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Short Communication

Biosafety Risk Control Strategies in Laboratory Animal Research

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ABSTRACT

To understand biosafety's current situation in laboratory animal research and risk factors affecting occupational health. Compliance surveys were conducted by questionnaire via Questionnaire Star (an application app on the Internet) in Chinese. Thirty-nine anonymous questionnaires were collected. The surveyed institution has established 24 types of ABSL (Animal Biosafety Laboratory) and biosafety management organizations and systems equipped with safety equipment. Our study also suggests that the principal of the laboratory establishment fails to perform supervision and inspection responsibilities, the inappropriate design of the animal biosafety laboratory, non-standardized personnel training and health management, non-strict waste management, and insufficient emergency management. The administrative department and work units should address certain safety and occupational health risks in laboratory animal research. The author proposes control strategies based on organizational guarantee, personnel management, emergency management, etc., to help prevent risks and ensure occupational health. Due to regional limitations and small sample size, the results may not be generalisable to all parts of the world. However, some of the key common issues may also be present in other regions, so we believe that this research still has some relevance.

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1. Introduction

The continuous deepening of the research activities on infectious diseases, chronic non-infectious diseases and biological hazardous agents has driven the construction of a group of biological safety animal laboratories. Laboratory animal work is special and complex, the nature of many animal experiments is to simulate a human condition, and the experiments are likely to involve multiple chemical, biological, physical, and/or radiological hazards [1]. Negligent laboratory management and accidents, such as improper technical operations, inadequate protection, irregular waste treatment, etc., can lead to the infection of laboratory personnel and environmental contamination. Accidental infections are not uncommon in global laboratories. A German virus scripture was accidentally stung by an acupuncture needle in a BSL-4 laboratory experimenting with the Ebola virus. Fortunately, the emergency response measures taken in time did not lead to a security incident [2]. The other 3 cases of the recorded Ebola virus needle injuries

occurred in the resulted in death [3–5] etc. Facing the biological safety incidents of laboratory animals, we must formulate strict management measures and scientific-technical guidelines to strengthen the protection of researchers and the environment.

2. Object and method

2.1. Research objects

Forty-two managers or researchers from 42 regional different institutions can understand the management status. These institutions include universities, research institutes, biopharmaceutical companies, etc., that have obtained laboratory animal licenses.

2.2. Method

Using Questionnaire Star as a platform to conduct a compliance survey (according to the relevant provisions of “the Regulations on

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the Biosafety Management of Pathogenic Microbial Laboratories" [6] and "the Regulations on the Management of Laboratory Animals" [7]) on specific institutions by secret ballot. The questionnaire survey includes 47 contents in seven aspects, including organizational management, facilities and equipment, laboratory animal management, personnel management, waste management, safety emergency management, humanized animal model research, etc. (Fig. 1)

3. Results and discussion

We received 39 questionnaires from the survey (response rate 92.9%, 39/42), including 17 managers and 22 researchers from different institutions. The survey objects and industry distribution colleges and universities, scientific research institutes, pharmaceutical companies, contract research organizations, etc., covered license holding units in the region (Table 1). The results show that the organizational management system in the working units is sound, the laboratory animal management organization and the Institutional Animal Care and Use Committee (IACUC) have been established, a number of biological safety animal laboratories have been built (categories and numbers are shown in (Table 1); a biological safety laboratory management system and technical specifications have been formulated, and an independent ventilation isolation cage (IVC), a negative pressure anatomical table, a biological safety cabinet, and a high-voltage sterilization cabinet, etc. have been equipped; the "Waste Disposal Agreement" has been signed with the Hazardous Waste Business Licensing Units. The survey results for the seven aspects of the questionnaire are shown in Tables 1 and 2. Due to the small sample size, the results may not be generalizable to all parts of the world. If management is neglected or if there is a random mentality, some of the key common issues such as skills training, waste disposal, emergency drill, humanized animal models research may also occur in other regions, so we believe that the conclusions of this study have a certain reference value for different readers in different regions.

