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ORIGINAL RESEARCH

Biosafety Management Based Upon Risk Assessment and Monitoring: Perspectives from a Clinical Laboratory, China

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Background and Objective: Inadequate risk assessment and a lack of risk monitoring are common deficiencies in clinical laboratory, and are also the main causes of biosafety incidents. Therefore, we summarized the experience of implementing adequate risk assessment and maintaining risk monitoring, and established a procedure for continuously improving biosafety management.

Methods: Learning from our laboratory's experience in implementing risk assessment, risk response, and risk monitoring before and during the COVID-19 epidemic, we summarized the procedures for fully identifying risks, accurately evaluating risks, maintaining risk monitoring, establishing and regular reviewing safety indicators. On this basis, we established a system for continuously improving biosafety management through risk monitoring and reviewing safety indicator.

Results: We identified a total of 30 unacceptable risks prior to the COVID-19 pandemic, and developed and implemented appropriate risk control measures. After risk control, residual risks were acceptable, and no biosafety incidents have occurred. During the COVID-19 pandemic, after multiple risk monitoring, we identified ten new risks, three ineffective risk control measures, and multiple control measures for excessive protection. Then, we timely adjusted risk control measures to avoid laboratory personnel infection and excessive protection. Meanwhile, We established eight safety indicators and identified two improvement opportunities through regular reviews.

Conclusion: Adequate risk identification and accurate risk assessment are particularly important for effectively controlling biosafety risks. Biosafety management should be continuously improved to deal with ineffective and excessive protection caused by various changes in experimental activities. Continuous improvement of biosafety management can be achieved through risk monitoring, regular review of safety indicators, and management reviews. This study will help laboratory managers to fully and accurately assess risks, as well as update risks and their control measures through risk monitoring, and the continuous improvement procedure established in the study has certain reference value for laboratories to effectively respond to emerging infectious diseases and avoid excessive protection.

Keywords: risk assessment, risk monitoring, management review, continuous improvement, biosafety management

Introduction

Risk assessment is the foundation of managing biosafety. Biosafety risks are associated with factors such as personnel, safety facilities or equipment, operating processes, disinfectants, experimental waste, emergency plans, etc. However, response measures are only developed and implemented for risks that exceed the acceptable limits of the laboratory. Therefore, accurately assessing the hazard degree of risks is crucial for developing appropriate risk response measures or avoiding excessive protection.[1] However, many institutional biosafety committees (IBC) only focused on the risks associated with operation processes, and the risk evaluation was also relatively superficial, which led to inadequate risk identification and inappropriate risk response measures. In addition, biosafety

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management should be a continuous improvement process based on risk monitoring and review of biosafety indicators. Risk monitoring is of great significance in identifying unidentified risks, improving risk response measures, avoiding excessive protection, and responding to emerging infectious diseases.[1] The factors that determine the risk-hazard degree in clinical laboratories include the types of pathogens that may be exposed and their biological characteristics (such as virulence, transmission ability, and transmission routes), operating procedures, and sample types. Once any factor changes, using the initial risk-response measures will inevitably lead to excessive protection or an ineffective response. However, the reality is that many laboratories are not aware of the importance of risk monitoring at all.[2] In recent years, biosafety incidents related to Brucella in laboratories in China, as well as the SARS CoV-2 infection among laboratory staff in Wuhan during the early stages of the COVID-19 pandemic in 2019, exposed the deficiencies in risk monitoring in these laboratories.[3] In response to these issues, we retrospectively summarize our successful experience in fully identifying risks, accurately evaluating risks, effectively responding to risks, maintaining risk monitoring, establishing and regularly reviewing safety indicators before and during the COVID-19 pandemic, explore the establishment of a procedure for continuously improving biosafety management based on the experience, and evaluate its value in responding to emerging infectious diseases or avoiding excessive protection. In this study, we will share the experiences and the procedure.

Methods

This study was conducted in the clinical laboratory of a designated hospital for COVID-19 patients in Chongqing City, China in 2021. Our research team collected qualitative data on fully identifying risks, accurately assessing the hazard degree of risk, maintaining risk monitoring, updating risks and adjusting control measures before and during the COVID-19 pandemic in 2019. Taking our experience in implementing safety management as an example, we summarized the procedures for the activities associated with the above data, such as procedures on adequate and accurate risk assessment, procedures on effective and non-excessive risk control, procedures on appropriate risk monitoring, and procedures for continuously improving biosafety management, and evaluated their implementation effect.

