave test

1. Unable to provide documents describing the specifications of the pore size of the filter used and information about the validation test before the autoclave is operated for sterilization. (in one laboratory)
2. During the autoclave vacuumizing phase, before the sterilizing conditions had been reached, exhaust air emitted from it might pose infection risk while being vented out if not properly filtered or treated. (in one laboratory)

v. Other equipment test

1. Failing to thoroughly implement annual routine tests of negative pressure and safety of laboratory equipment. (in two laboratories)
2. Fumigation equipment described in Laboratory Equipment Fermentation Standard Operating Procedure being totally different from the real equipment used in laboratory. (in one laboratory)
3. Failing to calibrate the differential pressure gauge and appropriately indicate its location inside the BSL-3 laboratory. (in one laboratory)
4. The air intake of BSL-3 laboratory being too near the emergency power generator in the engine room, leading to the possibility of waste air produced from generator getting into the BSL-3 laboratory through the intake. (in one laboratory)
5. Failing to keep the floor of engine room for BSL-3 laboratory neat, leading to the possibility of dust blocking the High Efficiency Particulate Airfilter (HEPA) placed at intake and consequently shortening the life span of HEPA. (in one laboratory)

C. Recommendations on laboratory management are as follows:

i. In consideration of laboratory's biosecurity, we recommend that IBCs establish internal security control policies and procedures for BSL-2 and higher infectious biomaterials to avoid the risk of stealing, misuse, abuse, private trade, or intentional release.
ii. The work of security tests for BSL-3 laboratory facilities and equipment should not be implemented by a contract company that then subcontract the job; in addition, test items (e.g. the test items and standards for BSC should at least include the items required by US NSF 49 or other international standards) and acceptance criteria (retrospectivity of approved calibration certificate for the tested facilities) should be specifically defined in the specification sheet of the procurement document to assure the accuracy of the test results.
iii. Personnel responsible for security management of BSL-3 laboratories should be familiar with the test items of the security facilities and equipment, such as installation test, on-site test, and validation and verification, and should make sure that the testers from the contract company are competent at the tests.
iv. The abbreviation for "biosafety level 3 laboratory" should be BSL-3, currently used by international peers, instead of P3.
v. Formaldehyde is one of the Group I carcinogen identified by International Agency for Research on Cancer (IARC). Therefore, personnel conducting the fumigation of laboratories should improve their own personal protection equipment to avoid the risk of exposure. In addition, the result from validation tests of fumigation should be read by laboratory personnel personally.
vi. Biological indicators specific for the validation test of autoclave should be

placed in the right site. Particularly, in places where the evaporation is difficult to reach, biological indicators must be placed to verify sterilization. Furthermore, bags for sterilization should be open to facilitate penetration of evaporation to achieve the goal of complete sterilization.

vii. We suggest that the floor map for the buffer zones in BSL-3 laboratories should be marked with the routes for the movement of personnel and goods as well as for the transportation of contaminated waste and for emergency evacuation.

Discussion and Recommendations

A. Functions of IBC need to be enhanced

The Guidelines for Management of Infectious Biomaterials and Sampling of Specimens from Patients of Infectious Disease enforced since March 26, 2006, have provided the legal basis for the designation of responsibilities and missions. In order to understand the progress of laboratory self-management by IBCs, we have included the review of IBC operation as part of these audit activities for BSL-3 laboratories. Several deficiencies on IBC operation have been found during this audit, including issues on the framework, missions, management rules, and tutelage personnel. Representatives from IBCs also pointed out some of the difficulties or hindrances they faced, including the following: (1) committee members are not clear about their responsibilities and missions, (2) committee members do not have relevant professional backgrounds, making it difficult for them to fulfill the responsibilities of review and evaluation, (3) the assigned biosafety tutelage personnel (or biosafety officers) either have very limited authorities or have insufficient expertise or are even in name only, making it difficult for them to fulfill the

supervision responsibilities vested by IBC. In order to resolve these problems, Taiwan CDC will organize a seminar for senior supervisors of IBCs in BSL-3 and higher laboratories to communicate with them about the policies and emphases pertaining laboratory biosafety management. Hopefully, this can improve the awareness of biosafety management among IBC members in a supervising position so that they can fully implement internal self-management.

B. Concepts about transfer management of infectious biomaterials remain to be developed

During the audits of thirteen BSL-3 and higher laboratories, two cases of involving the transfer of Class II and higher infectious biomaterials were found to have violated the requirements of Article 13 of the Guidelines (e.g. without permission from the IBC and failing to report to Taiwan CDC). One was the sharing the strain of *Burkholderia Pseudomallei* directly among several hospitals without permission from IBCs, and the other was the destruction of SARS virus incorrectly stored under the personal order of a laboratory chief without permission from the IBC. Because both of these cases violated the management requirement for transfer of the Class III infectious biomaterials and due to the fact that the Class III risk microorganisms included in this level of biomaterials could cause serious disease or even death in healthy adults, inappropriate management of their transfer might result in social panic and unease. Both cases mentioned underscore insufficient awareness about transfer management of infectious biomaterials among laboratory personnel. These incidents also suggest that to avoid similar violations in the future, it is necessary to continue education and dissemination about the transfer procedures of infectious biomaterials to laboratory personnel and to implement annual internal biosafety audits.

Following the issue of laboratory biosafety, laboratory biosecurity has become another focus of global attention. Therefore, Taiwan CDC is amending the Guidelines for Management of Infectious Biomaterials and Sampling of Specimens from Patients of Infectious Disease by adding the requirement of periodic stocktaking of Class II and higher infectious biomaterials. In case any addition, shortage, missing, and stealing of biomaterials was found, they should be reported to the IBC or biosafety officer, and also to the central competent authority, with a copy of report submitted to the local health bureau if the biomaterial belongs to the category of Class III or higher. Hopefully, the instances of private transfer of infectious biomaterials will not happen again and, therefore, the management of infectious biomaterials will be assured, through the requirement of biosecurity control about the Class II and higher infectious biomaterials.

