

ORIGINAL ARTICLE

Biological Select Agents and Toxins Management in Taiwan: From Past to Present

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Abstract

Introduction: Before 2016, there were no specific regulations or guidelines for the management of biological select agents and toxins (BSATs) in Taiwan. The Taiwan Centers for Disease Control responded to the global health security agenda in 2016 and made use of the Joint External Evaluation tool: International Health Regulations to evaluate Taiwan's epidemic prevention system capacities, including BSAT management. For technical areas that did not meet the highest requirements, the regulations and guidelines are now in place to strengthen the management of BSATs.

Methods: In 2017, a survey on the BSAT entities management status in Taiwan was conducted to understand the gap between BSAT practice and international policies, and to improve BSAT management based on the findings.

Results and Discussion: After 3 years of promotion, relevant management regulations and supervision mechanisms have been established. In 2021, the evaluation will be conducted again and it is expected that Taiwan's BSAT management capacity will reach the level of international biosafety and biosecurity.

Keywords: biological select agents and toxins, global health security agenda, joint external evaluation, laboratory management, biosafety, biosecurity

Introduction

In December 2003, an accident that infected a laboratory staff member with the severe acute respiratory syndrome (SARS) coronavirus occurred in Taiwan.¹ This accident caused serious impact on SARS testing and research at the time, prompting the government authorities to recognize the importance of laboratory biosafety. Therefore, the Taiwan Centers for Disease Control (Taiwan CDC) took responsibility for establishing regulations and guidelines for national laboratory biosafety management. Since 2004, the Taiwan CDC has actively developed laboratory biosafety regulations/guidelines, strengthened management responsibilities of the entities' Institutional Biosafety Committees (IBCs), regularly inspected high-containment laboratories (BSL-3/ABSL-3, BSL-4), developed verification regulations of Risk Group 3 (RG3) and Risk Group 4 (RG4) pathogen storage/transfer, promoted the International Air Transport Association triple packaging system for safe transport of infectious substances, and implemented laboratory biosafety training.

To make Taiwan's laboratory biosafety management comply with the international standards, the Taiwan

CDC follows the World Health Organization's announcement of laboratory biosafety management policies as the main policy. In 2012, the World Health Organization published the "Laboratory Biorisk Management Strategic Framework for Action 2012–2016,"² calling on the member states to introduce a biorisk management system into their domestic laboratory biosafety management. In 2015, the Taiwan CDC referred to CWA 15793: Laboratory Biorisk Management Standard and developed the "Laboratory Biorisk Management Standard Regulation" (draft) to promote the introduction into microbiology and biomedicine laboratories across the country. At present, there are >100 microbiology and biomedicine laboratories operating with the system in Taiwan.

In 2014, the United States with the World Health Organization (WHO), the World Organization for Animal Health (OIE), the Food and Agriculture Organization of the United Nations (FAO), the European Union (EU), other international organizations, and 29 countries launched the global health security agenda (GHSA).³ In view of the international epidemic of emerging infectious agents such as Ebola virus, Middle East Respiratory

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Syndrome Corona Virus (MERS-CoV), and Zika virus, the Taiwan CDC actively responded to the GHSA in 2016. The GHSA has a total of 11 action plans, including the Biosafety and Biosecurity Action Package,⁴ which mainly focuses on strengthening administration and training programs for biological select agents and toxins (BSATs). To assist the member states in implementing the International Health Regulations (IHR) requirements to achieve a comprehensive global epidemic prevention system, the WHO released the Joint External Evaluations (JEE) tool⁵ in 2016 for the member states to self-assess the level of national epidemic prevention capacity. In 2016, Taiwan used the JEE tool to generate an evaluation and evaluation score for the biosafety and biosecurity technical area, which was 3 (out of 5).⁶ In 2021, Taiwan will conduct another JEE and it is expected that the evaluation score will be increased to >4.