Risk Assessment

Determine the Scope of the Experiment

Firstly, determine the scope of all experimental activities conducted in the clinical laboratory.

Collection of Biological Information on Potential Exposed Pathogenic Microorganisms

We collected information on pathogenic microorganisms that we might be exposed to during all laboratory activities. This information included disease pathogenicity, transmission route, infection dose, infection symptoms, incubation period, infection host, diagnostic means, stability in the environment, whether there were effective preventive measures and therapeutic drugs, and sequelae of infection. SARS-CoV-2 was used as an example to gather its biological information.

(Due to the wide variety of potentially exposed pathogenic microorganisms, in order to avoid lengthy manuscripts, we only used SARS-CoV-2 as an example to introduce the biological information of pathogenic microorganisms that should be collected).

Risk Identification

We defined a laboratory biosafety incident as any inadvertent occurrence resulting in actual harm during experimental activities, such as infection, illness, injury to humans, or environmental contamination. We used fishbone diagrams to fully identify biosafety risks in experimental activities from factors such as personnel, equipment, facilities, disinfectants, experimental waste, and operation processes (Figure 1).

Risk Evaluation

The hazard degree of each biosafety risk identified was evaluated:

Risk hazard degree = risk severity × probability of risk occurrence.

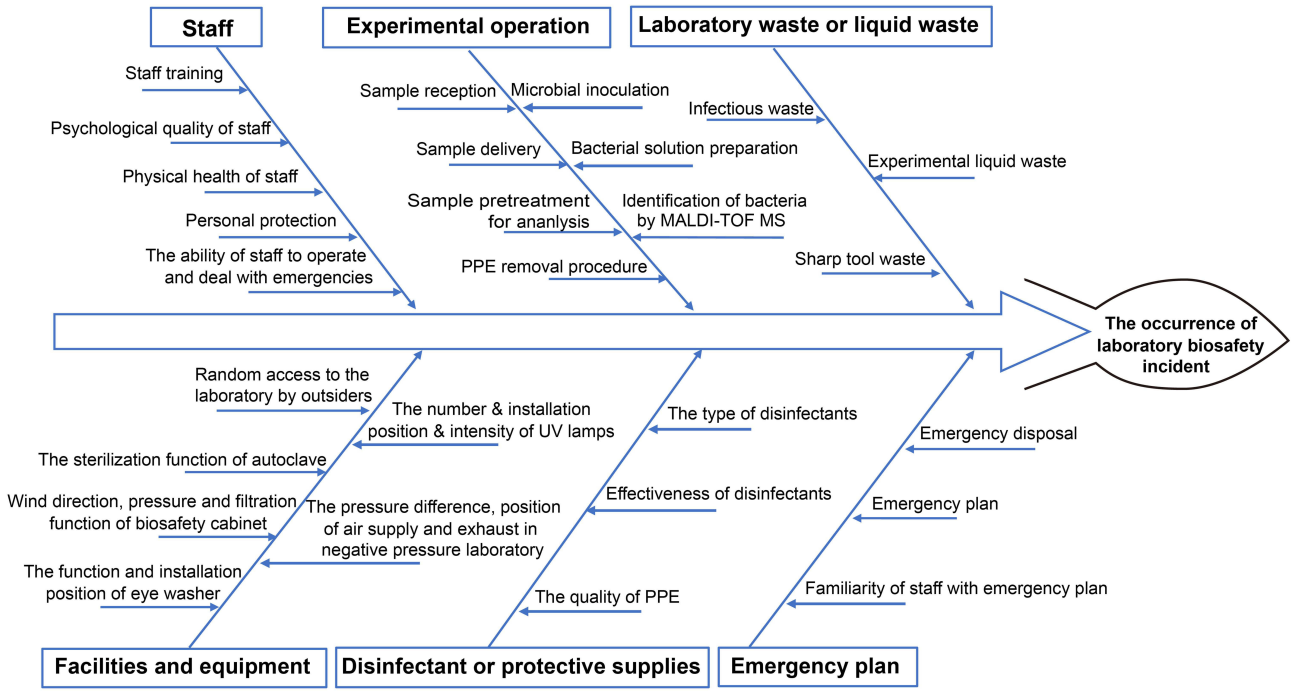

Figure 1 The fishbone diagram of risk identification.

