LABORATORY BIOSAFETY MANUAL
FOURTH EDITION
AND
ASSOCIATED MONOGRAPHS

RISK ASSESSMENT

World Health Organization

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Glossary of terms

Acceptable risk: The risk that is considered acceptable and allows work to proceed bearing in mind the expected benefit of the planned activities.

Accident: An inadvertent occurrence that results in actual harm such as infection, illness, injury in humans or contamination of the environment.

Aerosol: Liquid or solid particles suspended in air and of a size that may allow inhalation into the lower respiratory tract (usually less than 10 micrometres in diameter).

Aerosol/airborne transmission: The spread of infection caused by the inhalation of aerosols.

Biological agent: A microorganism, virus, biological toxin, particle or otherwise infectious material, either naturally occurring or genetically modified, which may have the potential to cause infection, allergy, toxicity or otherwise create a hazard to humans, animals, or plants.

Biological safety cabinet (BSC): An enclosed, ventilated working space designed to provide protection to the operator, the laboratory environment and/or the work materials for activities where there is an aerosol hazard. Containment is achieved by segregation of the work from the main area of the laboratory and/or through the use of controlled, directional airflow mechanisms. Exhaust air is passed through a high-efficiency particulate air (HEPA) filter before recirculating into the laboratory or into the building's heating, ventilation and air conditioning system. There are different classes (I, II and III) of BSCs that provide different levels of containment.

Biosafety: Containment principles, technologies and practices that are implemented to prevent unintentional exposure to biological agents or their inadvertent release.

Biosafety officer: An individual designated to oversee facility or organizational biosafety (and possibly biosecurity) programmes. The person fulfilling this function may also be termed biosafety professional, biosafety advisor, biosafety manager, biosafety coordinator, or biosafety management advisor.

Biosecurity: Principles, technologies and practices that are implemented for the protection, control and accountability of biological materials and/or the equipment, skills and data related to their handling. Biosecurity aims to prevent their unauthorized access, loss, theft, misuse, diversion or release.

Calibration: Establishment of the relationship between the measurement provided by the instrument and the corresponding values of a known standard, allowing correction to improve accuracy. For example, laboratory equipment such as pipetting devices may need calibration periodically to ensure proper performance.

Certification: A third-party testimony based on a structured assessment and formal documentation confirming that a system, person or piece of equipment conforms to specified requirements, for example, to a certain standard.

Consequence (of a laboratory incident): The outcome of an incident (exposure to and/or release of a biological agent) of varying severity of harm, occurring in the course of laboratory operations. Consequences may include a laboratory-associated infection, other illness or physical injury, environmental contamination, or asymptomatic carriage of a biological agent.

Containment: The combination of physical design parameters and operational practices that protect personnel, the immediate work environment and the community from exposure to biological agents. The term "biocontainment" is also used in this context.

Core requirements: A set of minimum requirements defined in the fourth edition of the World Health Organization (WHO) *Laboratory biosafety manual* to describe a combination of risk control measures that are both the foundation for, and an integral part of, laboratory biosafety. These measures reflect international standards and best practice in biosafety that are necessary to work safely with biological agents, even where the associated risks are minimal.

Engineering controls: Risk control measures that are built into the design of a laboratory or laboratory equipment to contain the hazards. Biological safety cabinets (BSCs) and isolators are forms of engineering control in order to minimize the risk of exposure to and/or unintended release of biological agents.

Exposure: An event during which an individual comes in contact with, or is in close proximity to, biological agents with the potential for infection or harm to occur. Routes of exposure can include inhalation, ingestion, percutaneous injury and absorption and are usually dependent upon the characteristics of the biological agent. However, some infection routes are specific to the laboratory environment and are not commonly seen in the general community.

Good microbiological practice and procedure (GMPP): A basic laboratory code of practice applicable to all types of laboratory activity with biological agents, including general behaviours and aseptic techniques that should always be observed in the laboratory. This code serves to protect laboratory personnel and the community from infection, prevent contamination of the environment and provide protection for the work materials in use.

Hazard: An object or situation that has the potential to cause adverse effects when an organism, system or (sub)population is exposed to it. In the case of laboratory biosafety, the hazard is defined as biological agents which have the potential to cause adverse effects to personnel and/or humans, animals, and the wider community and environment. A hazard does not become a "risk" until the likelihood and consequences of that hazard causing harm are taken into account.

Heightened control measures: A set of risk control measures as described in the WHO *Laboratory biosafety manual* that may need to be applied in a laboratory facility because the outcome of a risk assessment indicates that the biological agents being handled and/or the activities to be performed with them are associated with a risk that cannot be brought to an acceptable risk with the core requirements only.

Incident: An occurrence that has the potential to, or results in, the exposure of laboratory personnel to biological agents and/or their release into the environment that may or may not lead to actual harm.

Initial risk: Risk associated with laboratory activities or procedures that are conducted in the absence of risk control measures.

Laboratory-associated infection: Any infection acquired or reasonably assumed as a result of exposure to a biological agent in the course of laboratory-related activities. A person-to-person transmission following the incident may result in linked secondary cases. Laboratory-associated infections are also known as laboratory-acquired infections.

Likelihood (of a laboratory incident): The probability of an incident (that is exposure to and/or a release of a biological agent) occurring in the course of laboratory work.

Maximum containment measures: A set of highly detailed and stringent risk control measures described in the fourth edition of the WHO *Laboratory biosafety manual* that are considered necessary during laboratory work where a risk assessment indicates that the activities to be performed pose very high risks to laboratory personnel, the wider community and/or the environment, and therefore an extremely high level of protection must be provided. These are especially needed for certain types of work with biological agents that may have catastrophic consequences if an exposure or release were to occur.

Pathogen: A biological agent capable of causing disease in humans, animals or plants.

Personal protective equipment (PPE): Equipment and/or clothing worn by personnel to provide a barrier against biological agents, thereby minimizing the likelihood of exposure. PPE includes but is not limited to, laboratory coats, gowns, full-body suits, gloves, protective footwear, safety glasses, safety goggles, masks and respirators.

Propagation: The action of intentionally increasing or multiplying the number of biological agents.

Residual risk: Risk that remains after carefully selected risk control measures have been applied. If residual risk is not acceptable, it may be necessary to apply additional risk control measures or to stop the laboratory activity.

Risk: A combination of the likelihood of an incident occurring and the severity of the consequences (harm) if that incident were to occur.

Risk acceptance: The risk that is considered to be acceptable, typically after risk control measures have been applied and allows laboratory work to proceed.

Risk assessment: A systematic process of gathering information and evaluating the likelihood and consequences of exposure to or release of workplace hazard(s) and determining the appropriate risk control measures to reduce the risk to an acceptable risk.

Risk communication: An interactive and systematic process to exchange information and opinion on risk(s) that inclusively engages all relevant personnel of various categories as well as community leaders and officials where appropriate. Risk communication is an integral and ongoing part of the risk assessment, soliciting clear understanding of the risk assessment process and outcomes, aiming at proper implementation of risk control measures. Decisions on risk communication, including what, whom and how should be part of an overall risk communication strategy.

Risk control measure: Use of a combination of tools, which include communication, assessment, training, and physical and operational controls, to reduce the risk of an incident/event to an acceptable risk. The risk assessment cycle will determine the strategy that should be used to control the risks and the specific types of risk control measures required to achieve this.

Safety culture: A set of values, beliefs and patterns of behaviour instilled and facilitated in an open and trusting atmosphere by individuals and organizations working together to support or enhance best practice for laboratory biosafety, irrespective of whether it is stipulated in applicable codes of practice and/or regulations.

Sharps: Any device or object that is a puncture or wound hazard because of its pointed ends or edges. In the laboratory, sharps can include needles, syringes with attached needles, blades, scalpels or broken glass.

Standard operating procedures (SOPs): A set of well-documented and validated stepwise instructions outlining how to perform laboratory practices and procedures in a safe, timely and reliable manner, in line with institutional policies, best practice and applicable national or international regulations.

Transmission: The transfer of biological agent(s) from objects to living things, or between living things, either directly or indirectly via aerosols, droplets, body fluids, vectors, food/water or other contaminated objects.

Validation: Systematic and documented confirmation that the specified requirements are adequate to ensure the intended outcome or results. For example, in order to prove a material is decontaminated, laboratory personnel must validate the robustness of the decontamination method by measurement of the remaining biological agents against the detection limit by chemical, physical or biological indicators.

Verification: Confirmation that a given item (product, process or system) satisfies the specified requirements. For example, verification that the performance of an autoclave meets the standards specified by the manufacturer should be performed periodically.

Zoonotic diseases (zoonosis): Infectious disease that is naturally transmitted from animals to humans and vice versa.

Executive summary

Risk assessment is a systematic process of gathering information and evaluating risks to support a risk management strategy that is informed by the likelihood and consequences of an inadvertent release of and/or exposure to a biological agent. Risk assessment is essential to guide the selection of risk control measures and ensure biosafety within the laboratory when working with biological agents. This assessment requires consideration of many factors including: route(s) of transmission of the biological agent(s), pathogenicity and infectious dose, availability of prophylactic treatment or a vaccine, disease severity and mortality, contagiousness, endemicity, high-risk laboratory procedures (such as work with aerosols, high titres or volumes of the biological agent(s) being produced/handled, sharps, animals), competency of laboratory personnel, susceptibility of individual personnel and biosecurity (potential for misuse of biological agents/use as a weapon for harm). This monograph describes the process of carrying out a risk assessment of work with a biological agent(s) so that an informed decision can be made by a laboratory facility about the risk control measures needed for the work to be safely conducted. The targeted readership for this monograph is biosafety officers, laboratory personnel, laboratory managers and scientists who are doing the risk assessment.

The information in this monograph on risk assessment is designed to accompany and support the fourth edition of the WHO *Laboratory biosafety manual* (core document) and other associated monographs. The manual and the monographs adopt a risk- and evidence-based approach to biosafety rather than a prescriptive approach in order to ensure that laboratory facilities, safety equipment and work practices are locally relevant, proportionate to needs and sustainable. Emphasis is placed on the importance of a "safety culture" that incorporates risk assessment, good microbiological practice and procedure and standard operating procedures, relevant introductory, refresher and mentoring training of personnel, and prompt reporting of incidents and accidents followed by appropriate investigation and corrective actions. This new approach aims to facilitate laboratory design and ways of operating that ensure greater sustainability while maintaining adequate and appropriate control of biosafety.

The other associated monographs provide detailed information and help implement systems and strategies on the following specialized topics: laboratory design and maintenance, biological safety cabinets and other primary containment devices, personal protective equipment, decontamination and waste management, biosafety programme management and outbreak preparedness and resilience.

This monograph describes selecting a risk assessment team and completing a risk assessment as well as implementation strategies and lessons learnt. Two risk assessment templates, a short and long one, are provided that personnel can use as guides when carrying out a risk assessment. In addition, four examples of completed risk assessments with different scenarios are included.

SECTION 1

INTRODUCTION

Effective control of biological risk is the cornerstone of laboratory biosafety. All laboratories that handle or process biological agents have a responsibility to their personnel and the wider community to ensure that work is done in a way that brings the potential for incidents and accidents to a minimum. The fourth edition of the WHO *Laboratory biosafety manual (1)* promotes a situational approach to laboratory biosafety that is risk- and evidence-based, rather than fixed and inflexible operational requirements. This new approach is best implemented through risk assessment, a systematic process of gathering information and evaluating risks to support a risk management process. The need to select risk control measures, such as training and procurement of specific types of PPE, are all influenced by the results of a risk assessment. For these reasons, risk assessments must always be carried out in a standardized and systematic way to ensure that they are repeatable and comparable.

The information in this monograph on risk assessment is designed to accompany and support the fourth edition of the WHO *Laboratory biosafety manual (1)* (core document). The other associated monographs provide detailed information and help implement systems and strategies on the following specialized topics: laboratory design and maintenance *(2)*, biological safety cabinets and other primary containment devices *(3)*, personal protective equipment *(4)*, decontamination and waste management *(5)*, biosafety programme management *(6)* and outbreak preparedness and resilience *(7)*.

Conducting a comprehensive biological risk assessment relies on knowledge and a clear understanding of core concepts such as that risk is the likelihood of an incident with a hazard that has consequences. In the context of laboratory biosafety, a hazard is a biological agent whose pathogenic characteristics give it the potential to cause harm to people, animals and/or the environment. The risk associated with the hazard is defined as the combination of the likelihood of an incident and the severity of the harm (consequences) if that incident were to occur. Here, likelihood is the probability of an exposure to or release of the hazard occurring during laboratory work, and the consequence is the severity of the outcome if such an incident occurred. As such, the risks of manipulating any biological agent depend on many dynamic factors, including procedures to be performed, type of equipment available, inherent pathogenic properties of the biological agent itself, the range of hosts that can be affected and whether the biological agent is endemic in the population, susceptibility of local populations, and the competency of laboratory personnel carrying out the work.

1.1 Intended scope and objectives

The purpose of this monograph is to provide detailed, stepwise guidance in carrying out a thorough risk assessment for laboratory work with biological agents. Whether acting as a biosafety professional, laboratory scientist, facility manager or technician, the information in this monograph is intended for all personnel who handle biological agents so that they understand the key concepts and considerations of the risk assessment framework. The risk assessment framework (Figure 1.1) is a process with

Figure 1.1 The risk assessment framework

five steps or procedures based on the Plan-Do-Check-Act cycle:

- gather information,
- evaluate the risks,
- develop a risk control strategy,
- select and implement risk control measures and
- review risks and risk control measures.

Although each step in the risk assessment framework appears to be discrete and ordered, in reality, many biosafety professionals who perform risk assessments on a daily basis do not do so in a stepwise way. For instance, they might consider many elements, such as the biological agent, applicable procedures and available risk control measures, to simultaneously evaluate risk and develop a risk control strategy. Thus, the framework is not intended to mandate one "correct" way to carry out a risk assessment. Instead, the framework suggests a process that includes all the steps and key considerations needed to assess the likelihood and consequences of a potential exposure to and/or release of biological agents when working with these agents. It is important that this framework is applied in a transparent and consistent manner.

The actual steps of a risk assessment, and the order in which they are carried out, are not as important as carefully considering all relevant information before making decisions about the selection and implementation of risk control measures to ensure that the selected measures are relevant, effective and sustainable.

1.2 How to use this monograph

This monograph is not intended to supersede any existing regulations or guidelines and if used, it should be in conjunction and compliance with any national, local and/or institutional biosafety requirements or other risk assessment templates. The risk assessment framework and templates provided in this monograph (Annexes 1 and 2) are intended to be supplemented with relevant biosafety information in the fourth edition of the *Laboratory biosafety manual (1)* to guide laboratory professionals to assess risk at their own institutions. Alternatively, this monograph and the two risk assessment templates can be used to supplement any other risk assessment scheme or template that is already in use. In section 4 of this monograph, three situations are described which show the importance of conducting a risk assessment and provide insight into lessons learnt. In addition, four completed risk assessments are included in the annexes of this monograph to provide realistic and detailed examples of situations encountered in many laboratories (Annexes 3, 4, 5 and 6). They can be used as a guide to carrying out a risk assessment.

Comprehensive biological risk assessments identify and consider factors affecting all laboratory personnel. In general and in using the tools provided in this monograph, information should be collected from personnel with different laboratory roles and duties to ensure all perspectives have been represented. These personnel include: laboratory technicians and scientists, laboratory and quality managers, principal investigators, maintenance workers, and biosafety and biosecurity experts. Information should also be obtained from the scientific literature such as research papers or review articles, technical literature and web-based resources. By taking into consideration all relevant personnel and circumstances in the biological risk assessment process, the person or team conducting the risk assessment can make informed decisions for the benefit of all, thereby strengthening overall institutional biosafety practices.

While the templates were primarily developed for biosafety risk assessment, they can also be used for general safety risk assessment of laboratory activities, especially when biosafety and general safety risks are interlinked, for example, specimen collection and transport, where appropriate and applicable.

SECTION 2

GETTING STARTED

2.1 Selecting the risk assessment team

Risk assessment is the fundamental process that supports a broader biosafety management programme. Effective biosafety management integrates and cooperates with an organization's existing safety and quality management and leadership structures to promote evidence-based, continuous improvement, and an organization-wide biosafety culture. As such, risk assessment is an important responsibility of all members of the laboratory, and of stakeholders outside the laboratory. Careful selection of team members to contribute to the laboratory risk assessment process can directly support the establishment and maintenance of an improved biosafety risk culture by facilitating leadership and organizational involvement, ownership and understanding of biosafety responsibilities. These concepts are described in further detail in the *Monograph: biosafety programme management (6).*

A comprehensive, effective risk assessment requires input from laboratory personnel who understand the processes and procedures within the scope of the work being assessed. The first step in the risk assessment process is to identify the person to lead the assessment and the team who will contribute to it. The roles and responsibilities of all team members must be clearly defined before starting the assessment, although additional people may be consulted as needed. The members of the risk assessment team should have demonstrated skill in working with the biological agents being handled or similar biological agents and understand all the hazards associated with the protocols and procedures to be carried out in the laboratory. The team members must be familiar with the layout and condition of the laboratory facility as well as the equipment to be used in the procedure. The risk assessment team should also know the competency and experience of laboratory personnel who will be doing the laboratory work. Personnel on the risk assessment team may include, but are not limited to, principal investigators, laboratory and quality managers, laboratory technicians and biosafety officers. In situations where the number of personnel is limited, it may not be possible to gather a team of people qualified to carry out the risk assessment. The team may comprise one or more individuals but smaller teams have a greater workload and responsibility in carrying out the risk assessment. Alternative risk assessment teams are discussed in section 4 of this monograph. It is important to note that the involvement of the laboratory and/or organizational leadership in the risk assessment process, whether by direct participation in the risk assessment team or by communication with the team, is essential to establish organizational support for and sustainability of a biosafety management programme.

2.2 Factors to consider

After the risk assessment team has been formed, the risk assessment can proceed. As an example or to use as a template, a detailed step-by-step description of how to conduct a risk assessment is provided in the fourth edition of the *Laboratory biosafety manual (1)* (refer to section 2) and in the short (Annex 1) and long (Annex 2) risk assessment templates in this monograph. The team must gather information about the hazards associated with the biological agent and laboratory process(es) under consideration. This information should be collected from all relevant personnel through interviews, and relevant published material should be consulted as necessary. This information-gathering step is essential to the biological risk assessment because it influences all steps that follow. Missing pieces of information in this step (knowledge gaps) will negatively affect the evaluation of all the risks and the subsequent selection of risk control measures.

In Table 2.1 the steps of the risk assessment and key considerations are listed.

Table 2.1 Key considerations in the risk assessment framework

STEP	KEY CONSIDERATIONS
1. Gather information (hazard identification)	▪ What biological agents will be handled and what are their pathogenic characteristics? ▪ What type of laboratory work and/or procedures will be conducted? ▪ What type(s) of equipment will be used? ▪ What type of laboratory facility is available? ▪ What human factors exist (for example, what is the level of competency of personnel)? ▪ What other factors exist that might affect laboratory operations (for example, legal, cultural, socioeconomic, public perception)?
2. Evaluate the risks	▪ How could an exposure and/or release occur? ▪ What is the likelihood of an exposure and/or release? ▪ What information gathered influences the likelihood the most? ▪ What are the consequences of an exposure and/or release? ▪ Which information gathered influences the consequences the most? ▪ What is the overall initial risk of the activities? ▪ What is the acceptable risk? ▪ Which risks are unacceptable? ▪ Can the unacceptable risks be controlled, or should the work not proceed at all?
3. Develop a risk strategy	▪ What resources are available for risk control measures? ▪ What risk control strategies are most applicable for the resources available? ▪ Are resources sufficient to obtain and maintain those risk control measures? ▪ Are proposed control strategies effective, sustainable and achievable in the local context?

Table 2.1 Key considerations in the risk assessment framework (continued)

STEP	KEY CONSIDERATIONS
4. Select and implement risk control measures	▪ Are there any national/international regulations requiring prescribed risk control measures? ▪ What risk control measures are locally available and sustainable? ▪ Are available risk control measures adequately efficient, or should multiple risk control measures be used in combination to enhance efficacy? ▪ Do selected risk control measures align with the risk control strategy? ▪ What is the level of residual risk after risk control measures have been applied and is it now acceptable? ▪ Are additional resources required and available for the implementation of risk control measures? ▪ Are the selected risk control measures compliant with national/international regulations? ▪ Has approval to conduct the work been granted? ▪ Have the risk control strategies been communicated to relevant personnel? ▪ Have necessary items been included in the budget and purchased? ▪ Are operational and maintenance procedures in place? ▪ Have personnel been appropriately trained?
5. Review risks and risk control measures	▪ Have there been any changes in activities, biological agents, personnel, equipment or facilities? ▪ Is there any new knowledge available of biological agents and/or the processes being used? ▪ Are there any lessons learnt from incident reports and investigations that may indicate improvements to be made? ▪ Has a periodic review cycle been established?

Risk is assessed based on the likelihood of an exposure to or release of a biological agent and the consequences of such an exposure/release. For each step of the risk assessment cycle, there are several factors that can affect both likelihood and consequence of exposure to or release of the biological agent. The main factor affecting the consequences, or severity of harm, is the inherent pathogenic properties of the biological agent(s) that will be assessed. The likelihood of an exposure or release during laboratory operations is influenced by several factors, which include: the procedures to be performed, the surrounding laboratory environment, the personnel directly working with the biological agent involved and many others. The concepts of likelihood and consequence and the factors contributing to them, as they relate to biological risk assessment, are described in more detail in the fourth edition of the *Laboratory biosafety manual (1)* (refer to section 2 and Table 2.2 to Table 2.4 also in this monograph).

A full list of factors to consider is provided in the following sections and annexes to guide the collection of information. It is important to note that not all factors will affect risk in the same way but each should be carefully considered.

Table 2.2 Factors that affect the likelihood of an incident occurring

FACTORS ASSOCIATED WITH HIGH LIKELIHOOD OF INCIDENTS OCCURRING	RATIONALE
Laboratory activities associated with aerosolization (for example, sonication, homogenization, centrifugation)	When aerosols are generated by these methods, the likelihood of exposure through inhalation is increased, as is the likelihood of release of these aerosols into the surrounding environment where they might contaminate laboratory surfaces and also spread into the community.
Laboratory activities associated with sharps materials	When activities involve work with sharps, the likelihood of percutaneous exposure to a biological agent through a puncture wound is increased.
Low competency of personnel carrying out the work	Low proficiency of personnel in laboratory processes and procedures, through lack of experience, understanding or failure to comply with SOPs and GMPP, can lead to errors in performing the work which are more likely to result in exposure to and/or release of a biological agent. Cleaning and maintenance personnel must be trained before working close to a biological agent.
Highly environmentally stable biological agents	Biological agents that have settled on laboratory surfaces (for example, contamination caused by poor technique that allowed settling of aerosol or droplets after release) can be a source of inadvertent exposure as long as they remain stable in the environment, even if the contamination cannot be seen.
Inadequate or poor availability of electrical power, dilapidated laboratory facilities and building systems, malfunctioning equipment, damage from frequent severe weather and access of insects and rodents to the laboratory.	All these factors may result in partial breaches in, or complete failure of, biocontainment systems designed to reduce the likelihood of exposure to and/or release of biological agents.

GMPP = good microbiological practice and procedure; SOPs = standard operating procedures.

Table 2.3 Factors that affect the consequences of an incident if it were to occur

FACTORS ASSOCIATED WITH GREATER CONSEQUENCES IF AN INCIDENT WERE TO OCCUR	RATIONALE
Low infectious dose	For infection to occur in an exposed individual, a certain quantity (volume, concentration) of biological agent must be present. Even a small amount of an agent could result in severe consequences, such as a laboratory-associated infection. Furthermore, exposure to larger quantities of that agent (greater than the infectious dose) may result in a more severe presentation of the infection.
High communicability	Even one single exposure (causing carriage or a laboratory-associated infection) could rapidly spread from laboratory personnel or fomites to many individuals.
High severity and mortality	A laboratory-associated infection following exposure is more likely to cause personnel to become debilitated, lose their quality of life or die.
Limited availability of effective prophylaxis or therapeutic interventions	The symptoms or outcomes of a laboratory-associated infection cannot be effectively prevented, reduced or eliminated by a medical intervention. This may also include situations where medical intervention is not available, or emergency response capacity is limited.
Large susceptible population (including laboratory personnel at increased risk)	The larger the susceptible population, the more likely a laboratory-associated infection could rapidly spread and infect larger numbers of people.
Lack of endemicity (such as exotic disease)	When an agent is not endemic in the surrounding population, the population is more likely to be susceptible to the agent, leading to an increased likelihood of a laboratory-associated infection spreading to the community.

Table 2.4 Factors associated with both a high likelihood of and greater consequences from a potential incident

FACTORS ASSOCIATED WITH BOTH A HIGH LIKELIHOOD OF AND GREATER CONSEQUENCES FROM A POTENTIAL INCIDENT	RATIONALE
High concentration or volume of the biological agent	The more biological agent there is in the substance being handled, the more infectious particles there will be available for exposure, and the more likely the exposure volume will contain the infectious dose of that agent. Furthermore, being exposed to a higher concentration of the agent could result in a more severe infection, illness or injury.
Airborne route of transmission	Biological agents with an airborne route of transmission may be capable of remaining in aerosols for prolonged periods of time and may disseminate widely in the laboratory environment, increasing the likelihood that personnel may be exposed to the agent. Furthermore, following an exposure event, aerosolized biological agents may be inhaled and deposit on the respiratory tract mucosa of the exposed individual, possibly leading to a laboratory-associated infection.