BSAT Management Regulations and Guidelines

In the biosafety and biosecurity technical area, the 2016 JEE results showed that the BSAT management regulations were not sufficient and needed to be amended, which meant that Taiwan's BSAT management was still in the initial stage. If an internal or external threat had occurred in a BSAT entity, it might not be able to respond to the threat and cause harm. Therefore, it was necessary to improve the insufficient parts to strengthen the management. In 2019, the Taiwan CDC completed revision of Chapter III, "Management of Select Pathogens and Biotoxins," in "Regulations Governing Management of Infectious Biological Materials", and then amended the "Operation Directions Governing Management of Infectious Biological Materials, Ministry of Health and Welfare." At present, there are 40 BSATs on the list in Taiwan, consisting of 36 select agents and four select toxins (with control limit amount) (Table 1). Among them, the BSATs that have serious harm to public health and public safety are classified into the highly dangerous BSATs (i.e., Tier 1 BSATs), including 13 select agents and one select toxin. To make Taiwan's BSAT management more effective and complete, the Taiwan CDC has also developed the BSAT management guidelines, including the "Guidance for Suitability Assessment of Select Agents and Toxins Staff," the "Guidance of Select Agents and Toxins Security Plan," the "Select Agents and Toxins Incident Response Plan Guidance," the "Guidance for Drills and Exercise of Select Agents and Toxins," the "Select Agents and Toxins Biosafety/Biocontainment Plan Guidance, the "Guidance on the Inventory of Select Agents and Toxins" and the "Guideline for Review Research Programs of Highly Dangerous Pathogens and Biotoxins."⁷

BSAT Management Strategies

In Taiwan, BSAT management is more stringent than the management of general RG3 pathogens and biotoxins. If

entities will possess, store, or use BSATs, they must apply to the Taiwan CDC for review in advance. An entity would submit draft documents that detail training and assessment of the relevant personnel, planning of the laboratories or storage facilities, expected items and purposes, and development of biosafety/biosecurity/incident response plans for the BSATs. After documentary review and on-site inspection, the Taiwan CDC will approve the entity as a BSAT entity if no defects are identified or the deficiency is fixed. If an entity possesses, stores, or uses the amount of select toxins under the control limit amount, it will not be regulated by the BSAT-relevant regulations. The select toxins must still be handled in accordance with the relevant RG3 pathogen regulations.

The BSAT entities must comply with the relevant regulations from the Taiwan CDC to possess, store, use, handle, or export/import the BSATs. The strategies are as follows:

1. Internal management:
The BSAT entity must assign a responsible official (RO) and an alternative responsible official to supervise the entity's BSAT management.
2. External inspection:
The Taiwan CDC regularly conducts the on-site inspection for the BSAT entities every year.
3. BSATs transfer and adjust inventory:
The new addition and transfer of the BSAT items and/or amount shall be subject to the approval of the entity's IBC and the RO. And after the approval by the Taiwan CDC, these alterations can be done. For the BSAT transfer, the sending out entity and receiving entity must report the point in time (sending out/receiving) to the Taiwan CDC, respectively. If the receiving entity fails to receive on the scheduled delivery time, or if the package is found to be damaged or lost (i.e., abnormal situation), the entity must notify the Taiwan CDC within 48 h.
4. Training/assessment:
The BSAT entity that possesses, stores, or uses the highly dangerous BSATs must conduct annual insider threat awareness training and suitability assessment of the highly dangerous BSAT personnel every 3 years.
5. Drills/exercises:
BSAT entities are required to conduct drills at least annually and exercises every 3 years to test and evaluate the effectiveness of their security, biosafety, and incident response plans. According to the review after the drills and exercises, the plans' content should be revised in due course.

At present, there are ~10 BSATs possessed by BSAT entities in Taiwan, including *Burkholderia pseudomallei*, Botulinum neurotoxin-producing species of *Clostridium*, and Botulinum neurotoxins. There are seven BSAT entities and five entities that possess and store the select amount of toxins under the control limit amount.