The risk severity was quantified as follows:[4]

Score 4: very serious consequences, such as death.

Score 3: Causing widespread human infection or having very serious irreversible effects on the human body, with sequelae after treatment.

Score 2: Relatively serious injury, but recovery is possible after treatment.

Score 1: Slight harm that generally does not require special treatment.

Zero score: No harm.

The probability of risk occurrence was quantified as follows:

Score 4: Certain to happen (100% probability).

Score 3: Frequent occurrence (20%≤ probability < 100%).

Score 2: Occasional occurrence (1% < probability < 20%).

Score 1: Rare occurrence (0 < probability ≤1%).

Zero: score: Never happen (the probability of incident happening is zero).

Risk Response

First, the acceptable range of the risk-hazard degree should be determined. For risks with a hazard degree higher than the acceptable range, risk response measures should be considered, including eliminating risk sources, avoiding risks, controlling risks, and transferring risks. Risk control should be achieved by reducing the severity and/or occurrence probability of risk.

Risk Monitoring and Continuous Improvement of Biosafety Management

We established a risk monitoring approach based on internal or external review, analysis of biosafety incidents, employee recommendations, external information, reflection on internal incidents and warning from external incidents, and timely

input the risk monitoring results into management review. Through management review, we decided whether to restart risk assessment or update risk response.

At the same time, we also established annual biosafety indicators such as number of biosafety incidents, personnel training rate, number of failures in biosafety equipment and facilities occupational exposure frequency, number of improper personal protective measures, number of spills, unqualified rate of ultraviolet intensity, and the inefficiency rate of disinfectants. The biosafety indicators were reviewed annually, and the review results were input into the management review. Through management review, improvement measures and their required resources were output (Figure 2).

Statistical Analysis

The laboratory safety administrator should conduct annual statistics on annual statistics and analysis of safety indicators. The statistical methods were as follows:

Rate of personnel training = number of participants / number of expected participants ×100%.

Unqualified rate of ultraviolet intensity = Number of ultraviolet lamps with unqualified ultraviolet intensity / The total number of ultraviolet lamps ×100%.

The inefficiency rate of disinfectants = number of ineffective disinfectant monitoring times / number of disinfectant monitoring times ×100%.

Every year, the statistical safety indicators should be compared with the pre-set limits in the laboratory to identify non conformities and opportunities for improvement.

Results

Determine the Scope of the Experiment

The clinical experimental activities conducted in our laboratory include sample reception, sample transport, sample handling before testing, the testing process, sample preservation, and disposal of experimental waste. The testing process also included clinical blood testing, clinical body fluid testing, clinical microbial testing, clinical chemical testing, and nucleic acid testing.

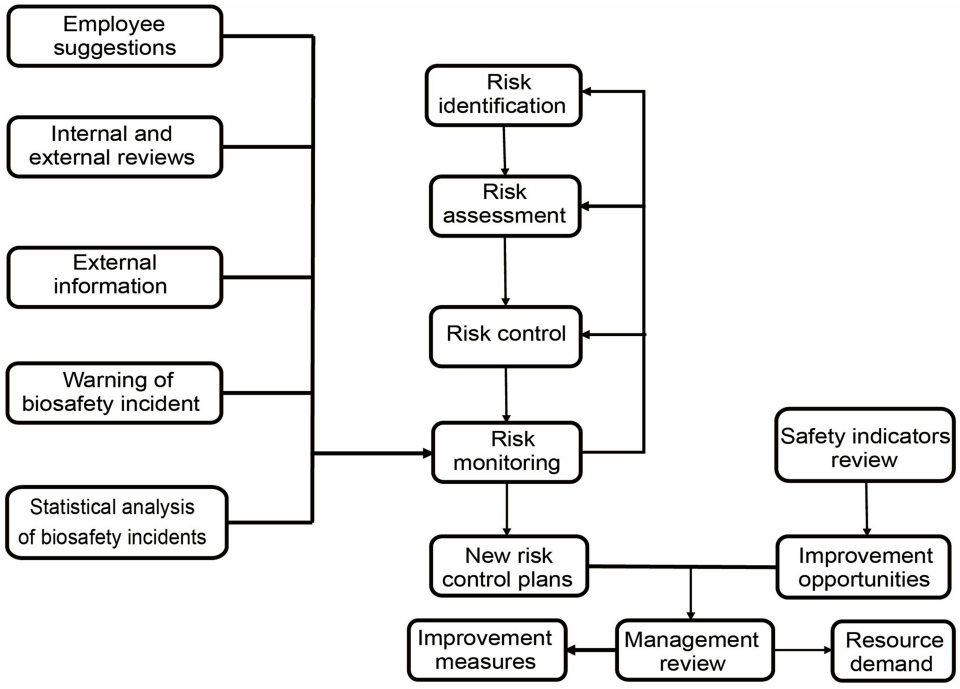

Figure 2 Flow charts for continuous improvement of biosafety management.