Once the factors associated with likelihood or consequence have been defined, a risk assessment matrix can be used to determine the extent to which these factors affect the risk. A qualitative matrix-based risk evaluation approach is described in this monograph in which both likelihood and severity are assigned a non-numerical classification, which allows the ranking of risk as, for example, "low", "medium" or "high." With this matrix-based approach, the range of classifications for likelihood and severity can be defined as shown below.

Likelihood of an exposure or release occurring during the proposed laboratory work

- Rare: almost impossible to occur
- Unlikely: not very possible to occur
- Possible: might occur
- Likely: very possible to occur
- Almost certain: highly probable to occur

Severity of the consequences of an exposure/release

- Negligible: Trivial incident or near miss requiring reporting and follow up
- Minor: Incident with self-limiting consequences
- Moderate: Incident that requires medical treatment and/or has insignificant environmental consequences
- Major: Incident with potential lost time due to infection but non-permanent consequence and/or limited environmental impact
- Severe: Potential fatality or serious illness with permanent disability and/or serious environmental impact

This detailed classification system can be found in Annex 2. Long risk assessment template and a simplified version in Annex 1. Short risk assessment template.

Although a qualitative approach to combining likelihood and severity parameters in a risk matrix is provided as a risk evaluation method here, it is important to note that quantitative (for example, simple numerical scoring schemes to complex mathematical models) and hybrid (semi-quantitative) methods can also be used for risk evaluation. Laboratories should use a risk evaluation/assessment method that best meets their unique needs, without excluding the possibility of developing customized evaluation approaches, scoring methods and definitions of the parameters.

2.3 Completing the risk assessment

Two optional templates are provided to help those conducting a risk assessment to document all the needed information (Annexes 1 and 2). The first version is shorter and simplified, and may be more useful for small laboratories with a well-defined and limited scope of work. The second version is longer and more detailed, which may be better suited for larger facilities with more complex laboratory operations or may serve as a training tool for risk assessment methodologies. For laboratories already using another risk assessment method, the templates may provide suggestions that can be used to complement their current method.

If using one of the templates, complete all sections following the instructions in the grey boxes, customizing and modifying as needed. The templates could be used as a tool to facilitate the risk assessment process. The instructions and bullet points in the grey boxes can be copied into the text boxes beneath the instructions and used as prompts to gather and record the necessary site-specific information.

The grey instruction boxes can then be deleted, and the text remaining will form a risk assessment draft. This draft must be carefully reviewed, edited as necessary and approved by the risk assessment team members.

The final draft, including the recommendations of the team, can then be shared with the laboratory management. If the work being assessed is approved, the process can move forward and work can begin with the recommended risk control measures in place to reduce risk, if needed.

A risk assessment is a continual, cyclical process as shown by the framework (Figure 1.1). Once the laboratory work begins, the risk assessment should be reviewed and reassessed periodically to address any procedural changes or newly available information. The template can also be used for future iterations of the continuous process of risk assessments. Changes that should prompt a reassessment include equipment or environmental changes, such as procurement of new PPE or laboratory equipment, or modifications to laboratory spaces. Regulatory changes that would prompt risk reassessment include changes in legislative oversight of laboratory operations, including pathogen classification or handling, and updates to biosafety and biosecurity laws. Changes in personnel, including changes in the health status of personnel, are also prompts to reassess risks associated with the laboratory work. In addition, changes in the pathogen status, such as an increase in the prevalence of disease, expansion of geographical boundaries or development of highly resistant strains, should prompt review of existing risk assessments. In "Step 5 Review risks and risk control measures" in the short (Annex 1) and long (Annex 2) risk assessment templates, the review and reassessment are scheduled. Special situations, such as an outbreak response, need a dynamic risk assessment that frequently reassesses the risk and adapts the risk control strategy when necessary. More information on risk assessment in outbreak situations can be found in *Monograph: preparedness and resilience for an outbreak response (7)*, section 2. Note that periodic review of risk must also include analysis of ongoing studies to ensure that they are adequately justified and the scientific benefits outweigh biosafety risks.

SECTION 3

APPLYING RISK ASSESSMENT TO CONTROL RISKS

Laboratories that work with biological agents can never eliminate all biological risks completely. Determining if the risks associated with the work are acceptable or controllable and hence the work can proceed safely, or if they are too high to allow the work to be done is part of the risk assessment process. The acceptable risk will vary from laboratory to laboratory, institution to institution, region to region and country to country and is influenced by several factors. These factors include but are not limited to: regulatory requirements overseeing risk, availability and sustainability of resources and measures for risk mitigation, endemicity of the biological agent or disease in the local population, value of the work to the community and the risk perception of stakeholders.

Risk acceptance is ultimately determined by the institution and its leadership. For institutions in regions where published guidance and/or regulations for developing an acceptable level are currently lacking, the information provided in this section, as well as in Annexes 1–6, can be used to begin understanding and developing an institutional approach to risk acceptance. Such an approach will help decide if the risk it is acceptable (very low or low, for example) or if the risk is unacceptable (medium, high or very high, for example) and requires risk control measures to bring the risk to an acceptable risk (very low or low, for example) for work to proceed, based on the following risk categories.

Table 3.1 Risk assessment matrix defining the risk based on the likelihood of exposure and/or release and the consequences

		Likelihood of exposure/release				
		Rare	Unlikely	Possible	Likely	Almost certain
Consequences of exposure/ release	Severe	Medium	Medium	High	Very high	Very high
	Major	Medium	Medium	High	High	Very high
	Moderate	Low	Low	Medium	High	High
	Minor	Very low	Low	Low	Medium	Medium
	Negligible	Very low	Very low	Low	Medium	Medium

It is important to note that there are various methods, in addition to the one described in this monograph, to determine the acceptable risk. Institutions should use a risk acceptance strategy that best meets their unique needs without excluding the possibility of developing customized approaches and risk categories that are better aligned with their laboratory operations.

Based on the initial risk of the laboratory activity, a risk control measure can be applied to lower this risk to an acceptable risk (Figure 3.1). In some cases, multiple risk control measures may be required for the risk to be adequately addressed.

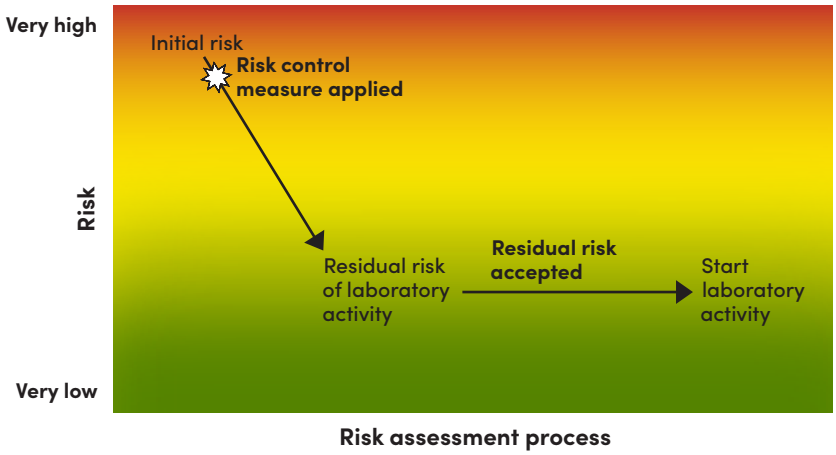

Figure 3.1 Example of how applying one risk control measure reduces the risk to an acceptable residual risk, which allows the laboratory activity to start

3.1 Application of key risk assessment steps

A progressive series of common laboratory situations is shown in Table 3.2 to illustrate how the risk assessment process is applied, and how different laboratory procedures will need different risk control measures.

The first example in Table 3.2 covers an example of low-risk laboratory work involving smear preparation and microscopy of sputum specimens. Core requirements (described in detail in section 3 of the fourth edition of the WHO *Laboratory biosafety manual (1)*) could be sufficient to control this low risk and no additional risk control measures are needed. However, it is important to note that despite the low risk, GMPP must be applied. In addition, to complete the risk assessment cycle, the work should be reviewed periodically to ensure that GMPP and core requirements are effectively implemented.

Table 3.2 Examples of the application of key steps in the risk assessment process

STEP 1: GATHER INFORMATION	**STEP 2:** EVALUATE RISKS	**STEP 3:** DEVELOP A RISK CONTROL STRATEGY	**STEP 4:** SELECT AND IMPLEMENT RISK CONTROL MEASURES	**STEP 5:** REVIEW RISKS AND RISK CONTROL MEASURES
Routine smear preparation and microscopy of sputum specimens Biological agent with a low infectious dose transmitted through aerosols Conducted by competent personal in a diagnostic laboratory	**Low** Specimen volume and concentration are small Aerosol production is unlikely Slide containing the smear has been heat-fixed resulting in partial inactivation	**Core requirements** Core requirements should be adequate to bring this low risk to an acceptable risk	Prepare SOPs on GMPP and core requirements Ensure proper operation and maintenance of microscope, including written SOPs Train personnel on SOPs	Observe laboratory work to ensure GMPP and core requirements are followed Conduct a review in the event of an incident, or changes to the characteristics of the biological agent or the procedures
Small-scale centrifugation of liquid cultures to prepare concentrated stocks for cryogenic storage Biological agent with a low infectious dose transmitted through aerosols Conducted by competent personal in a diagnostic laboratory	**Medium** Biological agent is being propagated in liquid media Specimen volume is small, concentration is high Aerosol production is possible	**Heightened control measures** In addition to core requirements, implementing certain heightened control measures (such as safety equipment) should be considered to bring the medium risk of a potential aerosol exposure to an acceptable risk Evaluate and ensure heightened control measures and any additional safety measures are locally available and sustainable (for example, cost–benefit analysis)	**In addition to above measures:** Consider potential heightened control measures (PPE, respiratory protective equipment, centrifuge safety buckets or sealed rotors, BSC) Ensure proper selection, operation and maintenance of heightened control measures and any additional safety measures (for example, restricted access to minimize potential exposure), including written SOPs Train personnel on SOPs and spill response	**In addition to above measures:** Observe laboratory work to ensure heightened control measures are followed Conduct a periodic review (for example, annual) Evaluate the effectiveness of the selected heightened control measures and availability of improved risk control measures of the biological agent or the procedures

Table 3.2 Examples of the application of key steps in the risk assessment process (continued)

STEP 1: GATHER INFORMATION	**STEP 2:** EVALUATE RISKS	**STEP 3:** DEVELOP A RISK CONTROL STRATEGY	**STEP 4:** SELECT AND IMPLEMENT RISK CONTROL MEASURES	**STEP 5:** REVIEW RISKS AND RISK CONTROL MEASURES
Large-scale culture of drug-resistant strains Biological agent with a low infectious dose transmitted through aerosols Conducted by competent personal in a pharmaceutical laboratory	**High** Biological agent is being propagated in liquid media Specimen volume is high, concentration is very high Aerosol production is likely Biological agent is known to be resistant to available medicines	**Heightened control measures** In addition to core requirements, consider implementing selected heightened control measures (for example, safety equipment and/or facility enhancements) to reduce the risk of a potential aerosol exposure or release of high-risk pathogen to an acceptable risk Ensure heightened control measures and any additional laboratory safety design criteria are locally sustainable (for example, cost–benefit analysis to include outsourcing versus doing the work in-house)	**In addition to above measures:** Consider potential heightened control measures (for example, segregation of the laboratory area where the higher-risk work is being done, controlled ventilation and/or waste disposal systems) Ensure proper selection, operation and maintenance of heightened control measures, and any additional criteria for facility design, including written SOPs Train personnel on SOPs, including emergency response and large spill management	**In addition to above**: Routinely conduct spill exercises and drills on potential incidents (for example, biannually) Continually evaluate training/mentorship programmes (for example, solicit feedback and input from the laboratory personnel) of the biological agent or the procedures

Table 3.2 Examples of the application of key steps in the risk assessment process (continued)

STEP 1: GATHER INFORMATION	**STEP 2:** EVALUATE RISKS	**STEP 3:** DEVELOP A RISK CONTROL STRATEGY	**STEP 4:** SELECT AND IMPLEMENT RISK CONTROL MEASURES	**STEP 5:** REVIEW RISKS AND RISK CONTROL MEASURES
Oral inoculation of rodents with a non-infectious rotavirus Conducted by newly trained personnel in a research laboratory	**Low** Non-pathogenic biological agent Percutaneous injury from oral inoculation is unlikely but rodent bite is possible	**Core requirements** Core requirements should be adequate to bring this low risk to an acceptable risk	Prepare SOPs on GMPP and core requirements Ensure proper performance of the experiments according to the SOPs New personnel must be trained and demonstrate competency on SOPs and safe animal handling procedures	Observe laboratory work to ensure GMPP and core requirements are followed Conduct a review in the event of an incident, or changes to the characteristics of the biological agent or the procedures
Intravenous inoculation of rodents with tick-borne encephalitis virus Conducted by newly trained personnel in a research laboratory	**Medium** Severe disease but vaccine may be available Percutaneous injury from intravenous inoculation or rodent bite is possible Aerosol generation is possible	**Heightened control measures** In addition to core requirements, implementing certain heightened control measures (safety equipment, vaccination) should be considered to bring the medium risk of a potential aerosol exposure and a needle stick injury to an acceptable risk Evaluate and ensure heightened control measures and any additional safety measures are locally available and sustainable (for example, cost–benefit analysis)	**In addition to above measures:** Consider potential heightened control measures (PPE, respiratory protective equipment, safety sharps devices, BSC) Ensure proper selection, operation and maintenance of heightened control measures (for example, restricted access to minimize potential exposure), including written SOPs New personnel must be trained and demonstrate competency on safe sharps handling	**In addition to above measures:** Observe laboratory work to ensure heightened control measures are followed Conduct a periodic review (for example, annual) Evaluate the effectiveness of the selected heightened control measures and availability of improved risk control measures

Table 3.2 Examples of the application of key steps in the risk assessment process (continued)

STEP 1: GATHER INFORMATION	**STEP 2:** EVALUATE RISKS	**STEP 3:** DEVELOP A RISK CONTROL STRATEGY	**STEP 4:** SELECT AND IMPLEMENT RISK CONTROL MEASURES	**STEP 5:** REVIEW RISKS AND RISK CONTROL MEASURES
Intravenous inoculation of rodents with Creutzfeldt-Jakob disease agent (prions) Conducted by newly trained personnel in a research laboratory	**High** Fatal disease, no available prophylaxis, vaccine or treatment Percutaneous injury from intravenous inoculation or rodent bite is possible Aerosol generation is possible Highly resistant to common disinfection/ sterilization methods	**Heightened control measures** In addition to core requirements, consider implementing selected heightened control measures (for example, work practices, safety equipment and/or facility enhancements) to reduce the risk of a potential percutaneous or aerosol exposure or release of high-risk pathogen to an acceptable risk Ensure heightened control measures and any additional laboratory safety design criteria are locally sustainable (for example, cost–benefit analysis to include outsourcing versus doing the work in-house)	**In addition to above measures:** Consider potential heightened control measures (for example, segregation of the laboratory area where the higher-risk work is being done, controlled ventilation and/ or specialized decontamination methods and waste disposal systems) Ensure proper selection, operation and maintenance of heightened control measures, and any additional criteria for facility design, including written SOPs New personnel must be trained, mentored and demonstrate competency on SOPs and rigid disinfection/ sterilization/waste management protocols	**In addition to above:** Routinely conduct spill exercises and drills on potential incidents (for example, biannually) Continually evaluate training/mentorship programmes (for example, solicit feedback and input from the laboratory personnel especially on safe sharps devices and handling)

BSC = biological safety cabinet; GMPP = good microbiological practice and procedure; PPE = personal protective equipment; SOPs = standard operating procedures.

Note: To simplify the process, the situations and scope of analyses are deliberately narrow and do not include all possible inputs and outcomes. An actual risk assessment is likely to have many more factors to consider and be more complex than the examples in the table. This table is intended to provide a high-level overview of how different laboratory procedures will affect the risk assessment process and outcomes.

Culturing of small volumes of human pathogenic biological agents could be an example of a medium-risk activity. For this type of laboratory activity, core requirements may be supplemented with selected heightened control measures (described in detail in section 4 of the fourth edition of the WHO *Laboratory biosafety manual (1)*), such as safety equipment, to bring risk to within an acceptable range.

High-risk laboratory activities may include work such as manipulation of large volumes of drug-resistant strains of biological agents and animal studies with zoonotic agents that can be transmitted through aerosols. Laboratory work of this nature needs careful consideration, and cost–benefit analyses of the work to determine if it should be done. These analyses should include a thorough evaluation of heightened control measures that could be implemented to improve the laboratory's facilities and reduce risks. Other factors to consider are the cost–benefit of outsourcing the work or whether the work should proceed at all.

It is important to note that some situations, unlike those in Table 3.2, present extremely high risks. For example, laboratory work with a biological agent that has been eradicated globally may be considered very high-risk work. Accidental exposure or release could result in a rapid spread of infection in a susceptible population causing severe disease and many deaths. For this type of work, maximum containment measures (described in detail in section 5 of the fourth edition of the WHO *Laboratory biosafety manual (1)*) may be the only suitable risk control measures to effectively control risks.

Such measures require specialized facilities and highly trained personnel. Maximum containment measures provide the highest level of protection against exposure to and release of dangerous pathogens with catastrophic consequences. These measures are costly to maintain, and require frequent and rigorous performance verification of procedures, equipment and laboratory facilities. It is therefore important to confirm that maximum containment measures can be effectively implemented and maintained before considering work with highly dangerous pathogens as described above.

Detailed examples of the risk assessment process and implementation of risk-based strategies and programmes for laboratories are provided in the risk assessment templates (Annexes 3, 4, 5 and 6).

3.2 Additional risk control measures

Biological risks are influenced by the pathogenic potential of the biological agents manipulated in the laboratory. However, to a greater degree, these risks are influenced by the physical state of these organisms and the specific manipulations to be done. Consultation with peers and periodic review of the literature may provide alternative or new methods that may supplement or replace high-risk activities with low-risk methods, which can reduce the initial risk of the laboratory activity before applying any risk control measures. These methods might reduce risk in several ways.

Some may allow work to be done using smaller volumes and concentrations of pathogens, while others may allow work to be done with inactivated biological agents thereby eliminating the need for active replication of pathogenic strains.

Molecular detection methods produce highly sensitive and specific results and pose less risk than standard bacterial and viral culture. Selecting low-risk (for example, attenuated) positive controls for assay verification is another way to reduce biological risk. Depending on the test method, attenuated strains of the biological agent may be used as positive controls providing results equivalent to highly pathogenic strains. This strategy is of particular interest to laboratories responsible for surveillance testing for severe and re-emerging epidemic diseases. Another example of reducing biological risk is the use of inactivated biological agents in vaccine production. Vaccine production requires manipulation of large volumes of organic material. However, in some cases, recombinant or attenuated strains of the biological agent are available which can replace highly virulent bacteria or viruses, thus greatly reducing risks to personnel and the environment if an accidental exposure or release occurred.

Substituting new molecular methods for traditional microbiological methods reduces risks and should be considered wherever possible. Although use of these methods may be costly to begin with, laboratories that have made use of them have ultimately experienced reduced operational costs and improved personnel performance. However, elimination or substitution of the hazardous laboratory activity is not always possible, and any laboratory activity should not proceed until risks are acceptable.

As a general rule, consider the following as ways to reduce risk.

- **Use microvolumes.** Wherever possible, reduce the volumes of biological materials for analyses by substituting small tubes (for example, microtubes, microcentrifuge tubes) and micropipetting for large tubes/bottles and pipettes.

- **Avoid culture and propagation of the pathogens.** Highly sensitive and specific molecular detection methods have become available for many pathogens. Nucleic acid amplification techniques can directly use clinical specimens without the need for culture. Using molecular methods, a small portion of DNA/RNA of the pathogen can be amplified from a clinical specimen, and this is usually sufficient to confirm infection. Currently, the costs of molecular genetic methods are comparable to classical microbiological methods.

- **Inactivate clinical specimens before analyses.** Specimens from biopsies or necropsies can often be placed directly into special inactivating buffers (for example, thiocyanate-based buffers or buffered formalin). These buffers make tissues non-infectious but conserve the important target for analysis, such as DNA, RNA or protein. After inactivation, organic specimens are safer and simpler to transport and often do not require a cold chain. They can be handled in the laboratory without risk of infection in the event of accidental exposure or release.

- **Use non-infectious control and production strains.** For diagnostic laboratories, the use of positive controls is important for instrument calibration and assay verification. Depending on the test, attenuated control strains may be available and can be substituted as positive controls for highly pathogenic strains. Similarly, using either attenuated or recombinant pathogens that express the antigens necessary for vaccine production will substantially reduce the biological risk and costs of vaccine production.

Eliminating or substituting the hazard in certain procedures, for example, by using DNA or inactivated/attenuated strains of the biological agent to reduce the initial risk, is the most effective means of risk reduction (Figure 3.2). However, administrative controls (for example, training, policies, guidelines, SOPs) should be in place before beginning any laboratory work. In most situations, selecting and implementing the right combination of risk control measures is necessary so that they complement each other in reducing biological risks. In order to select appropriate measures for risk control, an understanding of the purpose and strengths and weaknesses of each measure is required. Table 3.4 shows the advantages and disadvantages of the most common risk control measures. These features can be compared and contrasted during a laboratory risk assessment and the most appropriate control(s) selected for the work proposed.

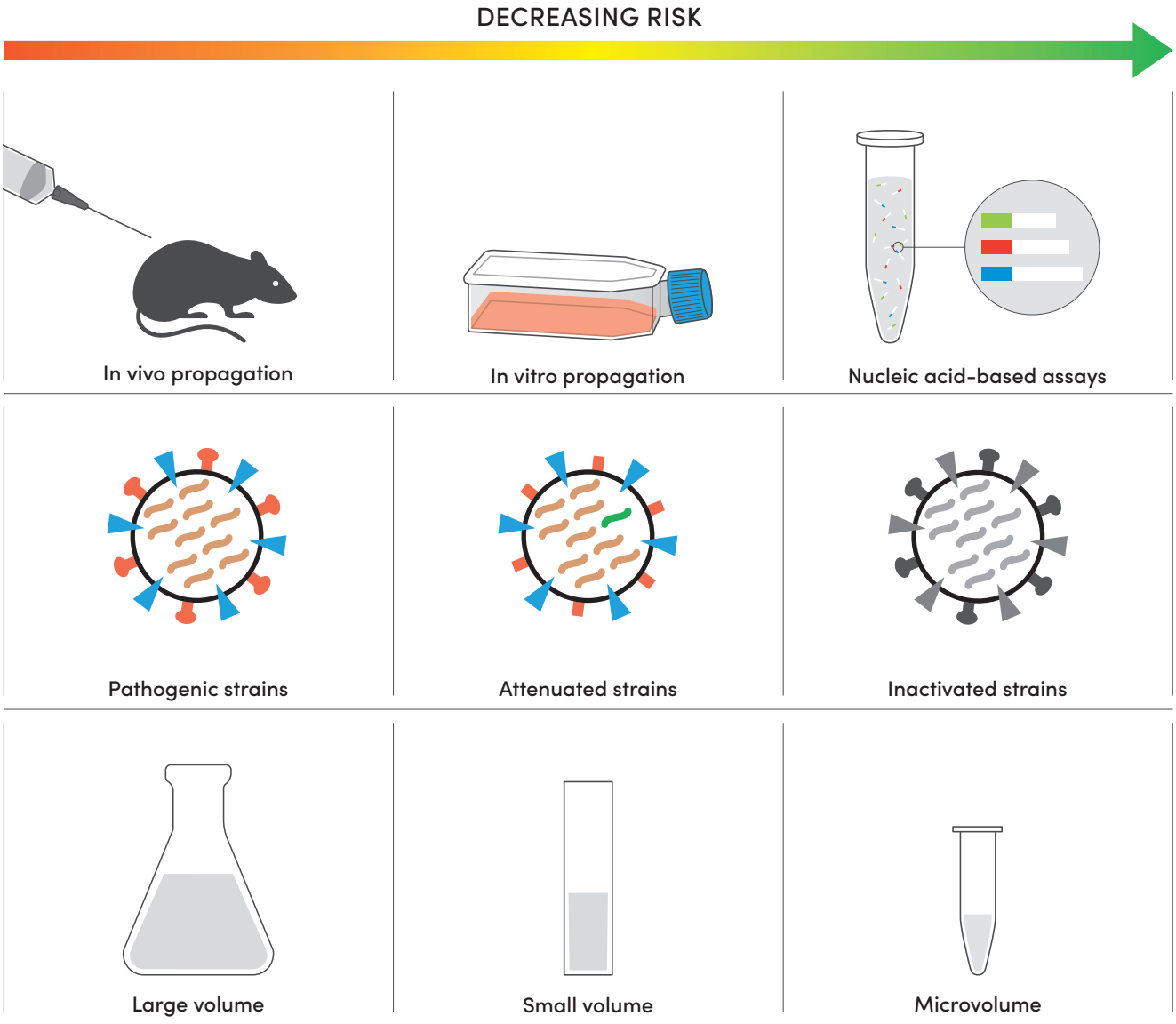

Figure 3.2 Examples of techniques to reduce or eliminate the risks of infection associated with manipulating biological agents. The lower risks reduce the need for risk control measures that would otherwise be required.