Table 1. List of biological select agents and toxins in Taiwan

No.	Item	Control type			Highly dangerous BSAT	
		Select agents	BSAT-positive specimen	Select toxins		Control limit amount
1	<i>Bacillus anthracis</i>	v			—	v
2	Botulinum neurotoxins			v	≧ 1 mg	v
3	Botulinum neurotoxin-producing species of <i>Clostridium</i> (such as <i>C. botulinum</i> , <i>C. baratii</i> , and <i>C. butyricum</i> , part of <i>C. argentinense</i>)	v			—	v
4	<i>Burkholderia mallei</i>	v			—	v
5	<i>Burkholderia pseudomallei</i>	v			—	v
6	<i>Brucella abortus</i>	v			—	
7	<i>Brucella melitensis</i>	v			—	
8	<i>Brucella suis</i>	v			—	
9	<i>Coxiella burnetii</i>	v			—	
10	Crimean–Congo hemorrhagic fever virus	v	v		—	
11	Diacetoxyscirpenol			v	≧ 10,000 mg	
12	Eastern Equine Encephalitis virus	v			—	
13	Ebola virus	v	v		—	v
14	<i>Francisella tularensis</i>	v			—	v
15	Hendra virus	v	v		—	
16	Kyasanur forest disease virus	v	v		—	
17	Lassa virus	v	v		—	
18	Lujo virus	v	v		—	
19	Marburg virus	v	v		—	v
20	Middle East Respiratory Syndrome coronavirus	v			—	v
21	Monkeypox virus	v			—	
22	Nipah virus	v	v		—	
23	Omsk hemorrhagic fever virus	v			—	
24	Reconstructed 1918 influenza virus	v			—	v
25	<i>Rickettsia prowazekii</i>	v			—	
26	Rift Valley fever virus	v			—	
27	Severe acute respiratory syndrome-associated coronavirus	v			—	v
28	South American hemorrhagic fever viruses: Chapare	v	v		—	
29	South American hemorrhagic fever viruses: Guanarito	v	v		—	
30	South American hemorrhagic fever viruses: Junin	v	v		—	
31	South American hemorrhagic fever viruses: Machupo	v	v		—	
32	South American hemorrhagic fever viruses: Sabia	v	v		—	
33	Staphylococcal enterotoxins A, B, C, D, E subtypes			v	≧ 100 mg	
34	T-2 toxin			v	≧ 10,000 mg	
35	Tick-borne encephalitis complex (flavi) viruses: Far Eastern subtype	v			—	
36	Tick-borne encephalitis complex (flavi) viruses: Siberian subtype	v			—	
37	Variola major virus (smallpox virus)	v	v		—	v
38	Variola minor virus (Alastrim)	v	v		—	v
39	Venezuelan equine encephalitis virus	v			—	
40	<i>Yersinia pestis</i>	v			—	v

BSATs, biological select agents and toxins; v, applicable.

In 2010, the Taiwan CDC developed the “Laboratory Biosafety Management Information System”⁸ to manage the entities that possess, store, or use the RG2 or mentioned pathogens and biotoxins. In 2018, the BSAT management interface was added to the information system, including the BSAT entity application review, transfer review and report, the BSAT-positive specimen (from the infectious disease patient or proficiency testing) notification, incident notification and disposal report, inventory management, and the Dual Use Research of Concern of the highly danger-

ous BSATs for future reference. By applying, reviewing, reporting, and notifying the BSAT management affairs online, the information system improves the efficiency of administrative operations.

BSAT Biosafety and Biosecurity Training and Train the Trainer Program

Both the GHSA and the JEE tool list the BSAT personnel training program as a key item/indicator. Since 2016, the Taiwan CDC has conducted training on the BSAT

management regulations and guidelines every year. The trained personnel include supervisors and staff from the BSAT entities, the entities that possess and store the select amount of toxins under the control limit amount, the laboratory testing institutions for the communicable diseases, and the high containment laboratories.

