LABORATORY BIOSAFETY MANUAL
FOURTH EDITION
AND
ASSOCIATED MONOGRAPHS

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Laboratory biosafety manual, fourth edition

(Laboratory biosafety manual, fourth edition and associated monographs)

ISBN 978-92-4-001131-1 (electronic version)
ISBN 978-92-4-001132-8 (print version)



**Suggested citation**. Laboratory biosafety manual, fourth edition. Geneva: World Health Organization; 2020 (Laboratory biosafety manual, fourth edition and associated monographs). Licence: CC BY-NC-SA 3.0 IGO.

**Cataloguing-in-Publication (CIP) data.** CIP data are available at http://apps.who.int/iris.

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Design and layout by Paul Bloxham

SECTION 2

# RISK ASSESSMENT

As described in the sections below, the control of biological risks – whether at national or organizational levels – is informed by performing a risk assessment. Risk assessment is the term used to describe the stepwise process in which the risk(s) arising from working with a hazard(s) are evaluated and the resulting information is used to determine whether risk control measures can be applied to reduce those risks to acceptable risks. Risk is the combination of the probability that a hazard will cause harm and the severity of harm that may arise from contact with that hazard.

In the case of laboratory biosafety, the hazards are biological agents whose pathogenic characteristics give them the potential to cause harm to humans or animals should they be exposed to these agents. The harm caused by exposure to biological agents can vary in nature and can range from an infection or injury to a disease or outbreak in larger populations (see Box 2.1).

**BOX 2.1** LIKELIHOOD AND CONSEQUENCE FOR LABORATORY BIOSAFETY

In the context of laboratory biosafety, likelihood refers to the potential for an exposure and/or a release outside of the laboratory. Consequence refers to the severity of the outcome from an exposure, if it were to occur. This could include a laboratory-associated infection, asymptomatic carriage, environmental contamination, spread of disease throughout the surrounding community or other illness or injury.

For this reason, factors that contribute to the occurrence of infection, such as routes of transmission, infectious dose and communicability, need to be considered in relation to the consequence of an exposure or release.

It is important to note that hazards alone do not pose a risk to humans or animals. For example, a vial of blood containing a biological agent such as Ebola virus does not pose a risk to the laboratory personnel until they come into contact with the blood contained within the vial. Therefore, the true risk associated with a biological agent cannot be determined by only identifying its pathogenic characteristics. Consideration must also be given to the types of procedure(s) that will be performed with the biological agent and the environment in which these procedures will take place. Any facility that handles biological agents has an obligation to their personnel and the community to perform a risk assessment on the work they will conduct and to select and apply appropriate risk control measures to reduce those risks to an acceptable risk. The purpose of the risk assessment is to gather information, evaluate it and use it to inform and justify the implementation of processes, procedures and technologies to control the risks present. Analysis of this information empowers laboratory personnel as it gives them a deeper understanding of the biological risks and the ways in which they can affect them. It helps create shared values, patterns of behaviour and perceptions of the importance of safety, and makes laboratory personnel more likely to conduct their work safely and maintain a safety culture in the laboratory.

Risk assessments must always be conducted in a standardized and systematic way to ensure they are repeatable and comparable in the same context. For this reason, many organizations offer risk assessment templates, checklists or questionnaires that provide stepwise approaches to identify, evaluate and determine risks associated with the hazards present, before using this information to identify appropriate risk control measures *(24,25)*. The various steps of the risk assessment process collectively form a risk assessment framework (Figure 2.1).


**Figure 2.1** The risk assessment framework

Where Figure 2.1 illustrates the steps in the risk assessment framework, Table 2.1 provides an overview of the key considerations that apply during each step of the cycle. It is important to note that not all factors will affect risk in the same way, but each should be carefully considered. When conducting a risk assessment, it must be remembered that the risk is not based on the pathogenicity of the biological agent alone, but on the likelihood and consequence of an incident occurring – in other words, the risk of exposure to and/or release of the biological agent during laboratory operations.