Table 3.4 Types of control

TYPE OF CONTROL	EXAMPLES	ADVANTAGES	DISADVANTAGES
Substitution or elimination	▪ Inactivated materials ▪ Attenuated/less virulent strain of a biological agent ▪ Molecular or immunological method instead of a culture for diagnosis	▪ Reduces or completely eliminates the hazard	▪ May not always be a scientifically and diagnostically possible option
Administration	▪ Policies, standards and guidelines used to control risks ▪ Changes to the way people work ▪ Signs and warning labels	▪ Limits or prevents exposure to the hazard ▪ Standardized procedural approach	▪ Does not always eliminate the hazard ▪ Relies heavily on personnel training, competency and compliance with SOPs
Practices and procedures	▪ GMPP ▪ SOPs		
PPE	▪ Laboratory coats ▪ Footwear ▪ Gloves ▪ Eye protection ▪ Respiratory protection	▪ Effective when correctly used ▪ Readily available ▪ Relatively low cost	▪ Does not eliminate the hazard ▪ Only protects the person wearing the PPE ▪ May be uncomfortable to wear ▪ May limit dexterity ▪ May be used incorrectly
Primary barriers or containment devices	▪ BSCs ▪ Sealed rotors and centrifuge safety buckets	▪ Eliminates and/or isolates personnel from the hazard ▪ Protects everyone in the laboratory ▪ Effective when used and maintained properly	▪ Increased cost ▪ May not be locally available/sustainable ▪ Increased complexity ▪ Relies on personnel training and competency
Secondary barriers	Facility design criteria such as: ▪ Separation of the laboratory work area from administrative areas and public access ▪ Decontamination facilities (for example, autoclaves) ▪ Handwashing facilities		

BSCs = biological safety cabinets; GMPP = good microbiological practice and procedure; PPE = personal protective equipment; SOPs = standard operating procedures.

SECTION 4

IMPLEMENTATION STRATEGIES AND LESSONS FROM THE FIELD

Risk assessments are generally conducted following the standard framework outlined in Figure 1.1; however, as mentioned previously, they may be conducted in different ways. Although the exact method of risk assessment may vary, all risk assessments are equally valid if they appropriately incorporate all the elements of the risk assessment framework (Figure 1.1). If choosing a risk assessment method that differs from the standard framework, it is important to consider issues such as the availability of resources and key personnel, the organizational and/or governmental structure, and the needs specific to a facility or region. A common problem when preparing to carry out a risk assessment is the lack of experienced personnel. In such cases, the risk assessment team may be led by a single experienced individual. However, other laboratory personnel should still be consulted for their input to ensure all elements of the laboratory work are properly considered. Examples of approaches to risk assessments where the number of personnel is limited are given in Table 4.1.

Table 4.1 Approaches to conducting risk assessments where the number of personnel is limited: advantages and disadvantages

PERSONNEL AND APPROACH	ADVANTAGES	DISADVANTAGES
▪ One designated individual, either a biosafety officer or laboratory manager/technician, is responsible for drafting the risk assessment for the laboratory ▪ Subsequent review by relevant subject-specific experts and the laboratory management	▪ Quick completion of the risk assessment if designated individual is highly motivated	▪ The assessment may not be prioritized if the individual is carrying out biosafety activities as an additional duty ▪ Relevant details may be missed if the level of expertise and experience with the laboratory activities of this individual is limited, especially if few experienced personnel are available for the subsequent review

Table 4.1 Approaches to conducting risk assessments where the number of personnel is limited: advantages and disadvantages (continued)

PERSONNEL AND APPROACH	ADVANTAGES	DISADVANTAGES
▪ A small team of laboratory and/or biosafety personnel	▪ Varied experience and expertise within the group to contribute to the risk assessment	▪ If roles and responsibilities are not clearly defined and applied, differing opinions and unresolved conflicts may affect completion of the assessment on time
▪ A blended version with a designated individual (laboratory manager/ principal investigator or biosafety officer) responsible for providing a first draft of the risk assessment ▪ A small team or committee of laboratory scientists or technicians to review the draft	▪ Laboratory management and the individuals directly responsible for conducting the laboratory work working together ▪ Integration of laboratory management needs with biosafety best practice	▪ If roles and responsibilities of the designated assessor and the committee are not clearly defined and applied, delays in completion of the assessment may occur ▪ Those not actively participating in the assessment may not feel accountable; it may therefore be necessary to prepare SOPs, charters and other mechanisms to ensure their engagement.

SOPs = standard operating procedures.

4.1 Lessons from the field: laboratory-associated *Salmonella* infection

BOX 4.1 LESSONS FROM THE FIELD: LABORATORY-ASSOCIATED *SALMONELLA* INFECTION

Jan, a junior member of the laboratory personnel in an enteric bacterial laboratory, was asked to prepare a subculture of *Salmonella* Typhimurium (causative agent for infectious diarrhoea) for another laboratory. She had prepared many subcultures before and had been trained to do so but her main role was to receive, check and record incoming cultures from satellite laboratories. All cultures received are stored frozen in Luria broth and 40% glycerol but old cultures were frozen in Luria broth and blood. Jan mentioned that the *S.* Typhimurium culture was frozen and she had not worked with frozen cultures before. The unit chief therefore asked an experienced member of the personnel to train her to manipulate the frozen culture.

BOX 4.1 LESSONS FROM THE FIELD: LABORATORY-ASSOCIATED *SALMONELLA* INFECTION (CONTINUED)

Less than a week later, Jan was sick for several days and off work. Later, it was found that she had been suffering from severe diarrhoea and cramping and visited the emergency room at a local hospital to receive treatment. When the doctor asked about any potential cause of the illness, Jan mentioned her work at the laboratory. A stool culture was taken and sent to the state public health laboratory for identification. Jan alerted the unit chief of her laboratory the following day. It was noted that she may be suffering from a laboratory-associated infection.

Results from the state health laboratory indicated that the bacterial species was indeed *S.* Typhimurium. Because of the serious implications of a laboratory-associated infection, DNA was sequenced in both the culture that was manipulated and the stool culture isolate. Comparative sequence analyses confirmed that it was a laboratory-associated infection. A root cause analysis was carried out to identify what had happened to cause Jan to become infected. This analysis showed that: 1) the training to work with frozen cultures did not occur, 2) this culture was manipulated outside of the biological safety cabinet (BSC) and no face shield was used, and 3) the frozen culture was not fully thawed before subculturing began. It is suspected that an ice chip containing the organism was ingested, either directly in the mouth during the procedure or through the laboratory coat or other environmental contamination before handwashing.

A completed risk assessment determined that culture manipulation was sometimes carried out at the bench with no shield in place, and that only *S.* Typhi (causative agent for typhoid) was routinely manipulated inside the BSC. As a result, all laboratory personnel received BSC training and were instructed to carry out all manipulations on solid and liquid media inside a BSC. After all hazards and risks were identified, other risk control measures were applied. These measures included the use of goggles when working (mixing capped tubes) with cultures in broth at the bench and the use of carts to transport any cultures in the laboratory to avoid spills. No further incidents have occurred.

4.2 Lessons from the field: risk assessment of a "near miss"

BOX 4.2 LESSONS FROM THE FIELD: RISK ASSESSMENT OF A "NEAR MISS"

The preparation of slides for microscopic evaluation from cytological specimens takes place in a laboratory in a department of pathology. In the same laboratory, other work is done such as immunohistochemistry but no potentially infectious material is used in this other work. To prevent the spread of potentially infectious biological agents from the work with cytological specimens, the handling of a specimen is done in a biological safety cabinet (BSC) with a small centrifuge. The range of specimens is wide (pleural effusion, sputum, ascites, urine, cerebrospinal fluid and others), and the presence of biological agents in most of the specimens is unknown, unless it is stated in the accompanying documents. These biological agents could include HIV, hepatitis B virus, hepatitis C virus and *Mycobacterium tuberculosis*, among others. Several methods are used in the laboratory to prepare cytological slides, such as the standard smear preparation, cytobloc preparation and cytospin, but most of the methods include a centrifugation step.

The centrifuge in the BSC had been recently replaced and, because no risk assessment had been done for the old centrifuge, the laboratory management did not consider carrying out a risk assessment for the new centrifuge. After a month, a member of the personnel reported a possible disruption in the airflow in the BSC. A smoke test was done which confirmed the initial suspicion of an airflow interruption.

Following this near miss, a risk assessment was done which identified that aerosols, potentially containing biological agents, could escape from the BSC as a result of the interrupted airflow caused by the centrifuge. To reduce this risk, the centrifuge was placed outside the BSC. The standard operating procedures for the preparation of cytological slides were amended to include a section explaining how to disinfect the surface of the microcentrifuge tube containing the biological agent before bringing it out of the BSC for centrifugation.

4.3 Lessons from the field: adapting risk control measures for a health condition

BOX 4.3 LESSONS FROM THE FIELD: ADAPTING RISK CONTROL MEASURES FOR A HEALTH CONDITION

An institute plans laboratory activities as well as animal infection studies with avian influenza. To date, only molecular methods were used in the laboratory. The biosafety team together with the responsible scientist undertook a risk assessment to determine the risk control measures for safe working. The responsible scientist rarely works in the laboratory and delegates the work to several people in his team.

**BOX 4.3 LESSONS FROM THE FIELD:
ADAPTING RISK CONTROL MEASURES FOR A HEALTH CONDITION (CONTINUED)**

One team member is a female laboratory assistant. However, this laboratory assistant suffers from a thrombocyte dysfunction. This means that coagulation of her blood is impaired if she is injured (by a cut, a needlestick injury). Therefore, severe bleeding injuries are dangerous because she can lose a large amount of blood in a very short time. Routine laboratory activities such as molecular biology methods do not pose an increased risk for her. In addition, no sharps are used in her work thus reducing the risk of injury.

The original risk assessment of the laboratory work including inoculation of eggs or mice and dissection of mice was based on healthy laboratory personnel. In this original risk assessment, sharps are routinely used, either to inoculate eggs or mice or to dissect infected mice. During the initial biosafety training, the laboratory assistant mentioned her medical status. This triggered a review of the existing risk assessment and additional risk control measures were defined for the laboratory assistant. She is not allowed to carry out any steps with a high risk of injury, such as working with sharps for mice inoculation or dissection. The use of a microtome is also prohibited. For mice dissection or removal of organs, only blunt scissors (for example, Baby Metzenbaum) instead of a scalpel are to be used. A second person must always be with her during animal work. All members of the group and all first responders are informed and instructed how to act in case of an injury to the laboratory assistant. In the first-aid room, medication and haemostatic cotton wool/plasters are stored, together with clear instructions on how to act in case of an emergency.

Risk communication is never more important than when working with personnel with greater susceptibility to a laboratory hazard and therefore at increased risk. Some personnel are willing, and are even insistent that they be allowed, to do their laboratory work despite their increased risk because of their medical status and/or disability. Depending on national regulations and local policies that typically govern these situations, certain restrictions and/or accommodations have to be made.

It is important that all potential risks are properly communicated to these individuals at increased risk. If they are permitted to work in laboratory areas, perhaps with increased risk control measures such as PPE, it is important that both they and others working in the area are made aware of these measures. This situation can be especially complicated when trying to preserve an individual's right to privacy but it is essential that others are not made to feel "less safe" than the at-risk person who is working with additional risk control measures. Proper communication is vital to make these types of situation workable and safe for all.

References

1. Laboratory biosafety manual, fourth edition. Geneva: World Health Organization; 2020 (Laboratory biosafety manual, fourth edition and associated monographs).

2. Laboratory design and maintenance. Geneva: World Health Organization; 2020 (Laboratory biosafety manual, fourth edition and associated monographs).

3. Biological safety cabinets and other primary containment devices. Geneva: World Health Organization; 2020 (Laboratory biosafety manual, fourth edition and associated monographs).

4. Personal protective equipment. Geneva: World Health Organization; 2020 (Laboratory biosafety manual, fourth edition and associated monographs).

5. Decontamination and waste management. Geneva: World Health Organization; 2020 (Laboratory biosafety manual, fourth edition and associated monographs).

6. Biosafety programme management. Geneva: World Health Organization; 2020 (Laboratory biosafety manual, fourth edition and associated monographs).

7. Outbreak preparedness and resilience. Geneva: World Health Organization; 2020 (Laboratory biosafety manual, fourth edition and associated monographs).

Further information

Biosafety and biosecurity: standard for managing biological risk in the veterinary laboratory and animal facilities. In: Manual of diagnostic tests and vaccines for terrestrial animals, 8th edition. Paris: World Organisation for Animal Health (OIE); 2018 (https://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/1.01.04_BIOSAFETY_BIOSECURITY.pdf, accessed 6 December 2019).

Biosafety in microbiological and biomedical laboratories, 5th edition. Washington, DC: US Department of Health and Human Services; 2009 (https://www.cdc.gov/labs/pdf/CDC-BiosafetyMicrobiologicalBiomedicalLaboratories-2009-P.PDF, accessed 6 December 2019).

Health Canada decision-making framework for identifying, assessing, and managing health risks. Health Canada; 2000 (https://www.canada.ca/en/health-canada/corporate/about-health-canada/reports-publications/health-products-food-branch/health-canada-decision-making-framework-identifying-assessing-managing-health-risks.html, accessed 26 November 2019).

The International Federation of Biosafety Associations Laboratory biosafety and biosecurity risk assessment technical guidance document. Albuquerque: Sandia National Laboratories; 2014 (https://prod-ng.sandia.gov/techlib-noauth/access-control.cgi/2014/1415939r.pdf, accessed 6 December 2019).

Public Health Agency of Canada. Pathogens safety data sheets. Government of Canada (https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment.html, accessed 26 November 2019).

Salerno RM, Gaudioso J, editors. Laboratory biorisk management: biosafety and biosecurity, 1st edition. Boca Raton (FL): CRC Press; 2015 (https://www.crcpress.com/Laboratory-Biorisk-Management-Biosafety-and-Biosecurity/Salerno-Gaudioso/p/book/9781466593640, accessed 26 November 2019).

ISO 35001:2019 Biorisk management for laboratories and other related organisations. Geneva: International Organization for Standardization; 2019 (https://www.iso.org/standard/71293.html, accessed 20 February 2020)

ANNEX 1. RISK ASSESSMENT SHORT TEMPLATE

Institution/Facility name	
Laboratory name	
Laboratory manager/Supervisor	
Project titles/Relevant standard operating procedures (SOPs)	
Date	

If using this template, complete all sections following the instructions in the grey boxes. The instructions and bullet points in the grey boxes can be copied into the text boxes beneath the instructions and used as prompts to gather and record the necessary site-specific information. The grey instruction boxes can then be deleted, and the text remaining will form a risk assessment draft. This draft must be carefully reviewed, edited as necessary and approved by the risk assessment team members.

STEP 1. Gather information (hazard identification)

Instructions: Provide a brief overview of the laboratory work and summarize the laboratory activities to be conducted that are included in the scope of this risk assessment.	
Describe the biological agents and other potential hazards (for example, transmission, infectious dose, treatment/preventive measures, pathogenicity).	
Describe the laboratory procedures to be used (for example, culturing, centrifugation, work with sharps, waste handling, frequency of performing the laboratory activity).	
Describe the types of equipment to be used (personal protective equipment (PPE), centrifuges, autoclaves, biological safety cabinets (BSCs)).	
Describe the type and condition of the facility where work is conducted.	
Describe relevant human factors (for example, competency, training, experience and attitude of personnel).	
Describe any other factors that may affect laboratory operations (for example, legal, cultural, socioeconomic).	

STEP 2. Evaluate the risks

Instructions: Describe how exposure and/or release could occur.	
What potential situations are there in which exposure or release could occur?	
What is the likelihood of an exposure/release occurring (unlikely, possible, likely)?	
What is the severity of the consequences of an exposure/release (negligible, moderate, severe)?	

Instructions: Evaluate the risk and prioritize the implementation of risk control measures. Circle the initial risk of the laboratory activities including risk control measures described in STEP 1 but before any additional risk control measures have been put in place.

Note:

- **When assigning priority, other factors may need to be considered, for example, urgency, feasibility/sustainability of risk control measures, delivery and installation time and training availability.**
- **To estimate the overall risk, take into consideration the risk ratings for the individual laboratory activities/procedures, separately or collectively as appropriate for the laboratory.**

		Likelihood of exposure/release		
		Unlikely	Possible	Likely
Consequences of exposure/release	Severe	Medium	High	Very high
	Moderate	Low	Medium	High
	Negligible	Very low	Low	Medium

Laboratory activity/procedure	**Initial risk (very low, low, medium, high, very high)**	**Is the initial risk acceptable? (yes/no)**	**Priority (high/medium/low)**

Select the overall **initial** risk.	☐ Very low	☐ Low	☐ Medium	☐ High	☐ Very high
Should work proceed without additional risk control measures?	Yes ☐ No ☐				

STEP 3. Develop a risk control strategy

Instructions: Describe the resources available for risk control and consider their applicability, availability and sustainability in the local context including management support.	
Are resources sufficient to secure and maintain potential risk control measures?	
Describe the measures advised by guidelines, policies and strategies (if any).	
Will work be able to proceed without any of the risk control measures; are there alternatives?	

STEP 4. Select and implement risk control measures

Instructions: List any requirements that have been prescribed by international and national regulations, legislation, guidelines, policies and strategies on biosafety and biosecurity. In addition, consider if there are any local regulations, guidelines or policies that restrict or govern certain laboratory activities and/or the handling and use of any biological agents.	
Describe the measures required by national legislation or regulations (if any).	
Describe the measures advised by guidelines, policies and strategies (if any).	

Instructions: Describe where and when risk control measures are needed, the residual risk when these risk control measures are in place, and an assessment of the availability, effectiveness and sustainability of the risk control measures.

Laboratory activity/procedure	Selected risk control measure(s)	Residual risk (very low, low, medium, high, very high)	Is the residual risk acceptable? (yes/no)	Are risk control measures available, effective and sustainable? (yes/no)

STEP 4. Select and implement risk control measures (continued)

Instructions: Evaluate the residual risk that remains after risk control measures have been selected to determine if the risk is now acceptable and whether work should proceed.
Circle the residual risk of the laboratory activities after risk control measures are in place.

		Likelihood of exposure/release		
		Unlikely	Possible	Likely
Consequences of exposure/release	Severe	Medium	High	Very high
	Moderate	Low	Medium	High
	Negligible	Very low	Low	Medium

Overall **residual** risk.	☐ Very low	☐ Low	☐ Medium	☐ High	☐ Very high

If the residual risk is still unacceptable, further action is necessary such as additional risk control measures, based on the initial risk evaluated in STEP 2, redefining the scope of work such that it is acceptable with existing risk control measures in place or identifying an alternative laboratory with appropriate risk control strategies already in place that is capable of conducting the work as planned.

Should work proceed with selected risk control measures?	Yes ☐ No ☐
Approved by (Name and title)	
Approved by (Signature)	
Date	

Instructions: Describe how to communicate risks and risk mitigation strategies to personnel. Provide a mechanism of communication within the laboratory. Describe the process and timeline for ensuring that all identified risk control measures are purchased, have associated SOPs and training has been completed before starting the laboratory work.

Communication of the hazards, risks and risk control measures	
Purchase (and budgeting) of risk control measures	
Operational and maintenance procedures	
Training of personnel	

STEP 5. Review risks and risk control measures

Instructions: Establish a periodic review cycle to identify: changes in laboratory activities, biological agents, personnel, equipment or facilities; changes in knowledge of biological agents or processes; and lessons learnt from audits/inspections, personnel feedback, incidents and/or near misses.	
Frequency of the review	
Person to conduct the review	
Describe updates/changes	
Personnel/procedures to implement the changes	
Reviewed by (Name and title)	
Reviewed by (Signature)	
Date	

ANNEX 2. RISK ASSESSMENT LONG TEMPLATE

Institution/Facility name	
Laboratory name	
Laboratory manager/Supervisor	
Location	
Project titles/Relevant standard operating procedures (SOPs)	
Date	

If using this template, complete all sections following the instructions in the grey boxes. The instructions and bullet points in the grey boxes can be copied into the text boxes beneath the instructions and used as prompts to gather and record the necessary site-specific information. The grey instruction boxes can then be deleted, and the text remaining will form a risk assessment draft. This draft must be carefully reviewed, edited as necessary and approved by the risk assessment team members.

STEP 1. Gather information (hazard identification)

1.1 Provide a brief overview of the laboratory work

Instructions: Summarize the laboratory activities to be conducted that are included in the scope of this risk assessment. If the laboratory conducts other similar work on a regular basis (for example, well-defined, routine diagnostic testing), consider using one assessment to cover all laboratory activities. However, large and more complex laboratories that carry out a variety of laboratory activities, such as diagnostic testing, confirmatory testing, characterization of biological agents and research, may want to conduct separate risk assessments.

1.2 Describe the biological agents and other potential hazards

Instructions: Identify the hazards. It is important to know the characteristics of the biological agent(s) when determining the risks it presents. When the specific biological agent is known, the following information will be useful for the risk assessment and should be thoroughly researched. When handling unknown or diagnostic specimens, it is important to try and obtain any information on the source of the specimens and/or a presumptive/suspected diagnosis. Typical information to be gathered about the biological agent(s) includes:

- **pathogenicity/severity of disease**
- **epidemiology and host range**
- **sources/specimens**
- **infectious dose, concentration and volume**
- **route(s) of transmission**
- **incubation period and communicability**
- **viability and susceptibility to disinfectants**
- **means of diagnosing the disease, type of testing done for diagnosis**
- **treatment, immunization and prophylaxis available**
- **unique laboratory hazards (laboratory-associated infections)**
- **additional information.**

1.3 Describe the laboratory procedures to be used

Instructions: Identify the laboratory activities that might cause exposure to the biological agent when it is being transported, handled or manipulated. Consider the following:

- **centrifuging**
- **cleaning up spills**
- **contact with fomites or contaminated surfaces**
- **inoculating media, including how frequently and in what concentration the biological agent is isolated/ propagated**
- **manipulating inoculation loops, pipettes, needles and other sharps, syringes**
- **mixing, blending, grinding, shaking, sonicating and vortexing**
- **pouring, splitting or decanting liquids**
- **preparing smears, heat fixing or staining slides**
- **spilling/dropping/splashing infectious material**
- **transporting specimens/materials inside and outside the laboratory, leaky specimen containers**
- **frequency of performing the laboratory activity**
- **using animals and insects**
  - **scratches, bites, stings**
  - **dissection, organ collection and disposal procedures**
  - **inoculation, injection or blood drawing**
- **handling biological waste**
  - **specimen/culture/pathogen transport procedures**
  - **inactivation procedures (for example, chemical, heat)**
  - **disposal procedures (for example, autoclaving, incinerating).**

1.4 Describe the types of equipment to be used

Instructions: Determine what instruments and equipment will be used to do the laboratory work. Please note that each type of equipment has its own inherent risks. For example, if centrifugation will be used, the potential for aerosols to be produced is a risk to consider. List any safety equipment that is available and likely to be used. Examples of equipment that may be used include:

- **personal protective equipment (PPE)**
  - **gloves**
  - **protective clothing**
  - **protective eyewear**
  - **respiratory protection (has it been fit tested?)**
- **autoclave (has it been validated?)**
- **biological safety cabinet (BSC) (has it been certified?)**
- **handwashing sink**
- **centrifuge (does it have sealed rotors or safety cups?)**
- **incubator**
- **refrigerator/freezer**
- **additional equipment, list:**

1.5 Describe the type and condition of the facility where work is conducted

Instructions: Consider the layout and type of facility where work will be done to determine if laboratory activities can be conducted safely and securely. The workflow of the laboratory activities from one area of the laboratory to another should also be considered, including specimen receipt, transport, processing and disposal. Consider the following factors. • **Will the work be carried out in a large, multipurpose space?** • **Are separate rooms or spaces available for high-risk laboratory activities?** • **Does the workflow and specimen transport create any special concerns for surface contamination or other laboratory accidents?** • **Are laboratory floors, bench tops and furniture non-porous and impervious to the biological agent?** • **Is laboratory furniture in good repair and ergonomically appropriate for the workstation?** • **Do laboratory areas have closable doors?** • **Are windows sealed or fitted with screens?**

1.6 Describe relevant human factors (for example, competency and suitability of personnel)

Instructions: Consider the competency and experience of laboratory personnel. Assess the training the personnel have had on the biological agent(s), and their experience of handling it and using relevant biosafety practices and safety equipment when performing laboratory work. Consider the following factors.

- **Do personnel have experience working with these biological agents or similar biological agents?**
- **Do personnel have experience performing these procedures and using this equipment?**
- **Are personnel trained to work with diagnostic specimens and unknown agents and do they have experience in this work?**
- **Have all personnel had relevant biosafety training or been briefed on laboratory biosafety, including cleaning and maintenance personnel and visitors, so that all personnel and people entering the laboratory are adequately informed about the hazards in the laboratory?**
- **Do personnel have positive attitudes to biosafety and adherence to safety procedures?**
- **Have there been prior incidents or laboratory-associated infections with this laboratory or these personnel?**
- **Are any personnel at increased risk because of greater susceptibility to laboratory hazards?**
- **Is there undue time pressure on personnel that may result in stress and fatigue?**

Use the following table to list the personnel and their training on the relevant SOP and safety.

Personnel		
Name	**SOP/Safety training**	**Date completed**

1.7 Describe any other factors that may affect laboratory operations

Instructions: Consider the legal, cultural and socioeconomic effects related to the work, and potential public perception of the work. Consider the following in relation to the local context.

- **Is the laboratory, institute or agency highly regarded by the government or the public such that this could influence decision-making?**
- **Is the level of organizational and financial resources available enough to manage the biological risks, including:**
  - **reliable utilities (electrical/water supply),**
  - **properly maintained facility infrastructure,**
  - **commitment to personnel development to prevent under-staffed laboratories with under-trained personnel?**
- **Is there potential for severe weather that could adversely affect laboratory operations?**
- **Is there political, economic or criminal activity/instability that could adversely affect laboratory operations?**
- **Do any of the laboratory activities or biological agents have the potential to cause fear or panic in the community?**
  - **Is the biological agent unusual or unfamiliar to the local community?**
  - **Does infection have very severe or potentially fatal consequences?**
  - **Is there potential for widespread transmissibility or an outbreak of disease?**
  - **Are preventative or therapeutic interventions locally available?**

STEP 2. Evaluate the risks

2.1 Describe how exposure and/or release could occur

Instructions: Based on the information gathered, and the biological and procedural hazards associated with the laboratory work that have been identified, give details of how a potential exposure or release could occur.