Biological Information of Potential Exposed Pathogenic Microorganisms

SARS-CoV-2

The source of infection is those infected with SARS-CoV-2, and the main route of transmission is through the respiratory tract and close contact. The dosage of the infection has not been reported yet. The main symptoms after infection include fever, muscle pain, a dry or sore throat, and loss of taste. Humans are generally susceptible to infection, and vaccination can reduce infection and morbidity. Infection can be prevented by wearing masks and practicing hand hygiene. The incubation period after infection is 2 to 4 days. The diagnostic method is nucleic acid and antigen testing. SARS-CoV-2 is sensitive to ultraviolet light, high temperatures, organic solvents (ether, 75% or 70% ethanol, H_2O_2, chloroform), 1 to 5% Hypochlo- rite bleach and CaviCide disinfectant, and chlorine-containing disinfectants. There are effective medicines and vaccines.[5–7]

Risk Assessment

We determined ≤ 1 as an acceptable range on hazard level of biosafety risk. Therefore, we had identified a total of 30 unacceptable risks, of which there were no risks that need to be avoided, received, or transferred. Then, we had developed and implemented appropriate risk control measures for these 30 risks (Table 1-3). Of course, We also reviewed and analyzed the suitability of risk assessment and the effectiveness of risk control. Prior to the COVID-19

Table 1 Risk Identification

Risk Number	Risk Identification
1	There is a risk of potential exposure or the environment pollution due to improper protection or misoperation.
2	Due to the poor psychological quality, there is a risk of potential exposure for laboratory staff caused by misoperation.
3	Laboratory staff with compromised immunity, such as those taking immunosuppressants or those with immunodeficiency, are at risk of being infected while engaged in laboratory activities.
4	When the protection level of the laboratory is inconsistent with the hazard degree of experimental activities, there is a risk of potential exposure for laboratory staff.
5	External personnel who enter laboratories without being informed of the biosafety risks and without wearing appropriate PPE are at risk of potential exposure.
6	Because the sterilization pressure, sterilization temperature, and sterilization time do not meet the requirements in the process of autoclaving, there is a risk that the waste cannot be effectively disinfected, leading to environmental pollution.
7	When using the biosafety cabinet, there is a risk of potential exposure for laboratory staff due to the abnormal filtration function, wind direction and pressure of the biosafety cabinet.
8	When the eye mucosa of staff is exposed, there is a risk that the eye mucosa was delayed disposal and was infected due to improper installation position of the eye wash device or abnormal function of the eye wash device.
9	During air disinfection, there is a risk that the height, quantity, and intensity of ultraviolet lamps do not meet the standards, and the purpose of air disinfection cannot be reached, resulting in potential exposure for staff and environmental pollution.
10	In mechanical ventilation laboratories, abnormal room pressure or improper location of air supply and exhaust may lead to exposure for laboratory staff or environmental pollution.
11	During the process of collecting samples from patients with respiratory infectious diseases, the surface of the sample tube may be contaminated. There is a risk of exposure when the receiving personnel come into contact with the contaminated surface of the sample tube during sample reception.
12	There is a risk of sample leakage during sample transportation due to improper sample packaging.

(*Continued*)

Table 1 (Continued).