3.1. Strengthen organizational leadership

Strengthening the organizational management and implementing safety subjects' responsibility is an important organizational

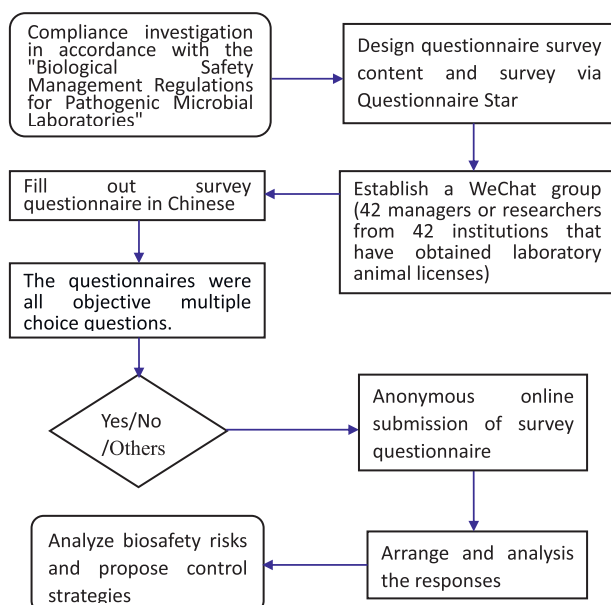


Fig. 1. Survey flow chart.

guarantee for the development of biological safety work. In Table 2, some units pay less attention to the safety of animal experiments, and the management responsibilities are not implemented; no laboratory biosafety management organization has been established (18.0%, 7/39); no safety management system (7.7%, 3/39); failure to perform supervision and inspection duties (5.1%, 2/39), etc. Whether it is routine animal experiments or pathogenic microbial experiments, the institute shall establish a biosafety management committee, coordinate the construction, operation and maintenance of biosafety laboratories, formulate laboratory biosafety manuals including "standard operating procedures," "emergency response plan," "injury and accident reporting," clarify the division of responsibilities and responsible persons in various links, establish a long-term supervision mechanism.

The laboratory shall hold regular work reports summarizing experiences and lessons learned and clarifying various safety risks. Provide regular safety warning training to enhance the sensitivity awareness of laboratory staff to identify risks and avoid risks. Turning laboratory incidents into shared lessons learned is likely to improve biosafety regardless of the biosafety level of the laboratory [8].

3.2. Improve standardization level

Standardization of animal biosafety laboratories is important in reducing cross-infection and preventing biosafety hazards. In Table 2, the laboratory design is unscientific, such as crossings in personnel flow lines (17.6, 3/17); key facilities and equipment are not maintained, monitored, verified, and calibrated according to the requirements of the procedures (29.4%, 5/17); the laboratory and activity projects of 2 institutions were not registered with the health or veterinary authorities of the people's government of the district city (11.8%, 2/17); particular animal experiments were conducted in conventional laboratories (5.9%, 1/17), etc., which are not in accordance with the relevant regulations and specifications. The Technical Specifications for the Construction of Laboratory Animal Facilities [9] require that "cross-contamination should be avoided between personnel flow lines, object flow lines, and animal flow lines of laboratory animal facilities." The Regulations on the Biosafety Management of Pathogenic Microbial Laboratories [6] stipulate that "primary and secondary laboratories should be registered with the health or veterinary authorities of the municipal government with districts." The institute should design, layout, and register facilities in accordance with relevant laws, regulations, and technical specifications.

Automatic and intelligent hardware/software management, such as robotic cage replacement workstation systems, should be considered wherever possible. The compliance of various environmental indicators should be monitored regularly. We should not ignore the possibility of biosafety accidents caused by equipment failure and other reasons, such as animal feeding equipment suffering from corrosion, deformation and ageing due to high temperature and pressure, strong acids and alkalis, resulting in loss of airtightness and laboratory air leakage.

It is necessary to carry out normative design and construction according to relevant technical standards to strengthen the management and maintenance of biosafety facilities and equipment. Special animal experiments conducted in conventional laboratories are strictly prohibited.

3.3. Strengthen personnel training and management

Management and technical personnel are important experimental research subjects and the first responsible person to avoid biological safety risks. In Table 3, some institutions lack practical

Table 1
The distribution of respondents in different institutions and the number of biosafety laboratories

Distribution of respondents	Number	Biosafety laboratory classification	Number
Colleges and Universities	21	Animal Biosafety Laboratory-1	6
Conventional laboratory animal research institutions	7	Animal Biosafety Laboratory-2	11
Scientific research institutes	6	Animal Biosafety Laboratory-2+	5
Pharmaceuticals	4	Animal Biosafety Laboratory-3	2
Contract Research Organizations	1		

Table 2
Survey results of organizational management and facilities and equipment management