- **Examples of how exposure to a biological agent could occur include:**
  - **direct contact with skin and/or mucous membranes from spills, splashes or contaminated work surfaces**
  - **percutaneous or parenteral exposure through inoculation or contaminated sharps**
  - **ingestion**
  - **inhalation of infectious aerosols**
  - **malfunction or misuse of PPE.**
- **Examples of how release of a biological agent could occur include:**
  - **improper packaging and transport, leaking containers**
  - **malfunction of safety equipment resulting in breaches of containment**
  - **spills**
  - **improper disinfection or waste handling and disposal.**

2.2 Determine the likelihood of exposure or release and what factors have the greatest influence on likelihood

Instructions: Based on the information gathered and the potential situations for exposure/release to occur, what factors influence the likelihood of an exposure to or release of a biological agent? Consider the questions below and identify any others that either increase or decrease the likelihood that an exposure/release will occur.

- **What laboratory activities are planned (for example, genetic modification, animal work, sonication, centrifugation or other procedures that may result in the production of aerosols)?**
- **What equipment is needed for the planned activities?**
- **What is the concentration and volume of the biological agent and potentially infectious material to be manipulated?**
- **What is the competency of the personnel carrying out the work?**
- **How often is the task performed and how long does it take to do?**
- **Has an exposure/release ever happened before? How often?**
- **How effective are current risk control measures in reducing risk?**
- **Are the hazards more likely to cause harm because of the working environment?**
- **Could the way people act and behave affect the likelihood of a biological agent causing harm?**
- **Do any of the above items make the harm more or less likely? If yes, list them and explain why.**
- **What is the likelihood of the exposure and/or release occurring?**
  - **Rare: almost impossible to occur**
  - **Unlikely: not very possible to occur**
  - **Possible: might occur**
  - **Likely: very possible to occur**
  - **Almost certain: highly probable to occur**

2.3 Determine the consequences of exposure or release and what has the greatest influence on consequence

Instructions: Based on the information gathered and consequences of an exposure and/or release, what factors influence the consequences? Consider the questions below and identify any others that either increase or decrease the severity and/or magnitude of these consequences if an exposure/release occurred.

- **What type of harm could occur? How severe is the harm? Could the hazard cause death, serious injuries or illness, or only minor injuries requiring first aid?**
- **What factors could influence the severity of harm that occurs? For example, the distance someone might fall or the concentration of a particular substance will determine the level of harm that is possible. The harm may occur immediately or it may take time to become apparent.**
- **How many people are exposed to the hazard and how many could be harmed inside and outside the workplace?**
- **Could one incident lead to other incidents?**
- **Could a small incident escalate to a much larger incident with more serious consequences?**
- **What is the consequence if an exposure and/or release occurred?**
  - **Negligible: Trivial incident or near miss requiring reporting and follow up**
  - **Minor: Incident with self-limiting consequences**
  - **Moderate: Incident that requires medical treatment and/or has insignificant environmental consequences**
  - **Major: Incident with potential lost time due to infection but non-permanent consequence and/or limited environmental impact**
  - **Severe: Potential fatality or serious illness with permanent disability and/or serious environmental impact**

2.4 Describe the initial risk of the laboratory activities before additional risk control measures have been put in place

Instructions: Circle the initial risk of the laboratory activities before additional risk control measures have been put in place. Based upon your evaluation of the likelihood and consequences of an exposure/release as listed above, assess the initial, or currently existing, risk of the laboratory activity using the table below. Find the likelihood of exposure (top row of the chart) and the consequences (left column of the chart).

		Likelihood of exposure/release				
		Rare	Unlikely	Possible	Likely	Almost certain
Consequences of exposure/ release	Severe	Medium	Medium	High	Very high	Very high
	Major	Medium	Medium	High	High	Very high
	Moderate	Low	Low	Medium	High	High
	Minor	Very low	Low	Low	Medium	Medium
	Negligible	Very low	Very low	Low	Medium	Medium

Instructions: Check the initial risk to determine the appropriate risk control measures required.

Assessed initial risk		**Potential consequences**	**Actions**
☐	Very low	If an incident occurred, harm would be very unlikely.	Undertake the laboratory activity with the existing risk control measures in place.
☐	Low	If an incident occurred, there would be a small likelihood of harm.	Use risk control measures if needed.
☐	Medium	If an incident occurred, harm would result that would require basic medical treatment and/or simple environmental measures.	Additional risk control measures are advisable.
☐	High	If an incident occurred, harm would result that would require medical treatment and/or substantial environmental measures.	Additional risk control measures need to be implemented before the laboratory activity is undertaken.
☐	Very high	If an incident occurred, a permanent, impairing harm or death and/or extensive environmental effects would be likely.	Consider alternatives to doing the laboratory activity. Comprehensive risk measures will need to be implemented to ensure safety.

2.4 Describe the initial risk of the laboratory activities before additional risk control measures have been put in place (continued)

Instructions (optional): For additional specification on the risks of individual laboratory activities, determine which risks can/should be reduced and prioritized. For each laboratory activity or procedure of the work under assessment, record the initial risks determined from the risk assessment above. Decide whether the work can proceed without additional risk control measures, or whether the risks posed by the work are unacceptable and further risk control measures are needed to reduce the risks. Use the right column of the table below to assign a priority for the implementation of risk control measures based on the identified risks.

Note:

- **When assigning priority, other factors may need to be considered, for example, urgency, feasibility/sustainability of risk control measures, delivery and installation time and training availability.**
- **To estimate the overall risk, take into consideration the risk ratings for the individual laboratory activities/ procedures, separately or collectively as appropriate for the laboratory.**

Risk of the laboratory activity/ procedure	Initial risk (very low, low, medium, high, very high)	Is the initial risk acceptable? (yes/no)	Priority (high/medium/low)

Select the overall **initial** risk.	☐ Very low	☐ Low	☐ Medium	☐ High	☐ Very high
Should work proceed without additional risk control measures?	Yes ☐ No ☐				
Will work require additional risk control measures?	Yes ☐ No ☐				

STEP 3. Develop a risk control strategy

3.1 Describe the resources available for risk control measures

Instructions: Consider the applicability, availability and sustainability of resources for all risks that require additional risk control measures. Consider the following questions. • **Are alternative detection methods or risk control measures available?** • **Are resources sufficient to secure and maintain potential risk control measures?** • **Does the management support the budget necessary for purchasing, operating and maintaining these risk control measures?** • **Does the management support training for personnel on the proper installation, operation and maintenance of these risk control measures?** • **What factors exist that may limit or restrict any of the risk control measures? Are there financial, legal, organizational or other factors that could limit or restrict the risk control measures?** • **Will work be able to proceed without any of risk control measures?**

STEP 4. Select and implement risk control measures

4.1 Describe the measures required by national legislation or regulations (if any)

Instructions: List any requirements that have been prescribed by international and national regulations, legislation, guidelines, policies and strategies on biosafety and biosecurity. In addition, consider if there are any local regulations, guidelines or policies that restrict or govern certain laboratory activities and/or the handling and use of any biological agents.

4.2 Describe where and when additional risk control measures are needed, including an assessment of their availability, effectiveness and sustainability

Instructions: For each laboratory activity or procedure of the work under assessment, record the unacceptable risks determined from the risk assessment above. Decide which risk control measures have been selected to reduce the unacceptable risks. Determine the new, residual risk after risk control measures have been implemented and whether it is acceptable (very low or low, for example) or unacceptable (medium, high or very high, for example) and further risk control measures are needed to reduce risk, or if the work should not proceed at all at this facility. Alternatively, and based on the local circumstances, consider adjusting the acceptable risk. Note that some procedures may require several risk control measures (that is redundancy in case of any failures) to reduce risk to an acceptable risk. Use the right column of the table below to assess the availability, effectiveness and sustainability of selected risk control measures and provide additional information to support this assessment as necessary. If any risks cannot be reduced to an acceptable risk using available, sustainable risk control measures, it is best not to undertake the laboratory activity or to coordinate with another laboratory with the capability to do the work.

Once the risks have been evaluated, risk control measures can be put into place to reduce them. Consider the following risk control measures.

- **Removing the hazard or substituting it for one that reduces risk (for example, substituting an attenuated or less virulent strain of a biological agent or working with inactivated materials)**
- **Enhancing personnel proficiency (for example, providing additional training and mentorship, competency assessments, exercises and drills)**
- **Applying safety policies and procedures (for example, minimizing propagation and concentration of biological agents, limiting the use of sharps, putting up hazard signs, implementing occupational health programmes)**
- **Using PPE (for example, gloves, protective clothing and respiratory protection), which should be evaluated for each risk to ensure it provides the intended protection to the user**
- **Using primary and secondary barriers such as safety equipment and certain facility design features respectively, such as centrifuge safety cups/sealed rotors, BSCs and autoclaves**
- **Routinely evaluating all risk control measures for effectiveness and failures; any failures should be documented and corrected**

Use the following table to list procedures, selected risk control measures and the residual risk, and indicate whether the risk control measure reduces risk to an acceptable risk and is effective and sustainable.

4.2 Describe where and when additional risk control measures are needed, including an assessment of their availability, effectiveness and sustainability (continued)

Risk of the laboratory activity/ procedure	Selected risk control measure(s)	Residual risk (very low, low, medium, high, very high)	Is the residual risk acceptable? (yes/no)	Are risk control measures available, effective and sustainable? (yes/no)

4.3 Evaluate the residual risk that remains after risk control measures have been selected

Instructions: Circle the residual risk of the laboratory activities after selection of risk control measures. Based on your evaluation of the effect of the additional risk control measures on the residual risk and their availability and sustainability, as listed above, assess the likelihood and consequences of an exposure/release from the laboratory activity using the chart below. Find the likelihood of exposure (top row of chart) and the consequences (left column of chart). Determine if the residual risk is acceptable and whether work should proceed, indicating who is responsible for the approval to conduct the work.

		Likelihood of exposure/release				
		Rare	Unlikely	Possible	Likely	Almost certain
Consequences of exposure/ release	Severe	Medium	Medium	High	Very high	Very high
	Major	Medium	Medium	High	High	Very high
	Moderate	Low	Low	Medium	High	High
	Minor	Very low	Low	Low	Medium	Medium
	Negligible	Very low	Very low	Low	Medium	Medium

4.3 Evaluate the residual risk that remains after risk control measures have been selected (continued)

Instructions: Check the residual risk to determine the appropriate actions required.

Assessed residual risk		Potential consequences	Actions
☐	Very low	If an incident occurred, harm would be very unlikely.	If the identified residual risk is acceptable, no further action is required for laboratory work to proceed.
☐	Low	If an incident occurred, there would be a small likelihood of harm.	
☐	Medium	If an incident occurred, harm would result that would require basic medical treatment and/or simple environmental measures.	If the identified residual risk is not acceptable, further action is required for laboratory work to proceed. Revisit subsection 2.4 and re-evaluate your risk control strategy based upon the initial risk of laboratory activities. Actions may include (but are not limited to): • Implementing additional risk control measures in accordance with the initial identified risk of laboratory activities to reduce residual risk to an acceptable risk, that is – If initial risk was assessed as medium/high, then further risk control measures need to be implemented before the laboratory activity is undertaken. – If initial risk was assessed as very high, then comprehensive risk measures will need to be implemented to ensure safety. • Redefining the scope of work such that the risk is acceptable with existing risk control measures in place • Identifying an alternative laboratory with appropriate risk control strategies already in place that is capable of conducting the work as planned
☐	High	If an incident occurred, harm would result that would require medical treatment and/or substantial environmental measures.	
☐	Very high	If an incident occurred, a permanent, impairing harm or death and/or extensive environmental effects would be likely.	

Select the overall **residual** risk.	☐ Very low	☐ Low	☐ Medium	☐ High	☐ Very high
Will work require additional risk control measures?	Yes ☐ No ☐				

4.3 Evaluate the residual risk that remains after risk control measures have been selected (continued)

Reviewed by (Name and title)	
Reviewed by (Signature)	
Date	

4.4 Communication of the hazards, risks and risk control measures

Instructions: Develop a plan to communicate risks and risk control strategies to laboratory and other relevant personnel. These plans should include the mechanism(s) of communication within the laboratory, such as in-person team meetings and/or training classes, published SOPs, and identification of an accessible place to store all risk assessments and documentation on the risk control strategy.

4.5 Purchase of required risk control measures

Instructions: Describe a process and timeline for ensuring that all needed equipment/supplies for the risk control measures are purchased on time. Consider the budgeting, financial sustainability, ordering, receipt and installation of all risk control measures to be purchased before starting the laboratory work.

4.6 Operational and maintenance procedures

Instructions: Describe a process and timeline for ensuring that all risk control measures have associated SOPs and that training on these risk control measures has been completed. The plan should include development of SOPs, training of personnel who will perform the work, and maintenance and/or calibration, certification, validation of equipment before starting the laboratory work.

4.7 Training of personnel

Instructions: Describe a process and timeline for ensuring that training has been completed for all risk control measures. Take into consideration that all personnel (laboratory and support/maintenance personnel) should have completed all training necessary to use all risk control measures before starting the laboratory work.

STEP 5. Review risks and risk control measures

5.1 Establish a periodic review cycle to evaluate the effectiveness of risk control measures and to identify any changes

Instructions: Describe the periodic review process. Reviews of risk assessments, risk control measures and risk control strategies should be done periodically to ensure that the laboratory procedures are safe and that the risk control measures that have been implemented to reduce risk are still effective. Components of periodic reviews may include laboratory inspections/audits and/or asking for feedback from personnel during training and team meetings. Reviews of risks and risk control measures must also include: • **updates on laboratory activities or procedures** • **new biological agents, or new information on existing biological agents** • **changes in personnel** • **changes in equipment and/or facilities** • **results of audits/inspections** • **lessons learnt from laboratory incidents or near misses** • **personnel feedback on procedures, risk control measures and residual risks** • **person responsible for doing the review and the frequency of reviews** • **method of documenting the updates and changes** • **procedures for implementing the changes.** **While annual reviews may be most common, the frequency of the review should be proportionate to the risks, and reviews should be conducted and risks reassessed whenever there are major changes in any elements of the work.**

Reviewed by (Name and title)	
Reviewed by (Signature)	
Date	

ANNEX 3. COMPLETED SHORT TEMPLATE: *MYCOBACTERIUM TUBERCULOSIS* TESTING

Institution/Facility name	Regional Public Health Laboratory (RPHL)
Laboratory name	Microbiology
Laboratory manager/Supervisor	Erika Sebiko, Laboratory Manager, RPHL
Project titles/Relevant standard operating procedures (SOPs)	Diagnostic testing for *Mycobacterium tuberculosis*
Date	12 July 2020

If using this template, complete all sections following the instructions in the grey boxes. The instructions and bullet points in the grey boxes can be copied into the text boxes beneath the instructions and used as prompts to gather and record the necessary site-specific information. The grey instruction boxes can then be deleted, and the text remaining will form a risk assessment draft. This draft must be carefully reviewed, edited as necessary and approved by the risk assessment team members.

STEP 1. Gather information (hazard identification)

Instructions: Provide a brief overview of the laboratory work and summarize the laboratory activities to be conducted that are included in the scope of this risk assessment.	
Describe the biological agents and other potential hazards (for example, transmission, infectious dose, treatment/preventive measures, pathogenicity).	• *M. tuberculosis* may be present in clinical specimens (sputum, urine, other body fluids or infected tissues) • Spread by airborne and percutaneous routes, ingestion, contact/fomites • ID_{50} (infectious dose) is estimated to be < 10 bacilli • Highly transmissible • Effective immunization is not routinely available • Antibiotics are available for post-exposure prophylaxis • Multidrug-resistant tuberculosis (TB) (MDR-TB) and extensively drug-resistant TB (XDR-TB) strains exist but are not likely in this setting • Susceptible to 5000 ppm hypochlorite, 10 minutes exposure time and autoclave at 121 °C for 15 minutes

STEP 1. Gather information (hazard identification) (continued)

Instructions: Provide a brief overview of the laboratory work and summarize the laboratory activities to be conducted that are included in the scope of this risk assessment.	
Describe the laboratory procedures to be used (for example, culturing, centrifugation, work with sharps, waste handling, frequency of performing the laboratory activity).	• Specimen receipt and recording • Direct smear microscopy to detect acid-fast bacilli • Autoclaving and disposal of waste (by external contractor) • Cleaning of laboratory after any spills
Describe the types of equipment to be used (personal protective equipment (PPE), centrifuges, autoclaves, biological safety cabinets (BSCs).	• PPE: laboratory coats, latex gloves • Equipment: refrigerator, heat block/flame, microscope, broken glass/sharps containers, autoclave (validated annually)
Describe the type and condition of the facility where work is conducted.	The microbiology laboratory is a room next to the patient waiting area and specimen collection/phlebotomy rooms. It is an older facility with some cracked vinyl tiles on the floor, open, screened windows and open doors that can be closed at the end of the work shift. Bench tops are impervious to disinfectants; however there are some cracks in the surface. All furniture is sturdy and able to be disinfected. Electric and water supply is adequate for laboratory work but there is only one sink that is used for staining and hand washing.
Describe relevant human factors (for example, competency, training, experience and attitude of personnel).	Personnel are trained on laboratory biosafety and compliance is generally good among senior personnel. Personnel turn-over, especially of the younger colleagues, is high. New personnel require mentorship but adequate supervision is not always available. Job aides with photographs are posted to remind personnel of laboratory and safety procedures.
Describe any other factors that may affect laboratory operations (for example, legal, cultural, socioeconomic).	There is occasional crime in the area (for example, burglary), but it is mostly of computer and office supplies and the laboratory or patient rooms have never been affected.

STEP 2. Evaluate the risks

Instructions: Describe how exposure and/or release could occur.	
What potential situations are there in which exposure or release could occur?	• Aerosol exposure to or release of *M. tuberculosis* from a spill • Contact with contaminated surfaces • Improperly treated waste
What is the likelihood of an exposure/release occurring (unlikely, possible, likely)?	• Aerosol exposure to or release of *M. tuberculosis* from a spill – possible • Contact with contaminated surfaces – possible • Improperly treated waste – possible
What is the severity of the consequences of an exposure/release (negligible, moderate, severe)?	Moderate

Instructions: Evaluate the risk and prioritize the implementation of risk control measures. Circle the initial risk of the laboratory activities including risk control measures described in STEP 1 but before any additional risk control measures have been put in place.

Note:

- **When assigning priority, other factors may need to be considered, for example, urgency, feasibility/sustainability of risk control measures, delivery and installation time and training availability.**
- **To estimate the overall risk, take into consideration the risk ratings for the individual laboratory activities/procedures, separately or collectively as appropriate for the laboratory.**

		Likelihood of exposure/release		
		Unlikely	Possible	Likely
Consequences of exposure/release	Severe	Medium	High	Very high
	Moderate	Low	(Medium)	High
	Negligible	Very low	Low	Medium

STEP 2. Evaluate the risks (continued)

Laboratory activity/procedure	**Initial risk** (very low, low, medium, high, very high)	**Is the initial risk acceptable?** (yes/no)	**Priority (high/ medium/low)**
Spill of patient specimens with production of aerosols	Medium	No	High
Spill of or contamination from patient specimens	High	No	High
Sharps injury from handling glass slides	Low	Yes	Low
Exposure to improperly treated waste	Medium	No	Medium

Select the overall **initial** risk.	☐ Very low	☐ Low	☒ Medium	☐ High	☐ Very high
Should work proceed without additional risk control measures?	Yes ☐ No ☒				

STEP 3. Develop a risk control strategy

Instructions: Describe the resources available for risk control and consider their applicability, availability and sustainability in the local context including management support.	
Are resources sufficient to secure and maintain potential risk control measures?	Yes, PPE is provided and readily available but additional PPE, such as respiratory protection, is not available.
Describe the measures advised by guidelines, policies and strategies (if any).	Limited financial resources are available to buy any additional PPE or safety equipment.
Will work be able to proceed without any of the risk control measures; are there alternatives?	Unknown; if liquid culture or antibiotic sensitivity testing needs to be done, or if MDR-TB or XDR-TB were present, additional PPE and safety equipment may need to be procured or specimens will have to be sent to another laboratory for confirmatory testing.

STEP 4. Select and implement risk control measures

Instructions: List any requirements that have been prescribed by international and national regulations, legislation, guidelines, policies and strategies on biosafety and biosecurity. In addition, consider if there are any local regulations, guidelines or policies that restrict or govern certain laboratory activities and/or the handling and use of any biological agents.	
Describe the measures required by national legislation or regulations (if any).	No national regulations or guidelines are available for this work
Describe the measures advised by guidelines, policies and strategies (if any).	• WHO guidelines on TB • WHO *Laboratory biosafety manual*, fourth edition

Instructions: Describe where and when risk control measures are needed, the residual risk when these risk control measures are in place, and an assessment of the availability, effectiveness and sustainability of the risk control measures.

Laboratory activity/procedure	**Selected risk control measure(s)**	**Residual risk (very low, low, medium, high, very high)**	**Is the residual risk acceptable? (yes/no)**	**Are risk control measures available, effective and sustainable? (yes/no)**
Spill of patient specimens, with production of aerosols	Transport in sealed container	Low	Yes	Yes
Spill of or contamination from patient specimens	Wear gloves when handling any patient specimens/ slides; disinfect work area daily; wash hands in sink available in adjacent room that is not used for laboratory work (contamination of doors and other items by contaminated gloves must be avoided)	Low	Yes	Yes
Sharps injury from handling glass slides	Use sharps containers whenever possible	Very low	Yes	Yes
Exposure to improperly treated waste	Autoclave will be validated monthly	Very low	Yes	Yes, if indicators for validating the autoclave are readily available

STEP 4. Select and implement risk control measures (continued)

Instructions: Evaluate the residual risk that remains after risk control measures have been selected to determine if the risk is now acceptable and whether work should proceed.
Circle the residual risk of the laboratory activities after risk control measures are in place.

		Likelihood of exposure/release		
		Unlikely	Possible	Likely
Consequences of exposure/release	Severe	Medium	High	Very high
	Moderate	(Low)	Medium	High
	Negligible	Very low	Low	Medium

Overall **residual** risk.	☐ Very low	☒ Low	☐ Medium	☐ High	☐ Very high

If the residual risk is still unacceptable, further action is necessary such as additional risk control measures, based on the initial risk evaluated in STEP 2, redefining the scope of work such that it is acceptable with existing risk control measures in place or identifying an alternative laboratory with appropriate risk control strategies already in place that is capable of conducting the work as planned.

Should work proceed with selected risk control measures?	Yes ☒ No ☐
Approved by (Name and title)	Omar Abubakr, Microbiology Laboratory Manager
Approved by (Signature)	Omar Abubakr
Date	29 July 2020

Instructions: Describe how to communicate risks and risk mitigation strategies to personnel. Provide a mechanism of communication within the laboratory. Describe the process and timeline for ensuring that all identified risk control measures are purchased, have associated SOPs and training has been completed before starting the laboratory work.

Communication of the hazards, risks and risk control measures	• SOPs will be updated with new risk control measures for specimen transport, PPE use, sharps disposal, hand washing, disinfection and decontamination. • Signs and job aides will be updated and displayed.
Purchase (and budgeting) of risk control measures	Additional gloves, sharps containers and biological indicators will be added to laboratory operating budget for approval and purchase.
Operational and maintenance procedures	Autoclave SOP will be updated for more frequent validation.
Training of personnel	Personnel will be trained on new SOPs.

STEP 5. Review risks and risk control measures

Instructions: Establish a periodic review cycle to identify: changes in laboratory activities, biological agents, personnel, equipment or facilities; changes in knowledge of biological agents or processes; and lessons learnt from audits/inspections, personnel feedback, incidents and/or near misses.	
Frequency of the review	This risk assessment will be reviewed in 6 months to ensure proper implementation of all recommended risk control measures and then annually after that.
Person to conduct the review	The laboratory manager
Describe updates/changes	• Any culturing of TB is prohibited. If culture becomes necessary, another risk assessment must be performed to evaluate the need for additional risk control measures such as PPE and safety equipment (BSC). • MDR-TB and XDR-TB strains exist but are not likely in this setting. If they were suspected in a patient specimen, work would stop for another risk assessment and specimens suspected to be positive for MDR-TB and XDR-TB shipped to another laboratory.
Personnel/procedures to implement the changes	Additional PPE and/or safety equipment may be necessary in those cases, or specimens could be sent to the central laboratory for further testing.
Reviewed by (Name and title)	Erika Sebiko, RPHL Laboratory Manager
Reviewed by (Signature)	Erika Sebiko
Date	31 July 2020

ANNEX 4. COMPLETED SHORT TEMPLATE: BLOODBORNE PATHOGENS

Institution/Facility name	Primary Reference Laboratory
Laboratory name	Bloodborne-Pathogen Testing Laboratory
Laboratory manager/Supervisor	Chen Shixin, Laboratory Manager
Project titles/Relevant standard operating procedures (SOPs)	Lateral flow diagnostic testing SOPs Biosafety manual
Date	15 March 2020

If using this template, complete all sections following the instructions in the grey boxes. The instructions and bullet points in the grey boxes can be copied into the text boxes beneath the instructions and used as prompts to gather and record the necessary site-specific information. The grey instruction boxes can then be deleted, and the text remaining will form a risk assessment draft. This draft must be carefully reviewed, edited as necessary and approved by the risk assessment team members.