Risk Number	Risk Identification
13	Sample centrifugation generates aerosols, therefore there is a risk of personnel exposure to the aerosols or environmental contamination from the aerosols during the centrifugation process.
14	There are risks that personnel may be exposed to aerosols from the sample tube and the environment may be contaminated by aerosols when removing the sample cap.[8]
15	There is a risk that the operator may expose to aerosols generated while adding samples with a pipette.
16	There may be a risk of exposure to a splattered sample during the smear process.
17	There are risks that operator may expose to aerosols generated during stirring or shaking the sample and the environment is polluted by the aerosols.
18	There is a risk of exposure to aerosols or splattered samples during bacterial inoculation and preparation of the bacterial solution.
19	During the process of using non automated nucleic acid extraction equipment to extract nucleic acids, there is a risk of operators being exposed to aerosols generated during the nucleic acid extraction process and a risk of environmental pollution.
20	When using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) to identify bacteria, there is a risk of exposure to aerosols generated during sample preparation if the chosen sample preparation method cannot inactivate the bacteria.[8–11]
21	There is a risk of environmental pollution caused by spilled samples during sample transfer or test operations.
22	In the process of disinfection, there are risks of laboratory staff infection and environmental pollution due to the improper selection of disinfectants.
23	In the process of disinfection, there is a risk that the disinfectant will lose its effectiveness and lead to personnel infection and environmental pollution.
24	Laboratory staff are at risk of becoming infected if they wear substandard PPE.
25	There is a risk of infectious waste being transported out of the laboratory without disinfection, and resulting in personnel exposure or environmental pollution.
26	Laboratory staff are at risk of being sharp instrument stab wounds while handling sharp instrument waste.
27	There is a risk of environmental pollution caused by discharge experimental waste liquids without disinfection.
28	When a safety incident occurs, there is a risk that laboratory staff do not know how to handle the incident, resulting in environmental pollution or personnel exposure.
29	Inadequate or inappropriate emergency planning has the potential to mislead laboratory staff in handling safety incidents, leading to the risk of personnel exposure or environmental contamination.
30	There is a risk of personnel exposure or environmental pollution due to laboratory staff being unfamiliar with emergency plans and delaying the handling of safety incidents.

pandemic, there were no biosafety incidents in our laboratory, which proved that our risk assessment was adequate and appropriate, and risk control was effective.

Risk Monitoring and Continuous Improvement of Biosafety Management

After identifying and responding to these risks, we maintained risk monitoring, and timely input the results of the risk monitoring into the management review. During the COVID-19 pandemic, we had twice updated risk identification and risk control through risk monitoring to address emerging risks or avoid excessive protection. At the beginning of

Table 2 Risk Assessment

Risk Number	Risk Severity	Risk Probability	Hazard Degree
1	3	3	9
2	2	2	4
3	3	2	6
4	3	2	6
5	3	3	9
6	2	2	4
7	3	4	12
8	3	3	9
9	2	2	4
10	3	2	6
11	3	3	9
12	3	2	6
13	3	4	12
14	3	4	12
15	2	3	6
16	2	3	6
17	3	4	12
18	3	4	12
19	3	4	12
20	3	3	9
21	2	3	6
22	3	3	9
23	3	3	9
24	3	2	6
25	3	2	6
26	3	3	9
27	3	3	9
28	3	3	9
29	3	3	9
30	3	3	9

COVID-19 in 2019, our laboratory undertook the task of laboratory testing for COVID-19 patients. Given the emergence of new potentially exposed pathogenic microorganisms in the experimental activities, we initiated risk monitoring before conducting laboratory testing. Based on the biological characteristics of SARS-CoV-2 and its distribution in various types of samples, as well as the upcoming experimental activities, the basis of the original risk assessment, we identified ten