C. Feedback from audited laboratories and response from Taiwan CDC

Feedback from audited laboratories about the audit procedures:

i. Because most of BSL-3 laboratories in operation are not actually used frequently and the cost for annual security examination of facilities and equipment is expensive, representatives from laboratories suggest that the interval for security examination of hardware could be longer for those used less frequently.

ii. Representatives from BSL-3 laboratories suggest that Taiwan CDC could inform them of the foci and items to be audited prior to conducting audit activities so that they could prepare well in advance.

iii. Representatives from laboratories suggest that an accreditation system should be established and a list of accredited companies capable of implementing security examination for BSC or BSL-3 laboratories could

be provided for their consideration.

iv. In order to enhance the use frequency of BSL-3 laboratories, to perform the test of Class II infectious biomaterials in BSL-3 laboratories could be encouraged if they are working for training purposes.

Response of Taiwan CDC to the feedback from BSL-3 laboratories:

i. Since the BSL-3 laboratories are running for a whole year except temporary interruption for periodic maintenance, repair and examination, the interval for security examination should have nothing to do with the use frequency. In addition, owing that the BSCs are the first line in protecting the safety of personnel, their functions should be assured to work efficiently at any time. As a result, we required that safety examination for facilities and equipment of BSL-3 laboratories should be conducted once in a year.

ii. The primary purpose of laboratory audit lies not in deficiency finding but in the establishment of routine self-control procedures so that we can avoid incidents of laboratory infection caused by faults in management or manipulation. These are the reasons why, starting from July 2007, we have provided the audited laboratories with a checklist used in audit and deficiency reports from previous audits for their reference in preparation.

iii. Biological Safety Cabinet (BSC) is the primary bioprotection equipment in BSL-2 and higher laboratories. Based on prescription of Paragraph 1 of Article 5 of the Labor Safety and Health Law [6], employers bear the responsibilities for providing the necessary safety and health facilities in conformity with established standards for, as prescribed in Provision 7 of Paragraph 1, preventing adverse effects resulting from biological agents. Also, in accordance with Paragraph 3 of Article 5, the mentioned standards for the necessary equipment and procedures shall be established

by the competent authority of the central government, e.g. Paragraph 1 of Article 3, the Council of Labor Affairs of the Executive Yuan; and, Paragraph 2 of Article 3, for health matters pertaining to this Law, the competent authority of the central government shall treat them in coordination with health authorities of the central government. Based on the regulations cited above, the competent authority in charge of the management of BSC examination companies shall be Council of Labor Affairs, that is to say, the Council has the responsibilities to stipulate the BSC examination standards and accreditation system. For BSL-3 laboratories, the facility security examination mainly focuses on the examination of unidirectional air distribution in the negative pressure system. Since this part was not included in Chapter 2, Safety and Health Installations, of the Labor Safety and Health Law, the competent authority for this in not clearly defined. Although Taiwan CDC is the competent authority in charge of laboratory's biosafety audits, the Communicable Disease Control Act [7] does not give it the power to establish the accreditation system of facility biosecurity examination for BSL-3 laboratories. Before the competent authorities in charge of the accreditation of safety and health facility examination have been defined, some civilian organizations may be able to construct the mechanism about the accreditation of security examination companies as practiced in some other countries. For example, based on the international standards, ISO/IEC 17020（CNS 14725）, credible accreditation institutions could establish an accreditation system for the examination companies of BSL-3 laboratory security and BSC and then send it to government for approval. Hopefully, this will solve the problems about the accreditation issue.

iv. Although BSL-3 laboratories could be used for testing of Class II infectious biomaterials, this operation should be agreed by the IBC, and all personnel should strictly follow the requirements and procedures for BSL-3 laboratories. Personnel should not have the misconception that Class II infectious biomaterial tests do not need follow the stricter regulation for BSL-3 laboratories.

D. Review of BSL-3 and higher laboratory audit activities

i. To integrate various hospital-related audit activities

Of the sixteen BSL-3 and higher laboratories currently in operation, eight are installed at hospitals that undergo several different accreditations, audits or inspections each year conducted by competent health authorities. In order to reduce their workload in preparing these activities, Taiwan CDC will do its best to incorporate all these relevant activities to be conducted on the same day, which this new initiative is scheduled to start from 2008.

ii. The audit system for BSL-3 laboratories is currently being completed by the way of conducting an annual on-site audit. Taiwan CDC is planning to adopt a rating system in the future. For those laboratories with a high rank, the audit activities will be modified by either changing from on-site audit to document review or extending the interval to be audited, to return the audit to the spirit of self-management.

iii. Because audit activities take nearly three hours for each laboratory, we, in the future, will enhance efficiency by dividing members of the committee into several groups to conduct audits of different parts simultaneously. In addition, the infectious waste treatment will be included in items to be audited.

Conclusions

We started to implement the audit activities for BSL-3 and higher laboratories three years ago, the results show that all of them have made improvements for each year. In order to achieve the purpose of establishing self-management system, starting from 2007, we have expanded our audit activities by adding the items of reviewing the functions and operations of IBC, and we have incorporated the component of biosecurity into the activities by requiring laboratories to establish their inventory management plans for infectious biomaterials. The only way to fully implement the biosecurity management system is to develop the biosecurity awareness in laboratories of each biosafety level so that they can fulfill the biosecurity management autonomously. By continuously enhancing the level of biosecurity culture and awareness in laboratories, we will be marching toward the goal of "zero-incidence" of laboratory infection.

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