STEP 1. Gather information (hazard identification)

Instructions: Provide a brief overview of the laboratory work and summarize the laboratory activities to be conducted that are included in the scope of this risk assessment.	
Describe the biological agents and other potential hazards (for example, transmission, infectious dose, treatment/preventive measures, pathogenicity).	Bloodborne pathogens: human immunodeficiency virus (HIV), and hepatitis A, B, C and D viruses. Unknown bloodborne pathogens (rarer). The most dangerous of the bloodborne pathogens is hepatitis B since it can survive outside the body (on surfaces) for up to 7 days and it is a common sexually transmitted infection. Hepatitis C can also survive outside the body on surfaces but only up to 4 days. Although Hepatitis A can survive on surfaces for long periods, this infection is always acute, is transmitted by the faecal/oral route and can be easily detected. • Hepatitis A: vaccine-preventable, post-exposure prophylaxis available, acute and recovery is spontaneous • Hepatitis B: vaccine-preventable, post-exposure prophylaxis available, acute and chronic forms • Hepatitis C: no vaccine, chronic, now treatable • HIV: no vaccine, post-exposure prophylaxis available, incurable, lifelong treatment with antiretroviral drugs All are transmissible; all can be prevented using good microbiological practice and procedure, and the specified risk control measures.

STEP 1. Gather information (hazard identification) (continued)

Instructions: Provide a brief overview of the laboratory work and summarize the laboratory activities to be conducted that are included in the scope of this risk assessment.	
Describe the laboratory procedures to be used (for example, culturing, centrifugation, work with sharps, waste handling, frequency of performing the laboratory activity).	We will be testing blood specimens collected in the field using a rapid diagnostic test that relies on lateral flow detection. We will follow the manufacturer's instructions to dilute individual specimens of patient blood (using the buffer supplied) in microfuge tubes before testing. The tubes will be incubated for 5 minutes and then put in a vortex mixer. Rapid diagnostic test strips, one per tube of patient specimen, will be submerged in the tube so that the specimen pad is wetted with the patient's diluted blood. Tubes with strips will be incubated for 5 minutes as per manufacturer's instructions and the test strips read and analysed according to manufacturer's instructions. Strips will be photographed with patient identifier for record keeping, and both used test strips and blood dilution tubes will be discarded as biohazardous waste.
Describe the types of equipment to be used (personal protective equipment (PPE), centrifuges, autoclaves, biological safety cabinets (BSCs).	• PPE will be worn, including disposable gloves and an open-front laboratory coat. • A vortex mixer will be used to mix blood specimen dilutions. • An autoclave will be used to destroy biological agents in biohazardous waste.
Describe the type and condition of the facility where work is conducted.	The facility is old but has adequate bench space. There is one BSC in the laboratory but it needs a new high-efficiency particulate air (HEPA) filter.
Describe relevant human factors (for example, competency, training, experience and attitude of personnel).	We have no personnel trained in this procedure but the manufacturer of the rapid diagnostic kit will send a trainer to our laboratory a month before the project begins.
Describe any other factors that may affect laboratory operations (for example, legal, cultural, socioeconomic).	Both hepatitis and HIV infection are culturally unacceptable in the community. All specimens will have identification removed by the personnel receiving the specimens before being forwarded to laboratory personnel. The clinic physicians will inform patients of their disease status and onsite counselling will be available for those found positive for infection.

STEP 2. Evaluate the risks

Instructions: Describe how exposure and/or release could occur.	
What potential situations are there in which exposure or release could occur?	• We are not using needles in this work, nor are we using any supplies made of glass. It is possible that a spill/fall situation could lead to accidental introduction of bloodborne biological agents through a skin wound. • Vortexing the microfuge tubes can create aerosols, so contact with mucous membranes is possible. • Laboratory surfaces contaminated with blood may harbour bloodborne pathogens, especially hepatitis B and C viruses, so these must be thoroughly cleaned with bleach solution or other approved disinfectants.
What is the likelihood of an exposure/release occurring (unlikely, possible, likely)?	• Hepatitis A: unlikely • Hepatitis B: possible • Hepatitis C: possible • HIV: unlikely
What is the severity of the consequences of an exposure/release (negligible, moderate, severe)?	• Hepatitis A: moderate • Hepatitis B: moderate • Hepatitis C: moderate • HIV: moderate

STEP 2. Evaluate the risks (continued)

Instructions: Evaluate the risk and prioritize the implementation of risk control measures. Circle the initial risk of the laboratory activities including risk control measures described in STEP 1 but before any additional risk control measures have been put in place.

Note:

- **When assigning priority, other factors may need to be considered, for example, urgency, feasibility/sustainability of risk control measures, delivery and installation time and training availability.**
- **To estimate the overall risk, take into consideration the risk ratings for the individual laboratory activities/procedures, separately or collectively as appropriate for the laboratory.**

		Likelihood of exposure/release		
		Unlikely	Possible	Likely
Consequences of exposure/release	Severe	Medium	High	Very high
	Moderate	Low	(Medium)	High
	Negligible	Very low	Low	Medium

Laboratory activity/procedure	**Initial risk (very low, low, medium, high, very high)**	**Is the initial risk acceptable? (yes/no)**	**Priority (high/medium/low)**
Hepatitis A	Low	Yes	Low
Hepatitis B	Medium	No	Medium
Hepatitis C	Medium	No	Medium
HIV	Low	Yes	Low

Select the overall **initial** risk.	☐ Very low	☐ Low	☒ Medium	☐ High	☐ Very high
Should work proceed without additional risk control measures?	Yes ☐ No ☒				

STEP 3. Develop a risk control strategy

Instructions: Describe the resources available for risk control and consider their applicability, availability and sustainability in the local context including management support.	
Are resources sufficient to secure and maintain potential risk control measures?	• We need to reduce the risk associated with 1) surface contamination and 2) contact of infectious droplets with mucous membranes. Working inside a BSC would reduce the risk of both potential hazards. We do not have immediate funding to repair the BSC but we will include this cost in the annual funding budget. We will begin our work (in about a month) using the BSC in a nearby laboratory of another department. We will develop SOPs for preparing the specimens for transport and their transport to the other laboratory, until the BSC in our laboratory is repaired. • We may have to begin work in our laboratory in about a month and will have to use the BSC without an appropriate filter. However, this choice is better than working on the open bench since it will isolate the blood and potential pathogens and will lower the number of people who could come into contact with any contamination. While the BSC is being used without a HEPA filter, additional PPE (face shield, double gloves, laboratory gown) will be necessary. Until the BSC is repaired, it will be prohibited to work in it with biological agents with r transmission. A notice with this prohibition will be attached to the front of the BSC.
Describe the measures advised by guidelines, policies and strategies (if any).	Only the delay in funding to replace the HEPA filter and certify the BSC.
Will work be able to proceed without any of the risk control measures; are there alternatives?	Yes – we will use the BSC as a containment area while we wait for repairs.

STEP 4. Select and implement risk control measures

Instructions: List any requirements that have been prescribed by international and national regulations, legislation, guidelines, policies and strategies on biosafety and biosecurity. In addition, consider if there are any local regulations, guidelines or policies that restrict or govern certain laboratory activities and/or the handling and use of any biological agents.	
Describe the measures required by national legislation or regulations (if any).	None
Describe the measures advised by guidelines, policies and strategies (if any).	None

Instructions: Describe where and when risk control measures are needed, the residual risk when these risk control measures are in place, and an assessment of the availability, effectiveness and sustainability of the risk control measures.

Laboratory activity/procedure	**Selected risk control measure(s)**	**Residual risk (very low, low, medium, high, very high)**	**Is the residual risk acceptable? (yes/no)**	**Are risk control measures available, effective and sustainable? (yes/no)**
Creation of infectious aerosols while using the vortex mixer	Working inside BSC workspace	Low	Yes	Yes
Contamination of work surfaces	Decontamination of surfaces after completing work and at the end of the day	Low	Yes	Yes

Instructions: Evaluate the residual risk that remains after risk control measures have been selected to determine if the risk is now acceptable and whether work should proceed.

Circle the residual risk of the laboratory activities after risk control measures are in place.

		Likelihood of exposure/release		
		Unlikely	Possible	Likely
Consequences of exposure/release	Severe	Medium	High	Very high
	Moderate	(Low)	Medium	High
	Negligible	Very low	Low	Medium

STEP 4. Select and implement risk control measures (continued)

Overall **residual** risk.	☐ Very low	☒ Low	☐ Medium	☐ High	☐ Very high
If the residual risk is still unacceptable, further action is necessary such as additional risk control measures, based on the initial risk evaluated in STEP 2, redefining the scope of work such that it is acceptable with existing risk control measures in place or identifying an alternative laboratory with appropriate risk control strategies already in place that is capable of conducting the work as planned.					
Should work proceed with selected risk control measures?	Yes ☒ No ☐				
Approved by (Name and title)	Manfred Gruber, Primary Reference Laboratory Head				
Approved by (Signature)	Manfred Gruber				
Date	15 May 2020				

Instructions: Describe how to communicate risks and risk mitigation strategies to personnel. Provide a mechanism of communication within the laboratory. Describe the process and timeline for ensuring that all identified risk control measures are purchased, have associated SOPs and training has been completed before starting the laboratory work.	
Communication of the hazards, risks and risk control measures	I will prepare an SOP specific to our laboratory that will include biosafety equipment to be used and practices that must be followed.
Purchase (and budgeting) of risk control measures	Risk control measures will be included in the annual budget. The laboratory manger will be responsible for inventory and usage records, and will inform me of expenditures so that budget adjustments can be made accordingly.
Operational and maintenance procedures	These will also be included in the annual budget
Training of personnel	All personnel will be invited to one-on-one training with the manufacturer of the rapid diagnostic kit. Personnel will be observed performing this assay and will have to be judged competent before working independently.

STEP 5. Review risks and risk control measures

Instructions: Establish a periodic review cycle to identify: changes in laboratory activities, biological agents, personnel, equipment or facilities; changes in knowledge of biological agents or processes; and lessons learnt from audits/inspections, personnel feedback, incidents and/or near misses.	
Frequency of the review	This procedure will be reviewed in one year from the start date of this risk assessment but sooner if needed because of personnel, equipment and/or protocol changes. The procedure will be reviewed before the one-year date if a laboratory incident occurs.
Person to conduct the review	The laboratory manager.
Describe updates/changes	Minor updates or changes to the SOP may be implemented to: 1) ensure accuracy of testing, or 2) improve workflow. These will be done on a case-by-case basis without review of the entire process.
Personnel/procedures to implement the changes	The laboratory manager.
Reviewed by (Name and title)	Chen Shixin, Laboratory Manager
Reviewed by (Signature)	Chen Shixin
Date	19 June 2020

ANNEX 5. COMPLETED LONG TEMPLATE: INFLUENZA RESEARCH

Institution/Facility name	Global Communicable Diseases Research Institute
Laboratory name	Influenza Laboratory
Laboratory manager/Supervisor	Dr Zhang Tian, Director, Global Communicable Diseases Research Institute
Location	City near the mountains
Project titles/Relevant standard operating procedures (SOPs)	• SOP for influenza research • SOP for spill cleaning • SOP for waste management • SOP for laboratory rules
Date	12 March 2020

If using this template, complete all sections following the instructions in the grey boxes. The instructions and bullet points in the grey boxes can be copied into the text boxes beneath the instructions and used as prompts to gather and record the necessary site-specific information. The grey instruction boxes can then be deleted, and the text remaining will form a risk assessment draft. This draft must be carefully reviewed, edited as necessary and approved by the risk assessment team members.

STEP 1. Gather information (hazard identification)

1.1 Provide a brief overview of the laboratory work

Instructions: Summarize the laboratory activities to be conducted that are included in the scope of this risk assessment. If the laboratory conducts other similar work on a regular basis (for example, well-defined, routine diagnostic testing), consider using one assessment to cover all laboratory activities. However, large and more complex laboratories that carry out a variety of laboratory activities, such as diagnostic testing, confirmatory testing, characterization of biological agents and research, may want to conduct separate risk assessments.

In order to define the determinants of interspecies transmission and pathogenesis of influenza A virus infections in the different host species, wild-type strains of influenza A virus or interferon-sensitive mutants (= deletion of *NS1*) will be inoculated on in vitro respiratory epithelium cell models of avian, porcine, human and bat species. We will use the well-established reverse genetic system to produce wild-type strains of influenza A virus or interferon-sensitive mutants (MxA-sensitivity (= deletion of *NS1*)) using 293T cell line. We will also use well-characterized chemical inhibitors or lentiviral-based short-hairpin RNA-mediated knockdown of host gene expression to determine the influence of host genes involved in the innate immunity on replication characteristics of the different virus strains and the dynamics of the host innate immune response.

1.2 Describe the biological agents and other potential hazards

Instructions: Identify the hazards. It is important to know the characteristics of the biological agent(s) when determining the risks it presents. When the specific biological agent is known, the following information will be useful for the risk assessment and should be thoroughly researched. When handling unknown or diagnostic specimens, it is important to try and obtain any information on the source of the specimens and/or a presumptive/suspected diagnosis. Typical information to be gathered about the biological agent(s) includes:

- **pathogenicity/severity of disease**
- **epidemiology and host range**
- **sources/specimens**
- **infectious dose, concentration and volume**
- **route(s) of transmission**
- **incubation period and communicability**
- **viability and susceptibility to disinfectants**
- **means of diagnosing the disease, type of testing done for diagnosis**
- **treatment, immunization and prophylaxis available**
- **unique laboratory hazards (laboratory-associated infections)**
- **additional information.**

- Influenza A virus PR8 (H1N1) wild type and *NS1* deletion mutant
  - Transmission of influenza A virus in humans can occur through respiratory infection by aerosols and droplets or from contact transmission from contaminated surfaces. Thus, if specimens containing influenza A are handled incorrectly, transmission to humans could occur at every working step in the laboratory.
  - The infectious dose for specific influenza A virus subtypes is unknown but even though high titre virus stocks are produced in the laboratory, cell cultures are inoculated with low multiplicities of infection (0,25). In an experimental set up/in vitro, influenza A virus can grow to a high titre (10^7) depending on the inoculated cell type.
  - Possible consequences of exposure: Influenza A virus induces influenza (flu) in humans which is characterized by cold-like symptoms, high fever, myalgia, malaise and occasionally pulmonary or cardiac complications. Death from flu is generally rare, except in those with chronic lung or heart conditions. Flu is a highly communicable disease. However, after an exposure to or release of influenza A virus PR8 wild type, no epidemic would be expected because influenza A virus subtype H1N1 is still circulating in the human population and is included in current vaccines. The influenza A virus PR8 strain is a mouse-adapted strain but can possibly induce flu in humans. In mice, the influenza A virus PR8 *NS1* deletion mutant is no longer pathogenic and, in vitro, its replication is attenuated in interferon-competent cells. Therefore, it is highly unlikely that the NS1 mutant would induce disease in humans.
- Primary cell cultures of human, bat, avian and porcine origin
  - Human: primary bronchial cells, the tracheobronchial material used for cell isolation, come from patients undergoing bronchoscopy or pulmonary resection in hospital. These patients tested negative for HIV, and hepatitis B and C viruses; nevertheless, cell cultures should be treated as potentially infected material as they may be contaminated with other biological agents.
  - Bat: the tracheobronchial material used for cell isolation comes from healthy bats from a zoo. Even though these animals are healthy, bats can harbour many potentially pathogenic biological agents and the cell cultures should always be treated as infectious material.
  - Avian and porcine: the tracheobronchial material used for cell isolation comes from in-house specific pathogen-free chickens and pigs. The health of these animals is monitored over a long time and cells are very unlikely to carry undetected human pathogens.
- Lentiviral particles mediating knockdown of host genes involved in innate immunity
  - Vesicular stomatitis virus G-protein pseudotyped lentiviral particles can infect a wide range of non-dividing and actively dividing cell types of different host species, including humans.
  - Transgenes used in our work target genes involved in innate immunity and are not oncogenic by themselves. However, depending on the site of integration, there is the potential for oncogenesis or other deleterious effects through insertional mutagenesis.
  - Lentiviral particles are replication incompetent; thus, the infection cannot spread in the body but is localized to the initially infected cells. However, if a person with HIV were accidentally infected, lentiviral particles could recombine with the native HIV and result in revertants that could replicate.

1.2 Describe the biological agents and other potential hazards (continued)

Instructions: Identify the hazards. It is important to know the characteristics of the biological agent(s) when determining the risks it presents. When the specific biological agent is known, the following information will be useful for the risk assessment and should be thoroughly researched. When handling unknown or diagnostic specimens, it is important to try and obtain any information on the source of the specimens and/or a presumptive/ suspected diagnosis. Typical information to be gathered about the biological agent(s) includes:

- **pathogenicity/severity of disease**
- **epidemiology and host range**
- **sources/specimens**
- **infectious dose, concentration and volume**
- **route(s) of transmission**
- **incubation period and communicability**
- **viability and susceptibility to disinfectants**
- **means of diagnosing the disease, type of testing done for diagnosis**
- **treatment, immunization and prophylaxis available**
- **unique laboratory hazards (laboratory-associated infections)**
- **additional information.**

- Chemical inhibitors of host genes involved in innate immunity are only used in low concentrations and in small quantities.
- Use of cryogenics (dry ice): cells are stored at –150 °C, viruses at –80 °C and the transport of both occurs on dry ice. Cryogenics can cause burns or frostbite. The gas of dry ice can cause health effects in lower concentrations (toxic hazard) and displaces oxygen in higher concentrations (asphyxiation hazard).
- Use of compressed gas (CO_2) for cell culturing: danger of a gas bottle bursting if it falls over or is heated.

1.3 Describe the laboratory procedures to be used

Instructions: Identify the laboratory activities that might cause exposure to the biological agent when it is being transported, handled or manipulated. Consider the following:

- **centrifuging**
- **cleaning up spills**
- **contact with fomites or contaminated surfaces**
- **inoculating media, including how frequently and in what concentration the biological agent is isolated/ propagated**
- **manipulating inoculation loops, pipettes, needles and other sharps, syringes**
- **mixing, blending, grinding, shaking, sonicating and vortexing**
- **pouring, splitting or decanting liquids**
- **preparing smears, heat fixing or staining slides**
- **spilling/dropping/splashing infectious material**
- **transporting specimens/materials inside and outside the laboratory, leaky specimen containers**
- **frequency of performing the laboratory activity**
- **using animals and insects**
  - **scratches, bites, stings**
  - **dissection, organ collection and disposal procedures**
  - **inoculation, injection or blood drawing**
- **handling biological waste**
  - **specimen/culture/pathogen transport procedures**
  - **inactivation procedures (for example, chemical, heat)**
  - **disposal procedures (for example, autoclaving, incinerating).**

- Preparation and handling of cells (airway cultures and cell lines)
  - Use of scalpels/scissors and forceps for preparation of tracheobronchial material to isolate primary epithelial cells
  - Incubation of tracheobronchial material in digestion solution on a rocking platform at 4 °C
  - Centrifugation of cell cultures
  - Freezing of cells to –150 °C
  - Incubation of cell cultures with chemical inhibitors directed against expression of host genes involved in innate immune response
  - Thawing of frozen cell stocks and transportation of frozen cells on dry ice
  - Renewal of compressed gas bottles (CO_2) for cell culturing
- Work with infectious viruses (influenza A virus and lentiviral particles): preparation of virus stock, infection of cell cultures, processing of infected cell cultures
  - Thawing of virus stock in water bath, vortexing and pipetting of virus stock, transfer of virus stock from storage location to the laboratory on dry ice, transfer of infected cell cultures from the biological safety cabinet to incubator, spills of infectious materials
  - A spill kit for biological and chemical material is in place and training on clean-up procedures is regularly done
- Waste handling
  - Separation of solid and liquid waste in order to inactivate both waste types using different autoclave programmes
  - Double wrapping of solid waste for transport to the in-house autoclave three floors below
  - After use, placing of serological pipettes back into their packing bags and removal from the BSC to an autoclaving bag without prior inactivation.
  - Pre-disinfection of liquid waste before transport to the autoclave in order to reduce the viral load
  - Collection and autoclaving of sharps in sharps boxes and their disposal according to local/community disposal guidelines

1.4 Describe the types of equipment to be used

Instructions: Determine what instruments and equipment will be used to do the laboratory work. Please note that each type of equipment has its own inherent risks. For example, if centrifugation will be used, the potential for aerosols to be produced is a risk to consider. List any safety equipment that is available and likely to be used. Examples of equipment that may be used include:

- **personal protective equipment (PPE)**
  - **gloves**
  - **protective clothing**
  - **protective eyewear**
  - **respiratory protection (has it been fit tested?)**
- **autoclave (has it been validated?)**
- **biological safety cabinet (BSC) (has it been certified?)**
- **handwashing sink**
- **centrifuge (does it have sealed rotors or safety cups?)**
- **incubator**
- **refrigerator/freezer**
- **additional equipment, list:**

- For cell isolation from primary tracheobronchial material, the following equipment is used: a BSC, scalpels, scissors and forceps, a room at 4 °C for enzymatic digestion, centrifuge, vortex, serological pipettes and pipette aid
- A humidified incubator with 5% CO_2 is used for cell culture
- Crystal violet is used to determine the viral titre after virus titration
- PPE: laboratory coat and gloves when working with infectious material, toxic chemicals or cell cultures; cold-resistant gloves and safety goggles when working with dry ice or liquid nitrogen
- BSC with self-checking system for downflow and inflow velocities with alarm functions, serviced annually: used when working with infectious material. However, one of the BSCs is 2 metres wide, which tempts people to work in twos at the BSC, irrespective of the work they do – this is discouraged
- Centrifuges: with safety buckets
- Vortex: outside the BSC; it is only used with closed tubes
- Freezer (–150 °C): run by electricity (no liquid nitrogen is used)
- Autoclave: validated each year for correct pathogen inactivation in liquid and solid waste
- Hygiene: hand washing facilities and hand disinfection available in every laboratory
- Spill kit: readily available and contains all necessary items to clean a spill which contains infectious viruses

1.5 Describe the type and condition of the facility where work is conducted

Instructions: Consider the layout and type of facility where work will be done to determine if laboratory activities can be conducted safely and securely. The workflow of the laboratory activities from one area of the laboratory to another should also be considered, including specimen receipt, transport, processing and disposal. Consider the following factors.

- **Will the work be carried out in a large, multipurpose space?**
- **Are separate rooms or spaces available for high-risk laboratory activities?**
- **Does the workflow and specimen transport create any special concerns for surface contamination or other laboratory accidents?**
- **Are laboratory floors, bench tops and furniture non-porous and impervious to the biological agent?**
- **Is laboratory furniture in good repair and ergonomically appropriate for the workstation?**
- **Do laboratory areas have closable doors?**
- **Are windows sealed or fitted with screens?**

Work will be done in a multipurpose laboratory dedicated for work with human viruses. The laboratory has closable doors, and windows are not to be opened (but are not sealed). The laboratory has appropriate ventilation (no negative air pressure) and room temperature is kept constant. Cell culture incubators are next to the two BSCs ensuring short transport routes for (infected) cell cultures. The laboratory also has benches for 10 people, a light microscope with a multiviewing system and a fluorescence microscope, four refrigerators, two large centrifuges and several table-top centrifuges, a water bath and two PCR machines. Some of the benches are high but are equipped with high chairs with foot-rests for ergonomic reasons.

Storage for consumables is outside the laboratory in a hallway or in other rooms on the same floor (4 °C room and chemical room). Storage room for viruses and cells (–150 °C and –80 °C freezers) is in the basement of the same building, so safety measures for transport of infectious material to these freezers must be taken.

The inactivation and sterilization unit for waste and reusable material from the laboratory is three floors below the laboratory in the same building. The laboratory waste is stored in the corridor next to the laboratories and is transported by a trained technician in sealed containers.

1.6 Describe relevant human factors (for example, competency and suitability of personnel)

Instructions: Consider the competency and experience of laboratory personnel. Assess the training the personnel have had on the biological agent(s), and their experience of handling it and using relevant biosafety practices and safety equipment when performing laboratory work. Consider the following factors.

- **Do personnel have experience working with these biological agents or similar biological agents?**
- **Do personnel have experience performing these procedures and using this equipment?**
- **Are personnel trained to work with diagnostic specimens and unknown agents and do they have experience in this work?**
- **Have all personnel had relevant biosafety training or been briefed on laboratory biosafety, including cleaning and maintenance personnel and visitors, so that all personnel and people entering the laboratory are adequately informed about the hazards in the laboratory?**
- **Do personnel have positive attitudes to biosafety and adherence to safety procedures?**
- **Have there been prior incidents or laboratory-associated infections with this laboratory or these personnel?**
- **Are any personnel at increased risk because of greater susceptibility to laboratory hazards?**
- **Is there undue time pressure on personnel that may result in stress and fatigue?**

Use the following table to list the personnel and their training on the relevant SOP and safety.

All laboratory personnel have had biosafety training on relevant engineering controls, PPE and procedures (for example, BSC, laboratory coats, hygiene) when working with infectious biological agents with respiratory transmission. New personnel and less experienced people (such as undergraduate and postgraduate students working there for a limited period – internship or scientific project) are always supervised and trained by experienced laboratory personnel on experimental procedures.

Many people are working in this influenza research team, which can limit the time available to use the BSC or make organization of the work more difficult. One of the BSCs is 2 metres wide, which tempts people to work in twos at the BSC, irrespective of the work they do, which is discouraged.

People with impaired immune systems are not allowed to work with human pathogens and can use the fluorescence microscope or PCR machines in this laboratory only when wearing a laboratory coat and gloves.

Cleaning and in-house maintenance personnel have only basic knowledge of laboratory procedures/cultures and basic biosafety training.