Table 3 Risk Control

Risk Number	Risk Control	Hazard Degree of Residual Risk
1	Establish a training procedure that requires laboratory staff to receive training on biosafety risk assessment, laboratory operation, emergency response plans, and other related aspects before engaging in experimental activities	≤1
2	Establish procedures for health monitoring and psychological counseling for laboratory staff.	≤1
3	Establish a health management system for laboratory staff that prohibits staff with immunodeficiency or who are on immunosuppressant drugs from entering the laboratory.	≤1
4	Based on our risk assessment, we have determined that the risk protection level of our laboratory is level 2 and have selected PPE that corresponds to the level of protection.	≤1
5	Establish laboratory access procedures, and set up access control facilities to restrict external personnel from entering the laboratory at will.	≤1
6	The standard operating procedure (SOP) of pressure steam sterilization was established. In addition to monthly biological monitoring, the effectiveness, duration, temperature, and pressure of each disinfection should also be monitored and recorded.	≤1
7	A use and calibration SOP for the biosafety cabinet should be established which stipulates that filtration function and wind direction are monitored before each use, and the filtration function, wind direction and pressure difference of the biosafety cabinet should also be calibrated annually.	≤1
8	According to the principle that it should take no more than 10 seconds for the occupationally exposed person to walk straight to the eyewash device, the eye wash device should be reasonably allocated and installed, and the SOP for weekly maintenance of eye wash devices should be established to ensure that effluent quality, flow and water pressure meet the requirements.	≤1
9	UV lamps should be reasonably configured and installed according to the principle that the power of UV lamps per cubic meter in the laboratory should be ≥1.5 W and the linear distance between UV lamps and the disinfection surface should be approximately 1 mm.[12] An SOP should be established for disinfecting laboratory air and surfaces and monitoring UV lamp intensity.	≤1
10	The laboratory should be designed according to the mechanical ventilation principle that air is discharged from the bottom and supplied from the top, and the distance between the bottom air duct and the ground is 0.1 m ~ 0.15 m. An SOP for monitoring pressure differences before laboratory activities should be established and implemented.[13]	≤1
11	An SOP should be established that states laboratory staff should wear level 2 biosafety protective equipment to receive samples in the biosafety cabinet and spray the surface of the sample tube with a 0.2% chlorine-containing disinfectant. If the specimen is found to be leaking when receiving the sample, it should be blotted with a moisture wipe first, and then the sample tube and the surface of the moisture wipe should be sprayed with a disinfectant containing 0.55% chlorine for disinfection.[14]	≤1
12	An SOP should be established that specifies samples should be placed in airtight containers for transport. For highly pathogenic microorganisms, the inner package must be a watertight, leak-proof primary container that can be completely sealed, the auxiliary package must be a strong, watertight, leak proof container, and absorbent material should be inserted between the inner package and the auxiliary package.	≤1
13	An SOP should be established that specifies sample tube should be closed with a sample tube cap and the centrifuge cover should be closed when centrifuging.	≤1
14	An SOP should be established that specifies the opening of the sample tube cap must be performed in a biosafety cabinet or using a special instrument.	≤1

(*Continued*)

Table 3 (Continued).

Risk Number	Risk Control	Hazard Degree of Residual Risk
15	An SOP should be established specifying that adding samples with a pipette should be performed in the biosafety cabinet.	≤I
16	It is specified in the SOP that smearing specimens should be performed in the biosafety cabinet.	≤I
17	It is specified in the SOP that mixing samples should be performed in the biosafety cabinet.	≤I
18	It is specified in the SOP that the operator should wear level 2 personal protective equipment to perform bacterial inoculation or prepare bacterial solution in the biosafety cabinet.	≤I
19	Nucleic acid was collected using a sample collection tube containing a virus inactivator.	≤I
20	An SOP should be established specifying that before bacteria are identified using MALDI-TOF mass spectrometry, the presence of slow-growing bacteria or bacillus should be determined by visual observation of bacterial colonies or Gram staining examination with the microscope, and if so, preparing samples should be performed in a biosafety cabinet. Samples containing the bacillus should be prepared by filtration centrifugation or identified with a bacterial identification instrument.	≤I
21	A Spill disposal procedure should be established, which includes covering the spill area with absorbent tissue, spraying the tissue wet with 0.55% chlorine-containing disinfectant, and removing the tissue with tweezers after 5 minutes of disinfection.[14] In addition, exercises should be organized regularly according to the procedure.	≤I
22	Chlorine-containing disinfectants and 75% alcohol should be selected as common disinfectants. 75% alcohol and 0.2% chlorine-containing disinfectant should be used for surface disinfection, and 0.55% chlorine-containing disinfectant should be used for spill disinfection.[14]	≤I
23	A disinfectant effectiveness monitoring SOP should be established, stipulating that laboratory staff should monitor and record the concentration of chlorine-containing disinfectants daily and periodically replace the 75% alcohol that has been opened for use.	≤I
24	It should be stipulated in the SOP to check the quality and integrity of PPE before wearing it.	≤I
25	An SOP for the disposal of laboratory waste should be established, requiring that infectious waste be autoclaved before it can be removed from the laboratory.	≤I
26	It is prohibited in the SOP to use a needle cap to remove the needle of syringe. Sharp instruments, such as needles shall be directly placed in the sharp instrument box after use, and then removed it from the laboratory after high-pressure steam disinfection.	≤I
27	Construct a medical wastewater treatment tank. Discharge laboratory waste liquid into the treatment tank, disinfect the waste liquid before discharging.	≤I
28	Emergency response procedures for safety incidents should be established, and all laboratory staff should be trained on these procedures.	≤I
29	Emergency response procedures to be established should at least include: spill, sharp injury, mucous membrane exposure, large amounts of aerosol spill, exposure to hazardous chemicals, experimental animal bites, wound exposure, loss of infectious substances, failure of safety equipment, fire, and earthquake.	≤I
30	The laboratory managers should formulate the emergency drill plan and drill script every year, implement the drill as planned, record it, and evaluate the drill effect.	≤I