In addition, to cultivate BSAT management training teachers, the Taiwan CDC has trained the BSAT supervisors with practical management experience and the experts/scholars with biosafety expertise since 2019. Through the BSAT seed teacher training program, it is expected that the BSAT biosafety and biosecurity training level will be improved.

2016 JEE Results

The JEE tool combines the GHSA's 11 action plans and the IHR's 8 core capacities (with a total of 19 technical areas). This can effectively evaluate a country's capacities for prevention/detection/response of major public health threats. Scores are determined on a 5-point scale: 1=no capacity, 2=limited capacity, 3=developed capacity, 4=demonstrated capacity, and 5=sustainable capacity. In the biosafety and biosecurity technical area, there are two indicators: (1) whole-of-government biosafety and biosecurity system is in place (mainly evaluates the current status including the BSAT legislation, inventory management and records, integration of the BSATs to minimum entities, reduction of culturing as a diagnosis method and support funds) and (2) biosafety and biosecurity training and practices (mainly evaluates the status including the BSAT personnel training/seed teacher training programs and support funds). Taiwan's evaluation score in the biosafety and biosecurity technical area was 3 (developed capacity) and the main defects were (1) comprehensive national BSAT legislation is being developed, but has not finalized; (2) BSAT is not yet consolidated into a minimum number of facilities; and (3) training programs are not specifically focused on BSATs.

2017 BSAT Entities Management Status Survey and Results

After the JEE in 2016, the Taiwan CDC commissioned the Taiwan Biological Safety Association (TBSA) to conduct a survey for the seven BSAT entities in Taiwan.⁹ The TBSA formed an expert working group to design a questionnaire that met the domestic BSAT management regulations. After the questionnaire was completed, the TBSA and the Taiwan CDC together confirmed the appropriateness and selected one of the BSAT entities to fill out the questionnaire for testing. After the expert working group once again confirmed the questionnaire's content, the TBSA distributed the finalized questionnaires to the seven BSAT entities. Before replying to the questionnaire, it was to be filled out by a BSAT supervisor or a desig-

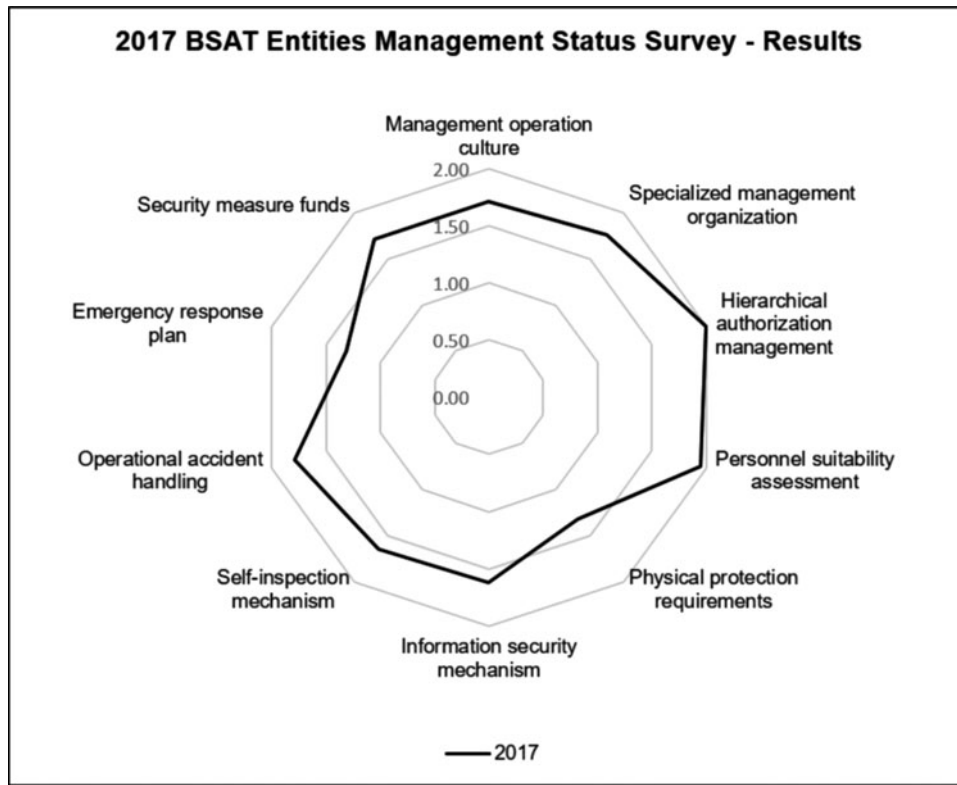
nated senior researcher and confirmed by the entity's IBC. The questionnaire's content included 10 topics and several subitems that were expanded in sequence:

1. Management operation culture (9 items):
The entity's BSAT plan should be able to foster laboratory leadership with trustworthiness and responsibility, as well as a good management operation culture.
2. Specialized management organization (10 items):
The entity should set up an organization for BSAT management.
3. Hierarchical authorization management (10 items):
Hierarchical authorization management is required based on the BSAT's nature and application.
4. Personnel suitability assessment (5 items):
The entity should develop preaccess and ongoing suitability assessments.
5. Physical protection requirements (4 items):
The entity's BSAT plan should specify minimum physical protection requirements at all levels, and personnel must understand these necessary procedures.
6. Information security mechanism (3 items):
The entity should take measures to protect information.
7. Self-inspection mechanism (2 items):
The entity should establish a mechanism for self-inspection.
8. Operational accident handling (2 items):
The entity should have operational accident handling procedures.
9. Emergency response plan (5 items):
The entity should have a plan for emergency response.
10. Security measure funds (1 item):
The entity should provide sufficient funds to establish a comprehensive security measure.

After the questionnaires were completed, the expert working group evaluated and determined the achievement scores of the BSAT entities based on the reply content. Next, the expert working group completed the BSAT entities management status survey result in 2017 (Figure 1).

The strengths were as follows:

1. Topic 3 (hierarchical authorization management)
The BSAT entities all complied with the relevant regulations and had a clear structure of authority and responsibility.
2. Topic 4 (personnel suitability assessment)
The BSAT entities all developed the personnel suitability assessment procedure based on the relevant guidelines and requested a police criminal record certificate as a review of the suitability assessment.



Score	Description
NA	Not applicable
2	All goals achieved
1	Some goals achieved
0	Minimum goals not achieved

Figure 1. 2017 BSAT entities management status survey result. Based on 10 topics. Calculated the average scores of all subitems from each entity, and then calculated the average score of each topic from all entities. BSATs, biological select agents and toxins.

The weaknesses were as follows:

1. Topic 5 (physical protection requirements)
The BSAT entities' authorization procedure, audit procedure, and unused BSAT disposal procedure were unclear. Moreover, some entities' access controls were lacking, as were procedures for preventing fraudulent use and a notification mechanism for reporting tampering or damage.
2. Topic 9 (emergency response plan)
The relationship between BSAT supervisors, bio-safety officers, and principal investigators and their lines of authority were not clearly understood. There was no awareness of the difference between

BSATs and other RG3/RG4 pathogens, so the management procedure had no independent standard, personnel responsibility, and emergency relocation plans for BSATs. Moreover, some entities were lacking planning for the BSAT drills or scenarios.