Personnel		
Name	**SOP/Safety training**	**Date completed**
Wasilisa Iwanow	Safety rules, biosafety, influenza A virus	13 January 2020
Joseph Dunn	Safety rules, biosafety	12 June 2020
Shivar Kumar	Waste handling	28 November 2019
Sabine Bernd	Safety rules, biosafety, influenza A virus	25 February 2020
Miguel Sanchez	Waste handling, influenza A virus	28 August 2020

1.7 Describe any other factors that may affect laboratory operations

Instructions: Consider the legal, cultural and socioeconomic effects related to the work, and potential public perception of the work. Consider the following in relation to the local context.

- **Is the laboratory, institute or agency highly regarded by the government or the public such that this could influence decision-making?**
- **Is the level of organizational and financial resources available enough to manage the biological risks, including:**
  - **reliable utilities (electrical/water supply),**
  - **properly maintained facility infrastructure,**
  - **commitment to personnel development to prevent under-staffed laboratories with under-trained personnel?**
- **Is there potential for severe weather that could adversely affect laboratory operations?**
- **Is there political, economic or criminal activity/instability that could adversely affect laboratory operations?**
- **Do any of the laboratory activities or biological agents have the potential to cause fear or panic in the community?**
  - **Is the biological agent unusual or unfamiliar to the local community?**
  - **Does infection have very severe or potentially fatal consequences?**
  - **Is there potential for widespread transmissibility or an outbreak of disease?**
  - **Are preventative or therapeutic interventions locally available?**

- The legal basis for handling infectious agents is the contained use ordinance (national legislation) and is applicable to every institution using infectious biological agents. The necessary permits were obtained before starting the laboratory activity.
- There is probably a pre-immunity against the influenza A virus H1N1 subtype in the human population, as an H1H1 strain is circulating and the annual vaccination against influenza includes an H1N1 subtype. Therefore, infection is not expected to have fatal consequences.
- Preparations have been made and drills conducted for emergency response activities such as medical emergencies, severe weather and criminal activity in the local community.

STEP 2. Evaluate the risks

2.1 Describe how exposure and/or release could occur

Instructions: Based on the information gathered, and the biological and procedural hazards associated with the laboratory work that have been identified, give details of how a potential exposure or release could occur.

- **Examples of how exposure to a biological agent could occur include:**
  - **direct contact with skin and/or mucous membranes from spills, splashes or contaminated work surfaces**
  - **percutaneous or parenteral exposure through inoculation or contaminated sharps**
  - **ingestion**
  - **inhalation of infectious aerosols**
  - **malfunction or misuse of PPE.**
- **Examples of how release of a biological agent could occur include:**
  - **improper packaging and transport, leaking containers**
  - **malfunction of safety equipment resulting in breaches of containment**
  - **spills**
  - **improper disinfection or waste handling and disposal.**

Infectious or toxic material

- Inhalation of aerosols
  - Aerosol-generating laboratory activities conducted outside the BSC (for example, pipetting, vortexing)
  - Spill on the floor or in the centrifuge while handling infectious material or contaminated waste

2.1 Describe how exposure and/or release could occur (continued)

Instructions: Based on the information gathered, and the biological and procedural hazards associated with the laboratory work that have been identified, give details of how a potential exposure or release could occur.

- **Examples of how exposure to a biological agent could occur include:**
  - **direct contact with skin and/or mucous membranes from spills, splashes or contaminated work surfaces**
  - **percutaneous or parenteral exposure through inoculation or contaminated sharps**
  - **ingestion**
  - **inhalation of infectious aerosols**
  - **malfunction or misuse of PPE.**
- **Examples of how release of a biological agent could occur include:**
  - **improper packaging and transport, leaking containers**
  - **malfunction of safety equipment resulting in breaches of containment**
  - **spills**
  - **improper disinfection or waste handling and disposal.**

- Direct contact with specimens and/or carry over of biological agents from contaminated work surfaces to mucous membranes (eyes, nose, mouth)
  - Contamination of hands/wrists/laboratory coat because of incorrect working techniques (in the BSC) and then:
    - touching mucous membranes with contaminated hands/wrists/laboratory coat
    - carrying over the contaminants to laboratory equipment where other laboratory personnel can contaminate their hands, PPE and then carry over to their mucous membranes
    - differing glove policies among laboratory personnel about which laboratory equipment must be touched with gloves and which not (some personnel keep gloves on after having worked with infectious material in the BSC and touch the incubator or microscope wearing the same gloves, whereas other personnel touch the incubator/microscope without gloves)
  - Incorrect removal of PPE resulting in contamination of clothing or the body
  - Working without PPE, working outside the BSC with infectious material (for example, discarding supernatants from infected cell cultures/spilling on oneself)
  - Uncontained infectious material outside the BSC. For example, after use in the BSC, serological pipettes are put back into their packaging bag and discarded in an autoclaving bag outside the BSC. However, there is often a last droplet of liquid at the tip of the pipette which could splash or contaminate the outside of the pipette packaging bag

Cryogenics

- Direct contact between cryogenic liquids or cold vapours and unprotected parts of the body resulting in burns to the skin or damage to the eyes
- Asphyxiation because of displacement of oxygen in closed rooms by gaseous CO_2 (from dry ice). Disregard of the gas alarm or unawareness of what it means. Malfunctioning of the gas alarm system

Compressed gas for incubators

- Gas bottles falling over and exploding
- Gas bottle leaking – the suffocation hazard is greater, the smaller the room

2.2 Determine the likelihood of exposure or release and what factors have the greatest influence on likelihood

Instructions: Based on the information gathered and the potential situations for exposure/release to occur, what factors influence the likelihood of an exposure to or release of a biological agent? Consider the questions below and identify any others that either increase or decrease the likelihood that an exposure/release will occur.

- **What laboratory activities are planned (for example, genetic modification, animal work, sonication, centrifugation or other procedures that may result in the production of aerosols)?**
- **What equipment is needed for the planned activities?**
- **What is the concentration and volume of the biological agent and potentially infectious material to be manipulated?**
- **What is the competency of the personnel carrying out the work?**
- **How often is the task performed and how long does it take to do?**
- **Has an exposure/release ever happened before? How often?**
- **How effective are current risk control measures in reducing risk?**
- **Are the hazards more likely to cause harm because of the working environment?**
- **Could the way people act and behave affect the likelihood of a biological agent causing harm?**
- **Do any of the above items make the harm more or less likely? If yes, list them and explain why.**
- **What is the likelihood of the exposure and/or release occurring?**
  - **Rare: almost impossible to occur**
  - **Unlikely: not very possible to occur**
  - **Possible: might occur**
  - **Likely: very possible to occur**
  - **Almost certain: highly probable to occur**

Highest viral titres and largest volumes to be handled occur when making the virus stocks, which are produced only every 2–3 months. The virus stock is then frozen in 1–2 mL aliquots. During experimental infection of cell cultures, smaller volumes of virus stocks are used. Current laboratory personnel are competent in manipulation of infectious viruses. However, because of the large number of people working in the laboratory, work is sometimes rushed or done less carefully and without following the same glove policy.

Primary cell cultures from human, avian, porcine and bat origin are always handled in a BSC because: 1) they have to stay sterile and 2) they could contain undetected biological agents, although this is very unlikely.

Chemical inhibitors are not volatile and are only handled inside a BSC because they have to stay sterile. Personnel wear gloves when working with these inhibitors.

When handling dry ice, personnel have to wear long-sleeved laboratory coats, goggles and cold protection gloves. However, they do not always wear these items of PPE because of laziness and underestimation of the hazard.

The dry ice stock is kept in a special container in a ventilated room which has a CO_2 sensor at the bottom of the room and a visual alarm. The flashing light can be seen from outside the room through a window in the door. The sensor is maintained on an annual basis.

Compressed CO_2 bottles are secured with chains and are only handled by trained technical personnel of the facility.

We have not had any known exposure so far.

2.2 Determine the likelihood of exposure or release and what factors have the greatest influence on likelihood (continued)

Instructions: Based on the information gathered and the potential situations for exposure/release to occur, what factors influence the likelihood of an exposure to or release of a biological agent? Consider the questions below and identify any others that either increase or decrease the likelihood that an exposure/release will occur.

- **What laboratory activities are planned (for example, genetic modification, animal work, sonication, centrifugation or other procedures that may result in the production of aerosols)?**
- **What equipment is needed for the planned activities?**
- **What is the concentration and volume of the biological agent and potentially infectious material to be manipulated?**
- **What is the competency of the personnel carrying out the work?**
- **How often is the task performed and how long does it take to do?**
- **Has an exposure/release ever happened before? How often?**
- **How effective are current risk control measures in reducing risk?**
- **Are the hazards more likely to cause harm because of the working environment?**
- **Could the way people act and behave affect the likelihood of a biological agent causing harm?**
- **Do any of the above items make the harm more or less likely? If yes, list them and explain why.**
- **What is the likelihood of the exposure and/or release occurring?**
  - **Rare: almost impossible to occur**
  - **Unlikely: not very possible to occur**
  - **Possible: might occur**
  - **Likely: very possible to occur**
  - **Almost certain: highly probable to occur**

Influenza A virus wild type	Rare
Influenza A virus mutant	Unlikely
Primary cell cultures from human, avian, porcine and bat origin	Rare
Influenza A virus for a person with an impaired immune system	Rare
Lentiviral particles	Rare
Chemical inhibitors	Rare
Burns from dry ice	Possible
Asphyxiation from cryogenics (CO_2)	Rare
Explosion of compressed CO_2	Rare

2.3 Determine the consequences of exposure or release and what has the greatest influence on consequence

Instructions: Based on the information gathered and consequences of an exposure and/or release, what factors influence the consequences? Consider the questions below and identify any others that either increase or decrease the severity and/or magnitude of these consequences if an exposure/release occurred.

- **What type of harm could occur? How severe is the harm? Could the hazard cause death, serious injuries or illness, or only minor injuries requiring first aid?**
- **What factors could influence the severity of harm that occurs? For example, the distance someone might fall or the concentration of a particular substance will determine the level of harm that is possible. The harm may occur immediately or it may take time to become apparent.**
- **How many people are exposed to the hazard and how many could be harmed inside and outside the workplace?**
- **Could one incident lead to other incidents?**
- **Could a small incident escalate to a much larger incident with more serious consequences?**
- **What is the consequence if an exposure and/or release occurred?**
  - **Negligible: Trivial incident or near miss requiring reporting and follow up**
  - **Minor: Incident with self-limiting consequences**
  - **Moderate: Incident that requires medical treatment and/or has insignificant environmental consequences**
  - **Major: Incident with potential lost time due to infection but non-permanent consequence and/or limited environmental impact**
  - **Severe: Potential fatality or serious illness with permanent disability and/or serious environmental impact**

Exposure to influenza A virus wild type strain could cause flu which is transmissible from person to person. Infected people are contagious before they show symptoms and can also infect people outside the laboratory. However, as other H1N1 strains are circulating in the general population, no epidemic would be expected. One of our personnel working in the laboratory has an impaired immune system because of drug treatment for an autoimmune inflammatory disease. For this person, the infectious dose could be smaller and the course of disease more serious or longer but this is not exactly known. Therefore, this person is not allowed to work with influenza A virus and only works in the laboratory dedicated to work on non-human viruses. He wears gloves when he has to use the microscope which is in the laboratory where influenza A virus work is done.

The influenza A virus *NS1* deletion mutant is attenuated and is not likely to cause disease after an exposure incident in a healthy person or in a person with an impaired immune system.

Lentiviral particles can infect human cells and will integrate their genetic material into the DNA of the host cell. However, as lentiviral particles cannot replicate, the infection will not spread in the body or to other people, and will be localized in the initially infected cell. (An exception to this would be a person infected with HIV where the lentiviral particles could recombine with the native HIV). The lentiviral particles inserted in this work are not oncogenic on their own; however, depending on the site of integration, an oncogenic effect cannot be completely discounted. After a splash incident, the cells that would most likely be exposed are skin or mucous membrane cells on the face. After injection with a syringe, blood cells or cells in the wound could also be involved. Because of their high turnover, skin cells are shed quickly. What happens to lentiviral particle-transduced cells of mucous membranes is not predictable; however, the development of a tumour can be monitored relatively easily because the mucous membranes are clearly visible. The effect of integration of lentiviral particles into blood cells cannot be predicted or monitored. Retroviral therapy, which has severe side-effects, or surgical excision of a tumour are the only therapies that exist. Therefore, the use of sharps when working with lentiviral particles is forbidden.

The primary cells from bat, avian, porcine or human origin are very unlikely to be contaminated with human pathogens because the health of the people and animals is monitored.

Chemical inhibitors will be used only in small quantities and will have no systemic effect on a person if exposed. Penetration of the membrane of skin cells by the inhibitors after exposure depends on the solvent used and whether they can inhibit several target molecules of the exposed cell. Penetration of mucous membrane cells is more likely. If penetration occurs, the inhibition will only be for a short time and will have no severe effects on the health of the person.

2.3 Determine the consequences of exposure or release and what has the greatest influence on consequence (continued)

Instructions: Based on the information gathered and consequences of an exposure and/or release, what factors influence the consequences? Consider the questions below and identify any others that either increase or decrease the severity and/or magnitude of these consequences if an exposure/release occurred.

- **What type of harm could occur? How severe is the harm? Could the hazard cause death, serious injuries or illness, or only minor injuries requiring first-aid?**
- **What factors could influence the severity of harm that occurs? For example, the distance someone might fall or the concentration of a particular substance will determine the level of harm that is possible. The harm may occur immediately or it may take time to become apparent.**
- **How many people are exposed to the hazard and how many could be harmed inside and outside the workplace?**
- **Could one incident lead to other incidents?**
- **Could a small incident escalate to a much larger incident with more serious consequences?**
- **What is the consequence if an exposure and/or release occurred?**
  - **Negligible: Trivial incident or near miss requiring reporting and follow up**
  - **Minor: Incident with self-limiting consequences**
  - **Moderate: Incident that requires medical treatment and/or has insignificant environmental consequences**
  - **Major: Incident with potential lost time due to infection but non-permanent consequence and/or limited environmental impact**
  - **Severe: Potential fatality or serious illness with permanent disability and/or serious environmental impact**

Consequences of exposure or release

Influenza A virus wild type	Moderate
Influenza A virus mutant	Negligible
Primary cell cultures from human, avian, porcine and bat origin	Negligible
Influenza A virus for a person with an impaired immune system	Major
Lentiviral particles	Minor
Chemical inhibitors	Negligible
Burns from dry ice	Moderate
Asphyxiation from cryogenics (CO_2)	Minor
Explosion of compressed CO_2 gas	Negligible

2.4 Describe the initial risk of the laboratory activities before additional risk control measures have been put in place

Instructions: Circle the initial risk of the laboratory activities before additional risk control measures have been put in place. Based upon your evaluation of the likelihood and consequences of an exposure/release as listed above, assess the initial, or currently existing, risk of the laboratory activity using the table below. Find the likelihood of exposure (top row of the chart) and the consequences (left column of the chart).

		Likelihood of exposure/release				
		Rare	Unlikely	Possible	Likely	Almost certain
Consequences of exposure/ release	Severe	Medium	Medium	High	Very high	Very high
	Major	Medium	Medium	High	High	Very high
	Moderate	Low	Low	(Medium)	High	High
	Minor	Very low	Low	Low	Medium	Medium
	Negligible	Very low	Very low	Low	Medium	Medium

Instructions: Check the initial risk to determine the appropriate risk control measures required.

Assessed initial risk		**Potential consequences**	**Actions**
☐	Very low	If an incident occurred, harm would be very unlikely.	Undertake the laboratory activity with the existing risk control measures in place.
☐	Low	If an incident occurred, there would be a small likelihood of harm.	Use risk control measures if needed.
☒	Medium	If an incident occurred, harm would result that would require basic medical treatment and/or simple environmental measures.	Additional risk control measures are advisable.
☐	High	If an incident occurred, harm would result that would require medical treatment and/or substantial environmental measures.	Additional risk control measures need to be implemented before the laboratory activity is undertaken.
☐	Very high	If an incident occurred, a permanent, impairing harm or death and/or extensive environmental effects would be likely.	Consider alternatives to doing the laboratory activity. Comprehensive risk measures will need to be implemented to ensure safety.

2.4 Describe the initial risk of the laboratory activities before additional risk control measures have been put in place (continued)

Instructions (optional): For additional specification on the risks of individual laboratory activities, determine which risks can/should be reduced and prioritized. For each laboratory activity or procedure of the work under assessment, record the initial risks determined from the risk assessment above. Decide whether the work can proceed without additional risk control measures, or whether the risks posed by the work are unacceptable and further risk control measures are needed to reduce the risks. Use the right column of the table below to assign a priority for the implementation of risk control measures based on the identified risks.

Note:

- **When assigning priority, other factors may need to be considered, for example, urgency, feasibility/sustainability of risk control measures, delivery and installation time and training availability.**
- **To estimate the overall risk, take into consideration the risk ratings for the individual laboratory activities/ procedures, separately or collectively as appropriate for the laboratory.**

Risk of the laboratory activity/ procedure	**Initial risk (very low, low, medium, high, very high)**	**Is the initial risk acceptable? (yes/no)**	**Priority (high/medium/low)**
Influenza A virus wild type	Low	Yes	Medium
Influenza A virus mutant	Very low	Yes	Low
Primary cell cultures from human, avian, porcine and bat origin	Very low	Yes	Low
Influenza A virus for a person with an impaired immune system	Medium	No	High
Lentiviral particles	Very low	Yes	Low
Chemical inhibitors	Very low	Yes	Low
Burns from dry ice	Medium	No	High
Asphyxiation from cryogenics (CO_2)	Very low	Yes	Low
Explosion of compressed CO_2	Very low	Yes	Low

Select the overall **initial** risk.	☐ Very low	☐ Low	☒ Medium	☐ High	☐ Very high
Should work proceed without additional risk control measures?	Yes ☐ No ☒				
Will work require additional risk control measures?	Yes ☒ No ☐				

STEP 3. Develop a risk control strategy

3.1 Describe the resources available for risk control measures

Instructions: Consider the applicability, availability and sustainability of resources for all risks that require additional risk control measures. Consider the following questions. • **Are alternative detection methods or risk control measures available?** • **Are resources sufficient to secure and maintain potential risk control measures?** • **Does the management support the budget necessary for purchasing, operating and maintaining these risk control measures?** • **Does the management support training for personnel on the proper installation, operation and maintenance of these risk control measures?** • **What factors exist that may limit or restrict any of the risk control measures? Are there financial, legal, organizational or other factors that could limit or restrict the risk control measures?** • **Will work be able to proceed without any of risk control measures?**
Substitution of any of the hazards is not possible but the management has supported necessary risk control measures through proper budgeting and allocation of resources. Regular training courses and posters showing pictures of good microbiological practice and procedure and PPE are carried out and are supported by the management.

STEP 4. Select and implement risk control measures

4.1 Describe the measures required by national legislation or regulations (if any)

Instructions: List any requirements that have been prescribed by international and national regulations, legislation, guidelines, policies and strategies on biosafety and biosecurity. In addition, consider if there are any local regulations, guidelines or policies that restrict or govern certain laboratory activities and/or the handling and use of any biological agents.
Chicken blood. Obtained from specific-pathogen-free white Leghorn chickens in compliance with the national legislation: Animal Welfare Act, Animal Welfare Ordinance and the Animal Experimentation Ordinance. The national and international regulation and guidelines were reviewed by the federal state ethical committee for animal experiments and approved by the federal veterinary authorities with the local agreement only for these experiments. Specific-pathogen-free pigs. Blood obtained from the Institute's specific-pathogen-free breeding unit. National regulation on protection of workers and contained use of organisms.

4.2 Describe where and when additional risk control measures are needed, including an assessment of their availability, effectiveness and sustainability

Instructions: For each laboratory activity or procedure of the work under assessment, record the unacceptable risks determined from the risk assessment above. Decide which risk control measures have been selected to reduce the unacceptable risks. Determine the new, residual risk after risk control measures have been implemented and whether it is acceptable (very low or low, for example) or unacceptable (medium, high or very high, for example) and further risk control measures are needed to reduce risk, or if the work should not proceed at all at this facility. Alternatively, and based on the local circumstances, consider adjusting the acceptable risk. Note that some procedures may require several risk control measures (that is redundancy in case of any failures) to reduce risk to an acceptable risk. Use the right column of the table below to assess the availability, effectiveness and sustainability of selected risk control measures and provide additional information to support this assessment as necessary. If any risks cannot be reduced to an acceptable risk using available, sustainable risk control measures, it is best not to undertake the laboratory activity or to coordinate with another laboratory with the capability to do the work.

Once the risks have been evaluated, risk control measures can be put into place to reduce them. Consider the following risk control measures.

- **Removing the hazard or substituting it for one that reduces risk (for example, substituting an attenuated or less virulent strain of a biological agent or working with inactivated materials)**
- **Enhancing personnel proficiency (for example, providing additional training and mentorship, competency assessments, exercises and drills)**
- **Applying safety policies and procedures (for example, minimizing propagation and concentration of biological agents, limiting the use of sharps, putting up hazard signs, implementing occupational health programmes)**
- **Using PPE (for example, gloves, protective clothing and respiratory protection), which should be evaluated for each risk to ensure it provides the intended protection to the user**
- **Using primary and secondary barriers such as safety equipment and certain facility design features respectively, such as centrifuge safety cups/sealed rotors, BSCs and autoclaves**
- **Routinely evaluating all risk control measures for effectiveness and failures; any failures should be documented and corrected**

Use the following table to list procedures, selected risk control measures and the residual risk, and indicate whether the risk control measure reduces risk to an acceptable risk and is effective and sustainable.

4.2 Describe where and when additional risk control measures are needed, including an assessment of their availability, effectiveness and sustainability (continued)

Risk of the laboratory activity/ procedure	Selected risk control measure(s)	Residual risk (very low, low, medium, high, very high)	Is the residual risk acceptable? (yes/no)	Are risk control measures available, effective and sustainable? (yes/no)
Work with infectious influenza A virus, lentiviral particles and primary cell cultures: avoiding exposure through aerosols or surface contamination and contact with mucous membranes	Engineering controls: Perform vortexing and manipulation only in the BSC. Use centrifuges with safety caps. Use a dedicated laboratory for work on influenza A virus and lentiviral particles. PPE: Use gloves also in BSC	Low	Yes	Yes

4.3 Evaluate the residual risk that remains after risk control measures have been selected

Instructions: Circle the residual risk of the laboratory activities after selection of risk control measures. Based on your evaluation of the effect of the additional risk control measures on the residual risk and their availability and sustainability, as listed above, assess the likelihood and consequences of an exposure/release from the laboratory activity using the chart below. Find the likelihood of exposure (top row of chart) and the consequences (left column of chart). Determine if the residual risk is acceptable and whether work should proceed, indicating who is responsible for the approval to conduct the work.

		Likelihood of exposure/release				
		Rare	Unlikely	Possible	Likely	Almost certain
Consequences of exposure/ release	Severe	Medium	Medium	High	Very high	Very high
	Major	Medium	Medium	High	High	Very high
	Moderate	Low	Low	Medium	High	High
	Minor	Very low	Low	Low	Medium	Medium
	Negligible	Very low	Very low	Low	Medium	Medium

4.3 Evaluate the residual risk that remains after risk control measures have been selected (continued)

Instructions: Check the residual risk to determine the appropriate actions required.

Assessed residual risk		Potential consequences	Actions
☐	Very low	If an incident occurred, harm would be very unlikely.	If the identified residual risk is acceptable, no further action is required for laboratory work to proceed.
☒	Low	If an incident occurred, there would be a small likelihood of harm.	
☐	Medium	If an incident occurred, harm would result that would require basic medical treatment and/or simple environmental measures.	If the identified residual risk is not acceptable, further action is required for laboratory work to proceed. Revisit subsection 2.4 and re-evaluate your risk control strategy based upon the initial risk of laboratory activities. Actions may include (but are not limited to): • Implementing additional risk control measures in accordance with the initial identified risk of laboratory activities to reduce residual risk to an acceptable risk, that is - If initial risk was assessed as medium/high, then further risk control measures need to be implemented before the laboratory activity is undertaken. - If initial risk was assessed as very high, then comprehensive risk measures will need to be implemented to ensure safety. • Redefining the scope of work such that the risk is acceptable with existing risk control measures in place • Identifying an alternative laboratory with appropriate risk control strategies already in place that is capable of conducting the work as planned
☐	High	If an incident occurred, harm would result that would require medical treatment and/or substantial environmental measures.	
☐	Very high	If an incident occurred, a permanent, impairing harm or death and/or extensive environmental effects would be likely.	

Select the **residual** overall risk.	☐ Very low	☒ Low	☐ Medium	☐ High	☐ Very high
Will work require additional risk control measures?	Yes ☐ No ☒				

4.3 Evaluate the residual risk that remains after risk control measures have been selected (continued)

Reviewed by (Name and title)	Dr Giulia Tresch, Director, Influenza Laboratory
Reviewed by (Signature)	Giulia Tresch
Date	11 April 2020

4.4 Communication of the hazards, risks and risk control measures

Instructions: Develop a plan to communicate risks and risk control strategies to laboratory and other relevant personnel. These plans should include the mechanism(s) of communication within the laboratory, such as in-person team meetings and/or training classes, published SOPs, and identification of an accessible place to store all risk assessments and documentation on the risk control strategy.
New SOPs on working procedures are developed by the biosafety team and laboratory members together. Protocols are stored in an electronic database. New laboratory personnel are required to attend several hands-on biosafety training courses covering relevant biosafety issues (good microbiological practice and procedure, BSC, spill clean-up, hygiene, putting on and removing PPE, transport within the facility and between facilities). Refresher courses are regularly offered to current personnel. New personnel and less experienced people (undergraduate and postgraduate students) are always supervised and trained on experimental procedures by experienced laboratory personnel.