Survey	Option	Respondent (n)	Yes (n1)	No (n2)	Unclear/Other (n3)	Ratio (Y/N)%
Organizational management	Is Biosafety Management Committee established?	39	30	7	2	76.9 (30/39)/18.0 (7/39)
	Is laboratory animal management committee established?	39	39	0	0	100 (39/39)/0
	Do the organization have supervision mechanism and work records?	39	32	2	5	82.1 (32/39)/5.1 (2/39)
	Is biosafety management system and technical specification established?	39	32	3	4	82.1 (32/39)/7.7 (3/39)
Facilities and equipment management	Do experts verify the layout of biosafety animal lab?	39	17	0	22	100 (17/17)/0
	Are facilities, equipment, and testing instruments maintained, monitored, verified, and calibrated?	17	12	5	0	70.6 (12/17)/29.4 (5/17)
	Is the biosafety animal laboratory registered?	17	15	2	0	88.2 (15/17)/11.8 (2/17)
	Special animal experiment conducted in regular laboratory?	17	1	16	0	5.9 (1/17)/94.1% (16/17)
	The inappropriate design of the animal biosafety laboratory?	17	3	14	0	17.6 (3/17)/88.3 (14/17)

Notes: Y = n1/n, N = n2/n. n-number of respondents, n1-number of Yes respondents, n2-number of No respondents, n3-number of Unclear/Other respondents.

training (7.7%, 3/39), unsatisfactory operational skills (7.7%, 3/39); safety protection does not meet the level requirements (5.1%, 2/39); activity projects not approved (5.9%, 1/17); no personnel health records (17.9%, 7/39). Research organizations need to formulate targeted training standards or plans, continue building capacity improvement and risk reminders, and strengthen occupational health surveillance. Projects must be approved.

Implementation of a professional training system: Institutions have more control over administrative practices meant to mitigate risks specific to the experimental protocol, including assurance of proper training and competence and occupational health assessment of research staff [10]. Before starting work, staff should receive ongoing training on laws and regulations, skills in experimental operation, use of equipment and emergency treatment. In particular, strengthen the training and learning of the "Good Microbiology Practice and Procedure (GMPP)", mastery of the most fundamental risk control measure for microbial experiments.

Establishment of strict project and personnel admittance systems of the laboratory: Without approval, no unit or individual may engage in experiments with highly pathogenic animal microorganisms. Applicants without professional and technical training or obtained laboratory qualification will be excluded from the laboratory access conditions. Immunocompromised individuals, patients in active stages of disease and individuals with allergies to animals and uncontrollable negative emotions are prohibited from participating in animal experiments involving pathogenic microorganisms.

Establishment of personnel health records: Basic information on persons exposed to pathogenic microorganisms, especially highly pathogenic microorganisms, and the experimental activities carried out should be recorded in detail. Conduct physical examinations and health monitoring to dynamically evaluate the possibility of health hazards caused by experimental activities.

Establish and improve the project risk assessment mechanism: Risk assessment is an ongoing and daily process, as new experiments and procedures are added to a research portfolio [1]. Risk assessment must consider the potential risks from the pathogen vector, experimental activities, including animal models and research methods, and equipment malfunction. Complete risk reports and implement risk control in practice. Some scholars have

found that the frequency of injuries in the biological safety laboratory, in turn, is stabbing, being caught by animals/bites, mucosal cutting, etc. [11].

3.4. Strengthen the quality control of laboratory animal

The quality of laboratory animals is an important part of biological safety. Poor management of laboratory animals will lead to related diseases, including zoonotic diseases. In Table 3, one institution is still using unqualified laboratory animals (the laboratory animals come from institutions that have not obtained the "Laboratory Animal Production License"; quality cannot be guaranteed) or laboratories for experiments/pre-experiments (2.6%, 1/39); fraudulent production and use licenses by some individual research teams (laboratory animals come from institutions without production licenses or carry out experimental activities in laboratories without use licenses, and falsely use a license) (5.1%, 2/39); used for scientific research without quarantine (7.7%, 3/39). It is essential to establish a working philosophy that gives equal importance to strengthening biosafety management and improving animal quality, and to establish and improve animal research health and safety programmes for animal research for responsible research [1]. Before animal experiments, quarantine should be carried out for a certain period to exclude the possibility that the latent infection of some diseases may become apparent due to transport stress or changes in environment, starvation and other conditions. Using unlicensed laboratory animals or laboratories for experimental research is strictly prohibited. The Measures for the Administration of Laboratory Animal Licenses (Trial) [12] stipulates that "units that have not obtained a license for the use of laboratory animals, or those that use laboratory animals and related products from units that have not obtained a production license or are of substandard quality, shall not accept the results of animal experiments."