Discussion

Appropriateness of the BSAT List

After the JEE in 2016, the Taiwan CDC began to strengthen the BSAT management. Owing to lack of the BSAT-related management experts for consultation, the Taiwan CDC referred to relevant management regulations and systems in Europe and the United States. At the beginning of implementation, portions of the

management policies and regulations were questioned by some BSAT entities. After continuous communication and explanation, the entities finally realized the meaning and purpose of legislation for the BSATs. For example, there were many entities that possessed and stored *B. pseudomallei*, and they did not consider it necessary to list the bacteria as a highly dangerous BSAT. They thought that the pathogen is prevalent in the soils of southern Taiwan and is often detected after a typhoon. Thus, it is unrealistic to include it in the regulations. However, in the previous study, the biological pathogens that might become biological weapons were classified into three categories: A, B, and C, and *B. pseudomallei* was classified into Category B.¹⁰ Besides, it is known that the WHO has listed this pathogen as a biological pathogen that could become a biological weapon in its guidance published in 2004.¹¹ The Public Health Agency of Canada has also determined *B. pseudomallei* as one of the security-sensitive biological agents, which pose a higher biosecurity risk because of their potential as biological weapons.¹² As for the Federal Select Agent Program in the United States, the BSATs that require additional security measures to be implemented are named Tier 1 BSATs, and *B. pseudomallei* is classified into Tier 1 BSAT.¹³ Based on these references and the features of *B. pseudomallei*, the Taiwan CDC still lists it as the highly dangerous BSAT.

2017 BSAT Entities Management Status Survey

1. Topic 3 (hierarchical authorization management) and Topic 4 (personnel suitability assessment)
The BSAT entities all followed the relevant regulations and guidelines to establish a management structure and a suitability assessment procedure and they indeed achieved each subgoal.
2. Topic 1 (Management operation culture), Topic 2 (Specialized management organization), and Topic 7 (Self-inspection mechanism)
The cooperation between authorities and entities is important. The Taiwan CDC not only conducts on-site inspections but also organizes symposiums with entities to improve the appropriateness of regulations and help them to establish management culture. After the continuous promotion of the BSAT management policy and laboratories be inspected by the Taiwan CDC in recent years, the BSAT entities have gradually developed good management culture and mechanisms and the defects have been significantly improved.
3. Topic 5 (Physical protection requirements), Topic 6 (Information security mechanism), and Topic 10 (Security measure funds)
At present, the BSAT entities have gradually raised their awareness of information security, and the rel-

evant management measures for physical protection have been improved. However, due to the limited allocation of resources, it is still necessary to continue to strive for funding. There are still challenges in updating software and hardware for facilities and equipment.

4. Topic 8 (Operational accident handling) and Topic 9 (Emergency response plan)
The Taiwan CDC published the “Select Agents and Toxins Incident Response Plan Guidance” in 2019, providing a reference for the BSAT entities. Therefore, it is expected that when on-site inspections are conducted at the end of this year, the BSAT entities should be able to establish a one-stop window for notification and can clarify the roles and responsibilities of personnel during an emergency.

The regulations were revised in 2016. Everyone who works in the BSAT laboratory must apply to the Taiwan CDC for approval and registration before they can use BSATs. Furthermore, in recent years, the Taiwan CDC has continued to hold relevant training programs for the BSAT laboratory staff on biosecurity and personnel suitability assessment. Therefore, the BSAT entities had better performance in Topic 3 and Topic 4. As for Topic 5 and Topic 9, the relative performance of the BSAT entities was weak due to their lack of experience in designing hardware security measures and response to various types of emergency.

Summary

Testing for and research on BSATs have become an important part of the GHSA. As part of that agenda, ensuring the safety of staff engaged in BSAT testing and research, so as to avoid laboratory-acquired infections, and ensuring the security of BSATs, so as to avoid unauthorized acquisition, theft, misuse, and deliberate release, are important topics in biosecurity management for BSAT entities. We are continuing to prepare for the future and must continue to strengthen BSAT management. Therefore, the Taiwan CDC will follow the WHO’s latest policy on BSAT management, strictly review the newly applied entities, regularly conduct on-site inspections, strengthen the personnel suitability assessment and insider threat awareness training, and implement the introduction of biorisk management system, so as to make BSAT management capacity in Taiwan in line with international standards.

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