4.5 Purchase of required risk control measures

Instructions: Describe a process and timeline for ensuring that all needed equipment/supplies for the risk control measures are purchased on time. Consider the budgeting, financial sustainability, ordering, receipt and installation of all risk control measures to be purchased before starting the laboratory work.
All the equipment needed is already in place with maintenance and service contracts.

4.6 Operational and maintenance procedures

Instructions: Describe a process and timeline for ensuring that all risk control measures have associated SOPs and that training on these risk control measures has been completed. The plan should include development of SOPs, training of personnel who will perform the work, and maintenance and/or calibration, certification, validation of equipment before starting the laboratory work.
Maintenance and calibration is done by the manufacturer annually (BSC, incubators and other devices).

4.7 Training of personnel

Instructions: Describe a process and timeline for ensuring that training has been completed for all risk control measures. Take into consideration that all personnel (laboratory and support/maintenance personnel) should have completed all training necessary to use all risk control measures before starting the laboratory work.
To keep track of the training level of the personnel, all personnel have to sign an attendance form after completing a course.

STEP 5. Review risks and risk control measures

5.1 Establish a periodic review cycle to evaluate the effectiveness of risk control measures and to identify any changes

Instructions: Describe the periodic review process. Reviews of risk assessments, risk control measures and risk control strategies should be done periodically to ensure that the laboratory procedures are safe and that the risk control measures that have been implemented to reduce risk are still effective. Components of periodic reviews may include laboratory inspections/audits and/or asking for feedback from personnel during training and team meetings. Reviews of risks and risk control measures must also include:

- **updates on laboratory activities or procedures**
- **new biological agents, or new information on existing biological agents**
- **changes in personnel**
- **changes in equipment and/or facilities**
- **results of audits/inspections**
- **lessons learnt from laboratory incidents or near misses**
- **personnel feedback on procedures, risk control measures and residual risks**
- **person responsible for doing the review and the frequency of reviews**
- **method of documenting the updates and changes**
- **procedures for implementing the changes.**

While annual reviews may be most common, the frequency of the review should be proportionate to the risks, and reviews should be conducted and risks reassessed whenever there are major changes in any elements of the work.

If there are incidents or significant changes in personnel and/or equipment, the SOPs will be reviewed by the biosafety team together with laboratory personnel. If an incident occurs or when improved technology or "best practice" information is available, changes will be implemented by the biosafety team and supported by the management.

Reviewed by (Name and title)	Dr Tian Zhang, Director, Global Communicable Diseases Research Institute
Reviewed by (Signature)	Tian Zhang
Date	14 June 2020

ANNEX 6. COMPLETED LONG TEMPLATE: ANTIMICROBIAL SUSCEPTIBILITY TESTING

Institution/Facility name	United Microbiology Laboratories
Laboratory name	Gastrointestinal Diseases/Bacterial Unit
Laboratory manager/Supervisor	Dr Jill Smith, Laboratory Manager
Location	City on the seaside
Project titles/Relevant standard operating procedures (SOPs)	Antimicrobial susceptibility testing
Date	6 May 2020

If using this template, complete all sections following the instructions in the grey boxes. The instructions and bullet points in the grey boxes can be copied into the text boxes beneath the instructions and used as prompts to gather and record the necessary site-specific information. The grey instruction boxes can then be deleted, and the text remaining will form a risk assessment draft. This draft must be carefully reviewed, edited as necessary and approved by the risk assessment team members.

STEP 1. Gather information (hazard identification)

1.1 Provide a brief overview of the laboratory work

Instructions: Summarize the laboratory activities to be conducted that are included in the scope of this risk assessment. If the laboratory conducts other similar work on a regular basis (for example, well-defined, routine diagnostic testing), consider using one assessment to cover all laboratory activities. However, large and more complex laboratories that carry out a variety of laboratory activities, such as diagnostic testing, confirmatory testing, characterization of biological agents and research, may want to conduct separate risk assessments.

The bacterial unit will begin testing bacterial isolates sent from local laboratories and hospitals in the state for antimicrobial susceptibility. Isolates will be identified to the genus and, if possible, species before submission to the bacterial unit. All isolates will be received on either Luria broth, or MacConkey or trypticase soy agar. Antimicrobial susceptibility testing will be by broth microdilution using minimum inhibitory concentrations established by the Clinical Laboratory and Standards Institute. Cultures received will be limited to Proteobacteria including pathogenic biological agents from Enterobacteriaceae (*Escherichia coli*, *Shigella* spp. *Salmonella* spp.) – except for *Klebsiella* (work on this bacterium is done in a separate laboratory) – *Campylobacter* spp. and *Vibrio* spp. Our laboratory has experience working with all these bacteria but has not done antimicrobial susceptibility testing using broth microdilution on this scale before. This testing is usually done on request and most often done using test strips on agar. We expect to receive between 30 and 100 isolates a month and think that this number may grow over time.

1.2 Describe the biological agents and other potential hazards

Instructions: Identify the hazards. It is important to know the characteristics of the biological agent(s) when determining the risks it presents. When the specific biological agent is known, the following information will be useful for the risk assessment and should be thoroughly researched. When handling unknown or diagnostic specimens, it is important to try and obtain any information on the source of the specimens and/or a presumptive/suspected diagnosis. Typical information to be gathered about the biological agent(s) includes:

- **pathogenicity/severity of disease**
- **epidemiology and host range**
- **sources/specimens**
- **infectious dose, concentration and volume**
- **route(s) of transmission**
- **incubation period and communicability**
- **viability and susceptibility to disinfectants**
- **means of diagnosing the disease, type of testing done for diagnosis**
- **treatment, immunization and prophylaxis available**
- **unique laboratory hazards (laboratory-associated infections)**
- **additional information.**

The hazards associated with the enteric pathogenic biological agents listed above are mostly associated with ingestion. This could occur from contact with contaminated surfaces in the laboratory or from splashes. Some of these bacteria can be acquired through inhalation of aerosol particles/droplets (in broth/liquid).

Infectious dose (ID), transmission routes (TR) other than ingestion, consequences of exposure (CE), prevention and treatment (P/T), severity of disease (SD) and association of the bacteria to be tested with laboratory-acquired infections (LAIs) of each biological agent are as follows.

***S.* Typhi**

- ID: 100–100 000 bacteria cells
- TR: inhalation of aerosols, contact with mucous membranes, needlestick, person-to-person
- CE: infection may not be apparent for weeks (usually 7–14 days, depending on dose); symptoms include sustained fever, weakness, stomach pain, headache, dry cough, diarrhoea or constipation, loss of appetite; up to 5% of people infected can become asymptomatic carriers
- P/T: regular vaccination is preventative; treatment is antibiotics, such as ciprofloxacin, azithromycin
- SD: can be very severe and require hospitalization (typhoid fever). Untreated death rate can reach 20%; illness duration is 4–40 days
- LAIs: more than 250 exposures reported with 20 deaths (as high as 8% mortality)

V. cholerae

- ID: 106–1011 bacteria cells
- TR: mucous membranes, aerosols, needlestick, wounds/cuts, intact skin
- CE: onset of illness is 4 hours to 4 days; symptoms include watery diarrhoea (rice-water stool), cramps, nausea, chills, fever
- P/T: vaccine available but not recommended; fluid replacement, antibiotics in severe cases
- SD: usually resolves in several days in healthy people
- LAIs: 13 cases reported with 4 deaths

1.2 Describe the biological agents and other potential hazards (continued)

Instructions: Identify the hazards. It is important to know the characteristics of the biological agent(s) when determining the risks it presents. When the specific biological agent is known, the following information will be useful for the risk assessment and should be thoroughly researched. When handling unknown or diagnostic specimens, it is important to try and obtain any information on the source of the specimens and/or a presumptive/suspected diagnosis. Typical information to be gathered about the biological agent(s) includes:

- **pathogenicity/severity of disease**
- **epidemiology and host range**
- **sources/specimens**
- **infectious dose, concentration and volume**
- **route(s) of transmission**
- **incubation period and communicability**
- **viability and susceptibility to disinfectants**
- **means of diagnosing the disease, type of testing done for diagnosis**
- **treatment, immunization and prophylaxis available**
- **unique laboratory hazards (laboratory-associated infections)**
- **additional information.**

***Vibrio* spp.**

- ID: 10^5–10^8 colony forming units
- TR: mucous membranes, wounds/cuts, needlestick
- CE: onset of illness is 2 hours to 7 days (depending on species and dose); symptoms are diarrhoea, cramps, nausea, redness around skin wound/cut; high-risk individuals may experience skin lesions, chills and shock
- P/T: no vaccine available; fluid replacement, supportive care, antibiotics if severe
- SD: usually resolves within one week
- LAIs: few cases reported

***Campylobacter* spp.**

- ID: 500–1000 bacteria cells
- TR: needlestick, rarely person-to-person
- CE: onset of illness is 2–10 days; symptoms are watery diarrhoea, nausea, vomiting, possibly fever
- P/T: no vaccine available; treatment is supportive – the illness is self-limiting in healthy people, antibiotics for severe infections
- SD: illness lasts one week
- LAIs: few cases reported

***Salmonella* spp.**

- ID: varies by species
- TR: mucous membranes, needlestick (*S.* Typhimurium causes the most severe disease of non-Typhi *Salmonella*)
- CE: onset of illness is 12–72 hours; symptoms are diarrhoea, cramps, vomiting, fever
- P/T: no vaccine available; supportive treatment, antibiotics for severe cases
- SD: illness lasts 4–7 days
- LAIs: 48 reported

1.2 Describe the biological agents and other potential hazards (continued)

Instructions: Identify the hazards. It is important to know the characteristics of the biological agent(s) when determining the risks it presents. When the specific biological agent is known, the following information will be useful for the risk assessment and should be thoroughly researched. When handling unknown or diagnostic specimens, it is important to try and obtain any information on the source of the specimens and/or a presumptive/suspected diagnosis. Typical information to be gathered about the biological agent(s) includes:

- **pathogenicity/severity of disease**
- **epidemiology and host range**
- **sources/specimens**
- **infectious dose, concentration and volume**
- **route(s) of transmission**
- **incubation period and communicability**
- **viability and susceptibility to disinfectants**
- **means of diagnosing the disease, type of testing done for diagnosis**
- **treatment, immunization and prophylaxis available**
- **unique laboratory hazards (laboratory-associated infections)**
- **additional information.**

***Shigella* spp.**

- ID: as low as 10–100 bacteria cells
- TR: mucous membranes, aerosols, skin/clothing; long-lived on surfaces (up to one week) and highly transmissible (flies, sexual contact, saliva, fomites)
- CE: onset of illness is 12 hours to 7 days; symptoms are watery or bloody diarrhoea, fever, cramps, nausea; *Sh. dysenteriae* may produce Shiga toxin which can lead to haemolytic uraemic syndrome, subgroup B may lead to reactive arthritis (Reiter syndrome) in people who are genetically predisposed
- P/T: no vaccine available; supportive care, antibiotics essential for *Sh. dysenteriae* infections to prevent complications of haemolytic uraemic syndrome
- SD: usually resolves within one week with supportive care. In cases of Reiter syndrome, mild to severe arthritis, urogenital inflammation and eye inflammation may occur (can be severe), and administration of antibiotics is necessary – symptoms can last one month with arthritis lasting as long as one year. In the case of haemolytic uraemic syndrome caused by *Sh. dysenteriae*, antibiotics should be administered as soon as diagnosed because this is associated with better outcomes. Shiga toxin targets blood vessels, kidneys and other organs and can lead to neurological disorders. Haemolytic uraemic syndrome is most common in children and has a fatality rate of 10%.
- LAIs: *Shigella* spp. is the most frequent biological agent associated with LAIs.

***E. coli* (non-commensal)**

- ID: as low as 10–100 bacteria cells
- TR: mucous membranes, aerosols, needlestick, animal bites
- CE: onset of illness is 2–8 days; duration is one week in non-severe cases; symptoms include diarrhoea (mild to severe and bloody), stomach pain and cramps, and sometimes nausea and vomiting. Several non-commensal strains (for example, O157:H7, O145) are Shiga toxin-producing *E. coli* and infection with theses strains may result in haemolytic uraemic syndrome.
- P/T: no human vaccine available; treatment is supportive for mild cases, antibiotics are needed for severe cases and for haemolytic uraemic syndrome.
- SD: mild to haemolytic uraemic syndrome (see *Shigella* spp.)
- LAIs: few reported/no data

1.3 Describe the laboratory procedures to be used

Instructions: Identify the laboratory activities that might cause exposure to the biological agent when it is being transported, handled or manipulated. Consider the following:

- **centrifuging**
- **cleaning up spills**
- **contact with fomites or contaminated surfaces**
- **inoculating media, including how frequently and in what concentration the biological agent is isolated/ propagated**
- **manipulating inoculation loops, pipettes, needles and other sharps, syringes**
- **mixing, blending, grinding, shaking, sonicating and vortexing**
- **pouring, splitting or decanting liquids**
- **preparing smears, heat fixing or staining slides**
- **spilling/dropping/splashing infectious material**
- **transporting specimens/materials inside and outside the laboratory, leaky specimen containers**
- **frequency of performing the laboratory activity**
- **using animals and insects**
  - **scratches, bites, stings**
  - **dissection, organ collection and disposal procedures**
  - **inoculation, injection or blood drawing**
- **handling biological waste**
  - **specimen/culture/pathogen transport procedures**
  - **inactivation procedures (for example, chemical, heat)**
  - **disposal procedures (for example, autoclaving, incinerating).**

1. Bacterial cultures will be checked on receipt by visualization and confirmation of primary container integrity. Compromised cultures (for example, broken primary container, mixed, dried out) will be rejected. Accepted cultures will be labelled and sorted by genus.
2. Cultures will be subcultured once onto Luria broth agar using sterile techniques and grown for 24 hours at 37 °C or 24–48 hours at 24 °C.
3. Bacterial cultures will be examined for growth and either subcultured again, or prepared for antimicrobial susceptibility testing.
4. Isolates to be tested will be programmed into the automated antimicrobial testing system along with pre-programmed quality controls (bacterial isolates from ATCC – American Type Culture Collection).
5. For each culture tested, a 96-well plate pre-loaded with antibacterial drug dilutions will be used for incubation and later reading of antimicrobial susceptibility testing using an automated spectrophotometric system.
6. Colonies will be isolated and transferred to pre-labelled tubes of sterile water to rinse for no longer than 10 minutes, vortexed briefly and the concentration measured using a nephelometer against a McFarland standard to obtain the density required to inoculate tubes with Luria broth.
7. Appropriate dilution (1:10) of bacteria will be added to Luria broth tubes and vortexed briefly.
8. The tubes will then be loaded into an automated dispenser for distribution and dispensing into the 96-well antimicrobial plates.
9. Plates will be covered with a plastic seal and placed in the incubator and the automated system started. Plates will incubate overnight and then be read.
10. All bacterial growth density readings will be confirmed using a digital reader of minimum inhibitory concentration.
11. Data on minimum inhibitory concentrations will be uploaded securely from the computer system and stored in a secure database.
12. Waste culture plates and titre plates will be deactivated by daily autoclaving.
13. Isolates of interest (resistant to one or more of the drugs) will be stored at –70 °C in cryogenic tubes containing Luria broth and 40% glycerol. The location of the frozen isolates will be recorded in a database and tracked.

1.4 Describe the types of equipment to be used

Instructions: Determine what instruments and equipment will be used to do the laboratory work. Please note that each type of equipment has its own inherent risks. For example, if centrifugation will be used, the potential for aerosols to be produced is a risk to consider. List any safety equipment that is available and likely to be used. Examples of equipment that may be used include:

- **personal protective equipment (PPE)**
  - **gloves**
  - **protective clothing**
  - **protective eyewear**
  - **respiratory protection (has it been fit tested?)**
- **autoclave (has it been validated?)**
- **biological safety cabinet (BSC) (has it been certified?)**
- **handwashing sink**
- **centrifuge (does it have sealed rotors or safety cups?)**
- **incubator**
- **refrigerator/freezer**
- **additional equipment, list:**

1. Bacteria will be subcultured in a BSC using large-ring disposable loops.
2. Incubation will take place in a 37 °C incubator or in sealed plastic sweater boxes on the bench top at 24 °C.
3. Bacteria will be inoculated into sterile water tubes using a small-ring disposable loop.
4. A pipette will be used to transfer/titrate rinsed bacterial isolates into Luria broth tubes.
5. A vortex mixer will be used to mix the broth dilution
6. A nephelometer will be used to read the concentration of the bacteria in the broth tubes.
7. The broth cultures will be dispensed from broth tubes into 96-well antimicrobial plates using an automated system.
8. Plastic plate covers will be applied manually.
9. Plates will be transferred to the bench that has the incubating automated spectrophotometer and placed inside overnight.
10. Isolates to be kept for storage will be transferred to cryotubes in a BSC.
11. Used culture plates will be transferred to cryogenic tubes for autoclaving.

PPE and other risk control measures already available in the laboratory include:

- disposable gloves
- bench shields
- long-sleeved disposable laboratory gowns
- goggles
- 2 BSCs (certified annually)
- autoclave (regularly maintained and tested/certified annually)
- two hand washing sinks and eyewash stations in the laboratory – one sink for "dirty" washing (for hand washing after working directly with the biological agents) and the other for "clean" washing (for hand washing after work not involving biological agents).

Note: need an incubator or Anoxomat® for *Campylobacter* spp. culture

1.5 Describe the type and condition of the facility where work is conducted

Instructions: Consider the layout and type of facility where work will be done to determine if laboratory activities can be conducted safely and securely. The workflow of the laboratory activities from one area of the laboratory to another should also be considered, including specimen receipt, transport, processing and disposal. Consider the following factors.

- **Will the work be carried out in a large, multipurpose space?**
- **Are separate rooms or spaces available for high-risk laboratory activities?**
- **Does the workflow and specimen transport create any special concerns for surface contamination or other laboratory accidents?**
- **Are laboratory floors, bench tops and furniture non-porous and impervious to the biological agent?**
- **Is laboratory furniture in good repair and ergonomically appropriate for the workstation?**
- **Do laboratory areas have closable doors?**
- **Are windows sealed or fitted with screens?**

The Gastrointestinal Disease facility will use a laboratory that has four benches with workspace on either side, giving a total of eight workspaces. One of these workspaces will be needed for the automated equipment such as an automated nucleic acid isolation device, computer and digital visualizer of minimum inhibitory concentrations. Another workspace will be needed for the broth manipulations, nephelometer and the automated plate dispenser. This leaves one workspaces for receipt/recording of cultures and up to five workspaces for other activities.

Chairs are in good condition and of the appropriate height for proper posture while working at the bench.

The laboratory has two BSCs for manipulation of cultures.

The laboratory has a closable door that opens onto a hallway where there is storage for supplies, large equipment and freezers. There are no windows in the laboratory but it has a glass viewing panel that allows the inside of the laboratory to be seen from the office corridor.

The laboratory has a negative-pressure ventilations system that is continually maintained and monitored and personnel are warned when the ventilation system is not working properly.

Workflow issues have not been identified yet.

Note: Freezers (–70 °C) are in the laboratory equipment room outside the laboratory, so special risk control measures will be taken for transport of cultures to this area, which is semi-clean.

1.6 Describe relevant human factors (for example, competency and suitability of personnel)

Instructions: Consider the competency and experience of laboratory personnel. Assess the training the personnel have had on the biological agent(s), and their experience of handling it and using relevant biosafety practices and safety equipment when performing laboratory work. Consider the following factors.

- **Do personnel have experience working with these biological agents or similar biological agents?**
- **Do personnel have experience performing these procedures and using this equipment?**
- **Are personnel trained to work with diagnostic specimens and unknown agents and do they have experience in this work?**
- **Have all personnel had relevant biosafety training or been briefed on laboratory biosafety, including cleaning and maintenance personnel and visitors, so that all personnel and people entering the laboratory are adequately informed about the hazards in the laboratory?**
- **Do personnel have positive attitudes to biosafety and adherence to safety procedures?**
- **Have there been prior incidents or laboratory-associated infections with this laboratory or these personnel?**
- **Are any personnel at increased risk because of greater susceptibility to laboratory hazards?**
- **Is there undue time pressure on personnel that may result in stress and fatigue?**

Use the following table to list the personnel and their training on the relevant SOP and safety.

Current personnel have experience manipulating these bacterial cultures, with the exception of *Campylobacter* spp. but they have little or no experience in this broth microdilution technique used for antimicrobial susceptibility testing. We expect to hire two new personnel with adequate experience but our personnel budget is limited so it is likely that they will be junior scientists.

The safety culture in the laboratory is good but the most senior scientist in the laboratory has developed incorrect habits that are hard to break. We may need to improve the safety culture in view of the new procedures that involve work with bacterial broth culture.

No one has reported becoming ill and there have been no chemical spills or major biological incidents/spills.

One of the current personnel is planning to start a family so she should also be trained to perform other duties that do not involve culturing these biological agents given her circumstances.

Maintenance personnel enter the laboratory when repair work is done but we are given advance notice so the laboratory is decontaminated before they enter. The maintenance department has begun a training programme for maintenance personnel on recognizing hazards and asking appropriate questions about work in the laboratory. The same is true for equipment technicians – the laboratory is decontaminated and no cultures are in the open. All external personnel are escorted by laboratory personnel while they are in the laboratory. External personnel also know that we work with *S.* Typhi and only vaccinated personnel are allowed to enter the laboratory.

Personnel		
Name	**SOP/Safety training**	**Date completed**
Marleen Fournier	BSC training	28.01.2020
Paulin Nilsson	Waste handling	03.06.2020
Simon Abramowitz	Waste handling, BSC training	26.07.2020
Carolin Aerbischer	BSC training	18.02.2020

1.7 Describe any other factors that may affect laboratory operations

Instructions: Consider the legal, cultural and socioeconomic effects related to the work, and potential public perception of the work. Consider the following in relation to the local context.

- **Is the laboratory, institute or agency highly regarded by the government or the public such that this could influence decision-making?**
- **Is the level of organizational and financial resources available enough to manage the biological risks, including:**
  - **reliable utilities (electrical/water supply),**
  - **properly maintained facility infrastructure,**
  - **commitment to personnel development to prevent under-staffed laboratories with under-trained personnel?**
- **Is there potential for severe weather that could adversely affect laboratory operations?**
- **Is there political, economic or criminal activity/instability that could adversely affect laboratory operations?**
- **Do any of the laboratory activities or biological agents have the potential to cause fear or panic in the community?**
  - **Is the biological agent unusual or unfamiliar to the local community?**
  - **Does infection have very severe or potentially fatal consequences?**
  - **Is there potential for widespread transmissibility or an outbreak of disease?**
  - **Are preventative or therapeutic interventions locally available?**

United Laboratories has a reputation to uphold but it is not under extreme scrutiny by an oversight authority except perhaps at the state level. We do not often make press announcements.

The laboratories of the gastroenterology bacterial unit are subject to federal occupational health and safety administration regulations. We have internal safety policies and practices as well but do not work with Tier 1 agents, so do not come under the Federal Select Agent Program. There are no special regulations for working with the pathogens listed earlier.

S. Typhi and *Shigella* spp. pose the most danger; we are familiar with manipulating these pathogens, although not in broth. All personnel working in the laboratory, or who will work in the laboratory, are immunized against *S.* Typhi. *S.* Typhi and *Shigella* spp. are also the most communicable agents, so any new personnel will be trained to handle these appropriately in the BSC.

Most infections with the bacteria listed earlier are self-limiting and do not require antibiotics, except in severe cases. Exceptions are *S.* Typhi, for which a person can become a carrier, and bacteria with Shiga toxin (*Shigella* spp. and *E. coli* subtypes). Haemolytic uraemic syndrome caused by these biological agents is rare in adults.

STEP 2. Evaluate the risks

2.1 Describe how exposure and/or release could occur

Instructions: Based on the information gathered, and the biological and procedural hazards associated with the laboratory work that have been identified, give details of how a potential exposure or release could occur.

- **Examples of how exposure to a biological agent could occur include:**
  - **direct contact with skin and/or mucous membranes from spills, splashes or contaminated work surfaces**
  - **percutaneous or parenteral exposure through inoculation or contaminated sharps**
  - **ingestion**
  - **inhalation of infectious aerosols**
  - **malfunction or misuse of PPE.**
- **Examples of how release of a biological agent could occur include:**
  - **improper packaging and transport, leaking containers**
  - **malfunction of safety equipment resulting in breaches of containment**
  - **spills**
  - **improper disinfection or waste handling and disposal.**

- Exposure to these bacterial pathogenic biological agents could occur during manipulation and environmental contamination if not done in a BSC.
- Aerosols could be produced if the broth tubes are damaged or compromised, so inoculation is also best done in a BSC.
- Exposure to or release of the pathogen could occur if culture plates or glass broth tubes are dropped on the floor.

2.2 Determine the likelihood of exposure or release and what factors have the greatest influence on likelihood

Instructions: Based on the information gathered and the potential situations for exposure/release to occur, what factors influence the likelihood of an exposure to or release of a biological agent? Consider the questions below and identify any others that either increase or decrease the likelihood that an exposure/release will occur.