new risks and three ineffective risk control measures. These new risks exist in the processes of doffing PPE, removal of experimental waste from biosafety cabinets, nucleic acid extraction, and so on. Three ineffective risk control measures included risk control measures for sample reception, risk control measures for bacterial liquid configuration, and PPE. Based on this, we had developed appropriate risk control measures for these newly identified risks and improved these

ineffective risk control measures. During the COVID-19 pandemic, no laboratory staff were exposed and we achieved favorable outcomes. In April 2019, China fully began using nucleic acid preservation solutions containing virus inactivators. After obtaining this information, we restarted the risk assessment. The result showed that, except for the unacceptable exposure risks that still existed during the sample reception process, the hazard degree of other risks identified in the early stages of the epidemic was acceptable Based on this, we promptly adjusted our risk control measures to avoid excessive protection.

Through reviewing safety indicators, we concluded that the established safety goals had been met, but we also identified opportunities for improvement in the effective rate of disinfectants and the number of spills. Then, through management review, we increased the limits of these two quality indicators.

Discussion

The clinical laboratory managers should conduct a risk assessment before starting experimental activities and develop risk response measures based on the risk assessment. The biosafety risks in clinical laboratories come from laboratory engineering controls, personnel, safety facilities and equipment, operations, disinfectants, experimental waste, and emergency plans. Unreasonable engineering controls, such as unreasonable division of laboratory areas, unreasonable configuration of safety facilities, and unreasonable negative pressure differentials, can also pose exposure risks to laboratory staff. Therefore, adequate risk identification is a prerequisite for clinical laboratories to effectively respond to risks.

For identified risks that cannot be controlled or eliminated in experimental activities, IBC can avoid or transfer risks by not conducting or outsourcing the experimental activity. For risks that can be controlled, IBC should develop appropriate risk control measures. These risk control measures include reasonable laboratory design, the establishment of management systems and SOPs, the configuration of appropriate safety equipment and facilities, the selection and management of appropriate personal protective equipment, and suitable disinfectants, and so on. The purpose of risk control is to reduce the probability of risk occurrence and/or the severity of risk to a acceptable level, rather than necessarily eliminating the risk source. Of course, the best result of risk control is to eliminate the risk source, but sometimes eliminating the risk source is impossible, or will pay a huge price, which is also unnecessary. For laboratories, the risk with a low hazard degree and low frequency of occurrence is acceptable Therefore, we considered a hazard degree of "≤1" as the acceptable range. Additionally, risk control measures should also be appropriate to the hazard degree of risk. For the same pathogenic microorganism, the risk is not the same for different experimental activities. For example, the inactivation of the Ebola virus needs to be carried out in the BSL-3 laboratory, while the nucleic acid extraction and amplification of the Ebola virus can be carried out in the BSL-2 laboratory.[15] Similarly, for the same pathogenic microorganism, different sample disposal methods before testing result in different risks during the testing process. For example, the risk of detecting samples that have undergone virus inactivation treatment is inconsistent with detecting samples that have not undergone virus inactivation. Therefore, the 2021 fourth edition of the WHO Laboratory Biosafety Manual removed the concept of biosafety levels for laboratories, emphasizing the need to develop effective and non-excessive risk control measures based on the economic conditions of the country and the risk assessment of the laboratory.[4] Excessive risk control not only affects work efficiency and wastes limited resources but also increases the risk of infection.[16] For example, during the COVID-19 pandemic, there was no longer an exposure risk in the SARS-CoV-2 nucleic acid testing process after the use of nucleic acid preservation solutions containing virus extinguishing agents. However, in China, almost all laboratory staff still wore PPE with Level 3 biosafety protection, which not only wasted resources but also reduced work efficiency. Although the Chinese government issued corresponding guidelines in April 2021 to correct this situation,[14] the above excessive protective measures were still implemented in many laboratories until outbreak control was lifted. If laboratory managers had maintained risk monitoring, restarted risk assessment and adjusted risk control measures accordingly, the above excessive protection could have been avoided.