3.5. Strict prevent disinfection and harmless disposal of waste

Disinfection/sterilization treatment is an important means of preventing biological safety incidents. Table 3 shows some laboratory waste management is not standardized, and the disposal records are incomplete. Solid waste was removed from the

Table 3

Survey results of personnel and experimental management, laboratory animal management, waste management, safety emergency management

Survey	Option	Respondent(N)	Yes(n1)	No(n2)	Ratio (Y/N)%
<i>Personnel and experimental management</i>	Are you proficient in experimental skills?	39	36	3	92.3 (36/39)/7.7 (3/39)
	Start working without training?	39	3	36	7.7 (3/39)/92.3 (36/39)
	Has the activity project been approved?	17	16	1	94.1 (16/17)/5.9 (1/17)
	Is health record established?	39	32	7	82.1 (32/39)/17.9 (7/39)
	Personal safety protection meet the safety level requirements?	39	37	2	94.9 (37/39)/5.1 (2/39)
	No environmental monitoring in sample storage room, and the handover and destruction records are incomplete?	17	4	13	23.5 (4/17)/76.5 (13/17)
<i>Laboratory animal management</i>	Are unqualified experimental animals or laboratories used for experiments/pre-experiments?	39	1	38	2.6 (1/39)/97.4 (38/39)
	Are production or use licenses are falsely used?	39	2	37	5.1 (2/39)/94.9 (37/39)
	Has the laboratory animal research project undergone ethical review?	39	38	1	97.4 (38/39)/2.6 (1/39)
	Undergone quarantine before the experiment?	39	36	3	92.3 (36/39)/7.7 (3/39)
<i>Waste management</i>	Solid waste is sterilized and removed from the laboratory?	39	37	2	94.9 (37/39)/5.1 (2/39)
	Are medical waste special bags used for classified packaging?	39	38	1	97.4 (38/39)/2.6 (1/39)
	Is there a specified temporary storage room?	39	34	5	87.2 (34/39)/12.8 (5/39)
	Waste liquid and exhaust gas be treated and discharged after reaching the standard?	39	36	3	92.3 (36/39)/7.7 (3/39)
	Carrying out the disinfection effect evaluation?	39	33	6	84.6 (33/39)/15.4 (6/39)
	Animal enter the market after the experiment?	39	2	37	5.1 (2/39)/94.9 (37/39)
<i>Safety emergency management</i>	Are emergency training and drills regularly carried out on "Emergency Response to Biosafety Emergencies"? "Incidents"?	39	32	7	82.1 (32/39)/17.9 (7/39)
	Clear about the disposal process?	39	33	6	84.6 (33/39)/15.4 (6/39)
	Are risk assessments conducted regularly?	39	31	8	79.5 (31/39)/20.5 (8/39)

Notes: Y = n1/n, N = n2/n. n-number of respondents, n1-number of Yes respondents, n2-number of No respondents, n3-number of Unclear/Other respondents.

laboratory without sterilization (5.1%, 2/39), and the waste liquid and exhaust gas were discharged after the standard was not treated (7.7%, 3/39); the disinfection effect evaluation was not carried out (15.4%, 6/39). Throughout the whole cycle of animal experiments, the operating procedures for the treatment of medical waste, dirt and wastewater and the applicable procedures for preventive disinfection, on-site disinfection and terminal disinfection should be established. During the experiment, timely preventive disinfection and sterilization of animal excreta, secretion or spillage pathogens and contaminated parts and environment were carried out. After the experimental procedure, the contaminated experimental equipment, animal cadavers, tissues, secretions, excretions, protective equipment, etc., should be sorted, classified, collected, sealed, packaged, and autoclaved before being removed from the laboratory and handed over to a professional disposal institution with disposal qualifications for centralized harmless treatment. After the experimental procedures, animal diets, experimental procedures, safety equipment, and laboratory components should be disinfected. Exhaust gas and wastewater should be discharged after treatment to meet standards. Laboratory disinfection should be carried out after each experimental batch, and the sterilization effect should be monitored. Prohibit the placing of laboratory animals on the consumer market to avoid becoming a "disseminator" of safety risks.