- **What laboratory activities are planned (for example, genetic modification, animal work, sonication, centrifugation or other procedures that may result in the production of aerosols)?**
- **What equipment is needed for the planned activities?**
- **What is the concentration and volume of the biological agent and potentially infectious material to be manipulated?**
- **What is the competency of the personnel carrying out the work?**
- **How often is the task performed and how long does it take to do?**
- **Has an exposure/release ever happened before? How often?**
- **How effective are current risk control measures in reducing risk?**
- **Are the hazards more likely to cause harm because of the working environment?**
- **Could the way people act and behave affect the likelihood of a biological agent causing harm?**
- **Do any of the above items make the harm more or less likely? If yes, list them and explain why.**
- **What is the likelihood of the exposure and/or release occurring?**
  - **Rare: almost impossible to occur**
  - **Unlikely: not very possible to occur**
  - **Possible: might occur**
  - **Likely: very possible to occur**
  - **Almost certain: highly probable to occur**

The cultures will not be grown to large volumes and will be at their highest concentration on the agar plates. Current laboratory personnel are competent in manipulation of all cultures except *Campylobacter* spp. but the two new personnel we expect to recruit may not be experienced in handling these biological agents. Further, no laboratory personnel that I am aware of are competent in this broth dilution procedure for antimicrobial susceptibility testing.

This work will be done at least weekly by more than one person based on the number of isolates that we receive. The procedure (start to finish) takes up to 4 days from receipt to freezing the desired isolates. As personnel become familiar with the procedure, they will become experienced in doing it and less likely to make mistakes, even though the chance of exposure is more frequent.

As well as their other duties, personnel will be assigned groups of pathogens that will be tested on different antimicrobial panels. The panels for *Shigella* spp., *E. coli* and *Salmonella* spp. are the same, and those bacteria will likely be the responsibility one person, who will be the main tester for antimicrobial susceptibility. These three bacteria are likely to make up most of the cultures received. *Campylobacter* is anaerobic and must be cultured using slightly different methods. It has its own panels for antimicrobial susceptibility testing and one person is assigned to do the testing. *Vibrio* spp. require a slightly different panel and are relatively rare in our area. *S.* Typhi requires slightly higher containment because of the long illness it can cause, its higher mortality rate and transmissibility factors. I plan to assign one person to work with *Vibrio* spp. and *S.* Typhi, preferably someone who has experience with both. This makes a total of three people who will be doing the antimicrobial susceptibility testing. I may assign a junior team member to handle receipt and recording of cultures, since there is less chance for exposure during that process because the primary containers are enclosed within a secondary container (clear sealable bag). The new procedure will therefore require four personnel, who will work in a dedicated laboratory for antimicrobial susceptibility testing.

We have not had any exposures that I am aware of, although exposures sometimes go unrecognized because symptoms are similar to other gastrointestinal biological agents (for example, norovirus) and infections.

Current risk control measures for bacterial manipulation are effective but I have only two BSCs and I may have to install another cabinet (or two) in order to accommodate the procedure and work load. Personnel do not currently use goggles because they rarely use the vortex mixer, so they will need goggles or the vortex mixer may have to be kept and operated in the BSC.

2.2 Determine the likelihood of exposure or release and what factors have the greatest influence on likelihood (continued)

Instructions: Based on the information gathered and the potential situations for exposure/release to occur, what factors influence the likelihood of an exposure to or release of a biological agent? Consider the questions below and identify any others that either increase or decrease the likelihood that an exposure/release will occur.

- **What laboratory activities are planned (for example, genetic modification, animal work, sonication, centrifugation or other procedures that may result in the production of aerosols)?**
- **What equipment is needed for the planned activities?**
- **What is the concentration and volume of the biological agent and potentially infectious material to be manipulated?**
- **What is the competency of the personnel carrying out the work?**
- **How often is the task performed and how long does it take to do?**
- **Has an exposure/release ever happened before? How often?**
- **How effective are current risk control measures in reducing risk?**
- **Are the hazards more likely to cause harm because of the working environment?**
- **Could the way people act and behave affect the likelihood of a biological agent causing harm?**
- **Do any of the above items make the harm more or less likely? If yes, list them and explain why.**
- **What is the likelihood of the exposure and/or release occurring?**
  - **Rare: almost impossible to occur**
  - **Unlikely: not very possible to occur**
  - **Possible: might occur**
  - **Likely: very possible to occur**
  - **Almost certain: highly probable to occur**

The facility design and condition do not pose any hazards to this work. Since some cultures will be stored frozen, I have to plan the safest strategy to transfer cultures from the laboratory to the linear equipment room. Adding a freezer in the laboratory may reduce some of the risk associated with the transfer of these cultures (they will be frozen and senescent and therefore less active during transport).

Taking the above into consideration as well as the characteristics listed for each biological agent, the likelihoods of exposure/release are as follows.

S. Typhi	Rare (this work is already performed in a BSC)
V. cholerae	Unlikely
Vibrio spp.	Unlikely
Campylobacter spp.	Unlikely
Salmonella spp.	Possible
Shigella spp.	Unlikely
E. coli	Unlikely

2.3 Determine the consequences of exposure or release and what has the greatest influence on consequence

Instructions: Based on the information gathered and consequences of an exposure and/or release, what factors influence the consequences? Consider the questions below and identify any others that either increase or decrease the severity and/or magnitude of these consequences if an exposure/release occurred.

- **What type of harm could occur? How severe is the harm? Could the hazard cause death, serious injuries or illness, or only minor injuries requiring first aid?**
- **What factors could influence the severity of harm that occurs? For example, the distance someone might fall or the concentration of a particular substance will determine the level of harm that is possible. The harm may occur immediately or it may take time to become apparent.**
- **How many people are exposed to the hazard and how many could be harmed inside and outside the workplace?**
- **Could one incident lead to other incidents?**
- **Could a small incident escalate to a much larger incident with more serious consequences?**
- **What is the consequence if an exposure and/or release occurred?**
  - **Negligible: Trivial incident or near miss requiring reporting and follow up**
  - **Minor: Incident with self-limiting consequences**
  - **Moderate: Incident that requires medical treatment and/or has insignificant environmental consequences**
  - **Major: Incident with potential lost time due to infection but non-permanent consequence and/or limited environmental impact**
  - **Severe: Potential fatality or serious illness with permanent disability and/or serious environmental impact**

Exposure to *S.* Typhi can cause serious illness and death and this pathogen is transmissible from person to person. Infected people can have no symptoms and can be carriers of the disease, inadvertently spreading it to others outside the laboratory.

Exposure to Sh. *dysenteriae* or some *E. coli* subtypes may result in haemolytic uraemic syndrome, a serious disease that can cause death or permanently damage organs and brain function. These pathogens are also likely to cause dysentery and severe illness. Although laboratory-associated infections with *Shigella* are very common, no deaths have been reported with these infections.

V. cholerae is transmissible if the biological agent is released in food or water but the likelihood of an undetected laboratory-associated infection is low as symptoms appear quickly and are quite characteristic of the infection (rice-water stools). Very few cases of laboratory-associated infections have been reported; these infections have resulted in four deaths. Other *Vibrio* species are rare in our area, since we are in the centre of the country and *Vibrio* spp. are associated with marine life.

Campylobacter spp. infections can be serious in certain populations but are zoonotic diseases and more common in livestock and wildlife than people. There are few data that support many laboratory-associated infections with this genus.

Taking the above into consideration as well as the characteristics listed for each biological agent, the consequences of exposure or release are as follows.

S. Typhi	Severe
V. cholerae	Major – few laboratory-associated infections, most people recover within one week without treatment
Vibrio spp.	Moderate
Campylobacter spp.	Moderate
Salmonella spp.	Moderate
Shigella spp.	Major – likelihood of haemolytic uraemic syndrome in healthy adults is extremely low
E. coli	Major – likelihood of haemolytic uraemic syndrome in healthy adults is extremely low

2.4 Describe the initial risk of the laboratory activities before additional risk control measures have been put in place

Instructions: Circle the initial risk of the laboratory activities before additional risk control measures have been put in place. Based upon your evaluation of the likelihood and consequences of an exposure/release as listed above, assess the initial, or currently existing, risk of the laboratory activity using the table below. Find the likelihood of exposure (top row of the chart) and the consequences (left column of the chart).

		Likelihood of exposure/release				
		Rare	Unlikely	Possible	Likely	Almost certain
Consequences of exposure/ release	Severe	Medium	Medium	High	Very high	Very high
	Major	Medium	Medium	High	High	Very high
	Moderate	Low	Low	(Medium)	High	High
	Minor	Very low	Low	Low	Medium	Medium
	Negligible	Very low	Very low	Low	Medium	Medium

Instructions: Check the initial risk to determine the appropriate risk control measures required.

Assessed initial risk		**Potential consequences**	**Actions**
☐	Very low	If an incident occurred, harm would be very unlikely.	Undertake the laboratory activity with the existing risk control measures in place.
☐	Low	If an incident occurred, there would be a small likelihood of harm.	Use risk control measures if needed.
☒	Medium	If an incident occurred, harm would result that would require basic medical treatment and/or simple environmental measures.	Additional risk control measures are advisable.
☐	High	If an incident occurred, harm would result that would require medical treatment and/or substantial environmental measures.	Additional risk control measures need to be implemented before the laboratory activity is undertaken.
☐	Very high	If an incident occurred, a permanent, impairing harm or death and/or extensive environmental effects would be likely.	Consider alternatives to doing the laboratory activity. Comprehensive risk measures will need to be implemented to ensure safety.

2.4 Describe the initial risk of the laboratory activities before additional risk control measures have been put in place (continued)

Instructions (optional): For additional specification on the risks of individual laboratory activities, determine which risks can/should be reduced and prioritized. For each laboratory activity or procedure of the work under assessment, record the initial risks determined from the risk assessment above. Decide whether the work can proceed without additional risk control measures, or whether the risks posed by the work are unacceptable and further risk control measures are needed to reduce the risks. Use the right column of the table below to assign a priority for the implementation of risk control measures based on the identified risks.

Note:

- **When assigning priority, other factors may need to be considered, for example, urgency, feasibility/sustainability of risk control measures, delivery and installation time and training availability.**
- **To estimate the overall risk, take into consideration the risk ratings for the individual laboratory activities/ procedures, separately or collectively as appropriate for the laboratory.**

Risk of the laboratory activity/ procedure	**Initial risk (very low, low, medium, high, very high)**	**Is the initial risk acceptable? (yes/no)**	**Priority (high/medium/low)**
S. Typhi	Medium	No	Medium
V. cholerae	Medium	No	Low
Vibrio spp.	Low	Yes	Low
Campylobacter spp.	Low	Yes	Low
Salmonella spp.	Medium	No	Medium
Shigella spp.	High	No	High
E. coli	Medium	No	Medium

Select the overall **initial** risk.	☐ Very low	☐ Low	☒ Medium	☐ High	☐ Very high
Should work proceed without additional risk control measures?	Yes ☐ No ☒				
Will work require additional risk control measures?	Yes ☒ No ☐				

STEP 3. Develop a risk control strategy

3.1 Describe the resources available for risk control measures

Instructions: Consider the applicability, availability and sustainability of resources for all risks that require additional risk control measures. Consider the following questions. • **Are alternative detection methods or risk control measures available?** • **Are resources sufficient to secure and maintain potential risk control measures?** • **Does the management support the budget necessary for purchasing, operating and maintaining these risk control measures?** • **Does the management support training for personnel on the proper installation, operation and maintenance of these risk control measures?** • **What factors exist that may limit or restrict any of the risk control measures? Are there financial, legal, organizational or other factors that could limit or restrict the risk control measures?** • **Will work be able to proceed without any of risk control measures?**
National guidelines for working with these pathogens are available in the fifth edition of the Biosafety in microbiological and biomedical laboratories (https://www.cdc.gov/labs/pdf/CDC-BiosafetyMicrobiologicalBiomedicalLaboratories-2009-P.PDF) and international guidelines are found in the fourth edition of the WHO Laboratory biosafety manual. Public Health Canada has biosafety data sheets which provide organism-specific guidance for many pathogens (https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment.html). All of these will be used to guide biosafety working practices and conditions related to this work. Personnel safety is also regulated according to the Occupational Safety and Health Administration and rules set out in their policies will be followed.

STEP 4. Select and implement risk control measures

4.1 Describe the measures required by national legislation or regulations (if any)

Instructions: List any requirements that have been prescribed by international and national regulations, legislation, guidelines, policies and strategies on biosafety and biosecurity. In addition, consider if there are any local regulations, guidelines or policies that restrict or govern certain laboratory activities and/or the handling and use of any biological agents.

As mentioned previously, I can add at least one BSC in the laboratory so that all work will be performed with appropriate engineering controls. Vortexing broth tubes will be carried out in the BSC also, further reducing risk. Purchase and mandatory use of goggles when performing procedures at the bench will further reduce the chances of exposure through mucous membranes.

The management is very supportive of this work and has approved the recruitment of two new personnel and allowed an adequate budget for laboratory modifications, supplies and equipment. We charge a fee for some of our work, so we do not have budgetary restrictions that would limit our ability to sustain this activity. The management understands that a laboratory-associated infection damages our reputation and is an indicator of inefficiency, so it is supportive of safety and quality needs and activities.

4.2 Describe where and when additional risk control measures are needed, including an assessment of their availability, effectiveness and sustainability

Instructions: For each laboratory activity or procedure of the work under assessment, record the unacceptable risks determined from the risk assessment above. Decide which risk control measures have been selected to reduce the unacceptable risks. Determine the new, residual risk after risk control measures have been implemented and whether it is acceptable (very low or low, for example) or unacceptable (medium, high or very high, for example) and further risk control measures are needed to reduce risk, or if the work should not proceed at all at this facility. Alternatively, and based on the local circumstances, consider adjusting the acceptable risk. Note that some procedures may require several risk control measures (that is redundancy in case of any failures) to reduce risk to an acceptable risk. Use the right column of the table below to assess the availability, effectiveness and sustainability of selected risk control measures and provide additional information to support this assessment as necessary. If any risks cannot be reduced to an acceptable risk using available, sustainable risk control measures, it is best not to undertake the laboratory activity or to coordinate with another laboratory with the capability to do the work.

Once the risks have been evaluated, risk control measures can be put into place to reduce them. Consider the following risk control measures.

- **Removing the hazard or substituting it for one that reduces risk (for example, substituting an attenuated or less virulent strain of a biological agent or working with inactivated materials)**
- **Enhancing personnel proficiency (for example, providing additional training and mentorship, competency assessments, exercises and drills)**
- **Applying safety policies and procedures (for example, minimizing propagation and concentration of biological agents, limiting the use of sharps, putting up hazard signs, implementing occupational health programmes)**
- **Using PPE (for example, gloves, protective clothing and respiratory protection), which should be evaluated for each risk to ensure it provides the intended protection to the user**
- **Using primary and secondary barriers such as safety equipment and certain facility design features respectively, such as centrifuge safety cups/sealed rotors, BSCs and autoclaves**
- **Routinely evaluating all risk control measures for effectiveness and failures; any failures should be documented and corrected**

Use the following table to list procedures, selected risk control measures and the residual risk, and indicate whether the risk control measure reduces risk to an acceptable risk and is effective and sustainable.

4.2 Describe where and when additional risk control measures are needed, including an assessment of their availability, effectiveness and sustainability (continued)

Risk of the laboratory activity/ procedure	Selected risk control measure(s)	Residual risk (very low, low, medium, high, very high)	Is the residual risk acceptable? (yes/no)	Are risk control measures available, effective and sustainable? (yes/no)
Vortexing Applies to: *Salmonella* spp. (non-Typhi), *Vibrio* spp., *E. coli, Campylobacter* spp. To avoid exposure through surface contamination and potential contact with mucous membranes	Engineering controls: Vortex and manipulation in a BSC	Low	Yes	Yes
Vortexing Applies to: *Shigella* spp. To avoid exposure through surface contamination and potential contact with mucous membranes	Engineering controls: Vortex and manipulation in a BSC	Low	Yes	Yes
Bench work including plating isolates in an autoinoculator Applies to: all biological agents To avoid exposure through surface contamination and potential contact with mucous membranes	PPE: Use goggles in the laboratory while not working in the BSC	Low	Yes	Yes
Specimen transport Applies to: all biological agents To avoid spills	Administrative controls: Transport all biological agents across the laboratory in sealed containers on carts, with no exceptions	Very low	Yes	Yes
Transport within the facility Applies to: all biological agents To avoid spills during the transport	Administrative controls: Install a –20 °C freezer in the main laboratory for freezing isolates before transfer to –80 °C. Handle freezer transfer as a within-facility specimen transport (cart and boxes will be decontaminated)	Very low	Yes	Yes

4.2 Describe where and when additional risk control measures are needed, including an assessment of their availability, effectiveness and sustainability (continued)

Risk of the laboratory activity/ procedure	Selected risk control measure(s)	Residual risk (very low, low, medium, high, very high)	Is the residual risk acceptable? (yes/no)	Are risk control measures available, effective and sustainable? (yes/no)
***S.* Typhi** To avoid spills during inoculation procedure	Engineering controls: Use dedicated bench and BSC for work on this biological agent	Medium	Yes	Yes

4.3 Evaluate the residual risk that remains after risk control measures have been selected

Instructions: Circle the residual risk of the laboratory activities after selection of risk control measures. Based on your evaluation of the effect of the additional risk control measures on the residual risk and their availability and sustainability, as listed above, assess the likelihood and consequences of an exposure/release from the laboratory activity using the chart below. Find the likelihood of exposure (top row of chart) and the consequences (left column of chart). Determine if the residual risk is acceptable and whether work should proceed, indicating who is responsible for the approval to conduct the work.

		Likelihood of exposure/release				
		Rare	Unlikely	Possible	Likely	Almost certain
Consequences of exposure/ release	Severe	Medium	Medium	High	Very high	Very high
	Major	Medium	Medium	High	High	Very high
	Moderate	Low	Low	Medium	High	High
	Minor	Very low	Low	Low	Medium	Medium
	Negligible	Very low	Very low	Low	Medium	Medium

4.3 Evaluate the residual risk that remains after risk control measures have been selected (continued)

Instructions: Check the residual risk to determine the appropriate actions required.

Assessed residual risk		Potential consequences	Actions
☐	Very low	If an incident occurred, harm would be very unlikely.	If the identified residual risk is acceptable, no further action is required for laboratory work to proceed.
☒	Low	If an incident occurred, there would be a small likelihood of harm.	
☐	Medium	If an incident occurred, harm would result that would require basic medical treatment and/or simple environmental measures.	If the identified residual risk is not acceptable, further action is required for laboratory work to proceed. Revisit subsection 2.4 and re-evaluate your risk control strategy based upon the initial risk of laboratory activities. Actions may include (but are not limited to): • Implementing additional risk control measures in accordance with the initial identified risk of laboratory activities to reduce residual risk to an acceptable risk, that is – If initial risk was assessed as medium/high, then further risk control measures need to be implemented before the laboratory activity is undertaken. – If initial risk was assessed as very high, then comprehensive risk measures will need to be implemented to ensure safety. • Redefining the scope of work such that the risk is acceptable with existing risk control measures in place • Identifying an alternative laboratory with appropriate risk control strategies already in place that is capable of conducting the work as planned
☐	High	If an incident occurred, harm would result that would require medical treatment and/or substantial environmental measures.	
☐	Very high	If an incident occurred, a permanent, impairing harm or death and/or extensive environmental effects would be likely.	

Select the overall **initial** risk.	☐ Very low	☒ Low	☐ Medium	☐ High	☐ Very high
Will work require additional risk control measures?	Yes ☒ No ☐				

4.3 Evaluate the residual risk that remains after risk control measures have been selected (continued)

Reviewed by (Name and title)	Professor Abed Achebe, Director, United Microbiology Laboratories
Reviewed by (Signature)	Abed Achebe
Date	30 May 2020

4.4 Communication of the hazards, risks and risk control measures

Instructions: Develop a plan to communicate risks and risk control strategies to laboratory and other relevant personnel. These plans should include the mechanism(s) of communication within the laboratory, such as in-person team meetings and/or training classes, published SOPs, and identification of an accessible place to store all risk assessments and documentation on the risk control strategy.

We have the SOPs from the state laboratory, which was doing this work before. We will develop our own SOPs based on the state laboratory SOPs and tailor them to conform to our laboratory set-up and workflow.

All SOPs are stored in an electronic database and relevant laboratory personnel are required to read them and sign that they understand them before they are trained to perform the procedures at the bench in the laboratory.

Technicians who install the automated equipment will train personnel on its use, and this training will be summarized in a job aid to supplement the SOPs.

The personnel will be individually trained to do broth microdilution antimicrobial susceptibility testing using the "see one, do one, teach one" method. I have found that this is a most effective method and that it is usually more effective to train one person at a time to avoid distractions and so that all questions that may arise can be answered. After training and practice with non-pathogenic bacteria, the personnel will be tested for competency in the procedure (a competency test is being prepared). If an individual passes the test and is considered competent, he/she can begin working with pathogenic bacteria and reporting actual results.

As Unit Chief, I will be responsible for maintaining necessary records, including personnel competency reports (confidential). These and other shared documents will be stored in our database to ensure accessibility for all authorized personnel who may need them.

This biological risk assessment will be one of the forms stored in the database, which houses all our records, including test results from (de-identified) specimens collected from patients around the state.

4.5 Purchase of required risk control measures

Instructions: Describe a process and timeline for ensuring that all needed equipment/supplies for the risk control measures are purchased on time. Consider the budgeting, financial sustainability, ordering, receipt and installation of all risk control measures to be purchased before starting the laboratory work.

We will require several equipment items and additional supplies. One of our personnel in the bacterial unit is responsible for all inventory purchasing (over and above his other duties) but he will need assistance and possibly my help for the first year. Work is planned to begin in 6 months and I have already ordered the larger equipment, including the automated incubating spectrophotometric plate reader. This unit holds 64 plates at once so should be more than adequate for our needs. The automated plate dispenser and the nephelometer have also been ordered.

Maintenance personnel will come to the (decontaminated) laboratory to discuss placement of the additional BSCs. The –20 °C freezer and BSCs will be ordered next week (after checking quality and value) because it often takes longer to receive these items.

The additional PPE, laboratory carts and supplies, such as three vortexes (we only have one at present) will be ordered in the next 3 months.

Supplies such as pipette tips, loops, plate covers, laboratory towels, will be ordered the month before work starts because these require storage space and need to be reordered frequently.

The antimicrobial plates will be received last because the antimicrobial drugs have a limited shelf life. We will have to evaluate our needs continually based on the number of cultures we receive and the number of clients who send them.

We do not foresee any budgetary or staffing problems that would affect the sustainability of this work because we are a private laboratory that generally charges a fee for its services.

4.6 Operational and maintenance procedures

Instructions: Describe a process and timeline for ensuring that all risk control measures have associated SOPs and that training on these risk control measures has been completed. The plan should include development of SOPs, training of personnel who will perform the work, and maintenance and/or calibration, certification, validation of equipment before starting the laboratory work.

As mentioned earlier, the protocols for the antimicrobial susceptibility testing work are from the state health laboratory and only slight adjustments will be made. I expect to have these adjustments completed within the next 2 months.

SOPs for specific risk control measures are already in place and current personnel have been trained to perform/understand these procedures. These include proper use of BSCs, putting on and removing laboratory coats and gloves, proper hand washing, and transport of biological agents within the facility. All of these need to be referenced in the SOP for antimicrobial susceptibility testing because we received only the technical part of the state health laboratory SOP.

Training for maintenance and calibration will be limited to one person. Beyond daily or weekly maintenance (for example, cleaning), most of the maintenance will be done by the manufacturer or their designated representative, because all the automated equipment will be under contract for the duration of this project or until it becomes obsolete.

4.7 Training of personnel

Instructions: Describe a process and timeline for ensuring that training has been completed for all risk control measures. Take into consideration that all personnel (laboratory and support/maintenance personnel) should have completed all training necessary to use all risk control measures before starting the laboratory work.

Current personnel have been trained to use the existing risk control measures but not in the context of the antimicrobial susceptibility testing protocol. For these personnel, we will review the risk control measures in a group training in the laboratory.

The newly recruited personnel will require training in all aspects of the antimicrobial susceptibility testing work, use of risk control measures and our laboratory-specific procedures, including use of our database, waste handling and restocking. Training on use of risk control measures and our laboratory-specific procedures should take about a month, after which these personnel should be ready to start training on antimicrobial susceptibility testing. I will request to start interviewing potential recruits at the beginning of next month. The jobs have already been advertised for a week so I hope to have several qualified candidates for interview by then.

STEP 5. Review risks and risk control measures

5.1 Establish a periodic review cycle to evaluate the effectiveness of risk control measures and to identify any changes

Instructions: Describe the periodic review process. Reviews of risk assessments, risk control measures and risk control strategies should be done periodically to ensure that the laboratory procedures are safe and that the risk control measures that have been implemented to reduce risk are still effective. Components of periodic reviews may include laboratory inspections/audits and/or asking for feedback from personnel during training and team meetings. Reviews of risks and risk control measures must also include:

- **updates on laboratory activities or procedures**
- **new biological agents, or new information on existing biological agents**
- **changes in personnel**
- **changes in equipment and/or facilities**
- **results of audits/inspections**
- **lessons learnt from laboratory incidents or near misses**
- **personnel feedback on procedures, risk control measures and residual risks**
- **person responsible for doing the review and the frequency of reviews**
- **method of documenting the updates and changes**
- **procedures for implementing the changes.**

While annual reviews may be most common, the frequency of the review should be proportionate to the risks, and reviews should be conducted and risks reassessed whenever there are major changes in any elements of the work.

Reviews will be conducted by the biosafety officer annually and if incidents or significant changes in personnel, equipment or SOP occur. Updates to risk control measures will be made as needed, such as after an incident or when improved technology or "best practice" information is available. Improvements will be implemented with management support.

Reviewed by (Name and title)	Dr Jill Smith, Laboratory Manager
Reviewed by (Signature)	Jill Smith
Date	19 June 2020

World Health Organization