Every risk assessment is not perfect. In clinical trial activities, factors associated with biosafety risks may change. Therefore, after each risk assessment, there may still be new or unidentified risks in the experimental activities, and initially established risk control measures may not always be effective. For example, the Ebola outbreak in West Africa in 2014–2016 expanded to unprecedented levels due to inadequate control measures put in place by medical institutions,

which led to multiple chains of transmission.[17] Therefore, it is necessary to continuously improve biosafety management through risk monitoring to respond to emerging infectious diseases.[18]

Risk monitoring can be achieved through various means, with employee suggestions and external information being particularly important. Employee suggestions often arise from observations made during laboratory activities, such as unidentified risks or inappropriate control measures, while external information includes information from sentinel laboratories,[19] current epidemiological information in the region or elsewhere, safety incidents in other laboratories, official reports, changes in the biological characteristics of pathogenic microorganisms, changes in relevant laws and regulations, and so on. For example, in the early days of the COVID-19 in Wuhan, China, in 2019, the local health management department did not listen to the feedback from medical staff that pneumonia of unknown origin may be a new infectious disease with strong infectivity, and did not further strengthen risk control, leading to infection of some medical staff.[3] A similar incident of ignoring external information also occurred in Dallas County, Texas, USA. If local medical institutions had noticed the Ebola outbreak information in Guinea, Liberia, and Sierra Leone at that time and taken targeted protective measures, these two nurses might not have been infected with the Ebola virus when receiving fever patients from Liberia.[20] Conversely, the successful case of valuing external information and updating risk control measures was the World Health Organization's timely reduction of risk levels and updating of control measures based on SARS-CoV-2 mutation information.

The focus of risk monitoring should be on changes in experimental activities, such as potential exposed pathogenic microorganisms, the amount of pathogenic microorganisms used, sample types, and sample processing methods. These changes may increase or decrease the number of risks, or alter the hazard level of the risk, so that the initial risk assessment and control measures are no longer applicable, resulting in ineffective or excessive protection.[21] In the early stages of the outbreak in Wuhan, China, we maintained risk monitoring and implemented stricter risk control measures before testing sputum and fecal samples from COVID-19 patients, achieving good control results. During this period, no laboratory staff were infected.[22]

The review of safety indicators is an effective way to analyze the reasons why safety indicators have not reached the limit, evaluate the suitability of laboratory safety indicators, and identify improvement opportunities. Therefore, the establishment and regular review of safety indicators are also effective ways to continuously improve biosafety management. Inputting the results of regular reviews into management reviews is an effective means of achieving continuous improvement.

Conclusions

Adequate risk identification and accurate risk evaluation are particularly important for effectively controlling risks. Therefore, when implementing risk assessment, it is necessary to fully consider the risk sources from engineering control, personnel, PPE, equipment and facilities, emergency plans, disinfectants, experimental waste, operational processes, and quantitatively evaluate their hazard degree.

Effective control measures for risks include developing SOPs, employee training, immunization, the use of effective disinfectants, maintaining the normal functioning of safety equipment and facilities, and developing appropriate emergency plans. Among them, immunization and employee training should also be implemented before employees engage in experimental activities, and SOPs should comply with ethics and local laws and regulations. The continuous improvement of biosafety management is of great significance in reducing the occurrence of safety incidents, responding to emerging infectious diseases, and avoiding excessive protection. The mechanism for continuously improving biosafety management is as follows: implement risk monitoring through various channels to evaluate the suitability and adequacy of risk assessment, as well as the effectiveness of control measures, and analyze high-risk sources. Meanwhile, identify opportunities for improvement through the review of safety indicators. Then the evaluation results, high-risk sources, and improvement opportunities were input into the management review, and improvement measures and the resources required for implementing these measures are output through the management review.

The improvement measures include correcting the reason why the biosafety indicator does not meet the limit value, improving risk assessment and risk response (such as identifying new or unidentified risks, correcting inappropriate risk evaluations, improving response measures for risks). Reviewing safety indicators and risk monitoring are the ways to continuously improve biosafety management, and management review is the means to achieve continuous improvement (Figure 2).

Ethics Approval and Consent to Participate

This manuscript does not involve animal experiments, and does not involve ethical materials or patients.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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