3.6. Improve laboratory infection emergency drills

Biosafety emergency management is an effective means to properly manage laboratory emergencies, control and eliminate hazards, and guarantee the health of researchers. Table 3 shows that biosafety emergency management is not in place in some institutions and is poorly implemented. For example, risk assessment is not carried out regularly (20.51%, 8/39), emergency training and drills for biosafety incident management are not carried out (17.95%, 7/39); the staff were not clear about the emergency treatment procedures (15.4%, 6/39). Training is the best way to eliminate the risk of biological contamination in animal facilities. It is recommended to incorporate the basic principles of facility biosafety training and the preventive measures and procedures that employees must know in case of an accident or emergency into various training modes [13]. Incorporate emergency training and drills into the emergency response management system and

conduct them at least once a year, familiarising employees with incident reporting and emergency response procedures. Accident reporting is the best opportunity for proper and standardized handling of accidents at an early stage. Laboratory workers may be reluctant to report because of embarrassment, fear of retribution, or the belief that an incident is not worth reporting [8]. This situation should be strongly discouraged. At the end of the emergency drill, the drill's effectiveness can be evaluated by all participants' ability to identify emergency risks, the use of emergency treatment techniques, the coordination and cooperation between participants, and the satisfaction with the on-site disposal.

Maintain a reserve of protective equipment, disinfectant supplies, first aid drugs and other emergency supplies related to experimental risks and update them as appropriate. Respirators are very important protective equipment in the practice of highly pathogenic microorganisms, and should be used as a back-up method of protection for certain aerosol-generating activities [14–16].

3.7. Strengthen the storage and management of pathogenic microorganism (virus) species and samples

Pathogenic microorganism species and samples are critical biological resources. In Table 3, the management of bacterial and viral species/biological specimens is not standardized, e.g. the handover and destruction of specimens was not recorded, there was no environmental control in the specimens storage room (23.5%, 4/17), etc. Strengthening storage management is one of the important measures to prevent laboratory infections. According to the pathogenic characteristics of different pathogenic microorganisms, storage institutions should formulate a strict storage system, accurately record the type, source, quantity, import and export, transportation and destruction of pathogenic microorganisms, standardize the environmental conditions and monitoring of sample storage rooms, designate particular persons to be responsible for it.

3.8. Attach importance to biosafety risk management in the research of humanized animal models

The laboratory animal model is an irreplaceable foundation and support in the field of biomedicine, which is of great importance for elucidating pathogenesis and developing drugs

and vaccines. In recent years, PDX (patient-derived xenografts) models and gene-edited animal models have been widely used in the research fields of tumors, infectious diseases, degenerative diseases, hematology, etc. It can be predicted that due to the research in animals, their biosafety risk is higher than that of non-animal experiments [17]. In practice, there is a lack of attention and prevention of biosafety problems in the operation of tumor tissues carrying retrovirus, hepatitis B virus, and herpes virus. Experiments with product aerosols were not carried out in biosafety equipment, researchers did not take safety precautions, and waste was removed from the laboratory without sterilization. Biosafety risk assessment and management should be strengthened in this field, and technical specifications should be established to prevent the occurrence of biosafety accidents in the laboratory.

4. Conclusion

The investigated personnel are distributed in all laboratory animal license units and have a certain representativeness. The survey showed that 69.2% (27/39) believed that the risk of biosafety animal experiments in this institution was at a low level (low probability of biosafety accidents occurring), and 30.8% (12/39) believed that the risk was certain (based on the existing problems, it is assumed that there are certain biosafety risks). Although this type of survey has certain limitations, for example, we do not know the background or status of the respondents in the institution, whether they are familiar with the management status, and whether the answers are subjective and one-sided. Still, the problems of waste management, humanized animal model research, emergency management and other segments issues should attract the attention of authorities and research institutions. We propose building an efficient, comprehensive biosafety prevention and control system to establish an “occupational health firewall” from the hardware and software perspective. Meanwhile, relevant regulations or guidelines should clarify that biosafety animal laboratories must first obtain a licence for using laboratory animals. Incorporate humanized animal model research in the scope of biosafety management.

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Ethical statements

Not required.

Author contributions

Shun-tai Weng: Methodology, Writing-Reviewing and Editing. **Qu-wen Li:** Supervision, Writing-Reviewing and Editing. **Ya-dong Gao:** Investigation, Writing-Reviewing. **Yu-feng Qiu:** Investigation, Writing-Original draft preparation.

Conflicts of interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately

influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

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Appendix A. Supplementary data

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