**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?<br>▪ What type of laboratory work and/or procedures will be conducted?<br>▪ What type(s) of equipment will be used?<br>▪ What type of laboratory facility is available?<br>▪ What human factors exist (for example, what is the level of competency of personnel)?<br>▪ 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?<br>▪ What is the likelihood of an exposure and/or release?<br>▪ What information gathered influences the likelihood the most?<br>▪ What are the consequences of an exposure and/or release?<br>▪ Which information/factor influences the consequences the most?<br>▪ What is the overall initial risk of the activities?<br>▪ What is an acceptable risk?<br>▪ Which risks are unacceptable?<br>▪ Can unacceptable risks be controlled, or should the work not proceed at all? |
| **3. Develop a risk control strategy** | ▪ What resources are available for risk control measures?<br>▪ What risk control strategies are most applicable for the resources available?<br>▪ Are resources sufficient to obtain and maintain those risk control measures?<br>▪ 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?<br>▪ What risk control measures are locally available and sustainable?<br>▪ Are available risk control measures adequately efficient, or should multiple risk control measures be used in combination to enhance efficacy?<br>▪ Do selected risk control measures align with the risk control strategy?<br>▪ What is the residual risk after risk control measures have been applied and is it now acceptable?<br>▪ Are additional resources required and available for the implementation of risk control measures?<br>▪ Are the selected risk control measures compliant with national/international regulations?<br>▪ Has approval to conduct the work been granted?<br>▪ Have the risk control strategies been communicated to relevant personnel?<br>▪ Have necessary items been included in the budget and purchased?<br>▪ Are operational and maintenance procedures in place?<br>▪ 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?<br>▪ Is there any new knowledge available of biological agents and/or the processes being used?<br>▪ Are there any lessons learnt from incident reports and investigations that may indicate improvements to be made?<br>▪ Has a periodic review cycle been established? |

It should be noted that laboratories worldwide could face unique challenges that will influence how various parts of the risk assessment framework are conducted. Challenges may include: the level of organizational and financial resources available to manage biological risks; absence of a reliable electrical supply; inadequate facility infrastructure; severe weather; under-staffed laboratories; and under-trained personnel. Furthermore, the status of national regulatory frameworks may influence the way in which risks are identified and controlled at a level higher than laboratory management, and compliance with any regulations should be a primary focus. For these reasons, the results of a risk assessment and the risk control measures implemented may vary considerably from laboratory to laboratory, institution to institution, region to region and country to country.

The following subsections describe in more detail the activities in each step of the risk assessment framework. They provide an overview of the most important components of risk assessments and the key considerations for conducting them. More detailed information on additional considerations and relevant templates can be found in *Monograph: risk assessment (18)*.

## 2.1 Gather information

Those conducting a risk assessment must collect and consider a wide range of information in order to accurately evaluate the risks and appropriately select the risk control measures needed to reduce risks to acceptable risks in the laboratory. This information goes beyond identifying the hazards – the biological agents being used – and considers the procedural and contextual situations that contribute to the overall risk *(26)*. Key information to be gathered should include, for example:

- laboratory activities planned (for example, procedures, equipment, animal work, sonication, aerosolization and centrifugation),
- competency of the personnel carrying out the work,
- concentration and volume of the biological agent and potentially infectious material to be manipulated,
- potential routes of transmission,
- infectious dose of the biological agent,
- communicability of the biological agent,
- severity of infection with the biological agent,
- local availability of effective prophylaxis or therapeutic interventions,
- stability of the biological agent in the laboratory and external environment,
- susceptibility of laboratory personnel (for example, at-risk individuals),
- range of hosts of the biological agent (that is zoonotic potential),
- endemicity of the biological agent in the local population,
- frequency of equipment and building failures (for example, power, building infrastructure and systems).

All of the above-mentioned information collectively informs a much broader, multifactorial evaluation of risk that may exist in the laboratory. Information on all of these factors is essential as various combinations of biological agents and activities may pose greater risks in some situations than in others. For example, culturing a biological agent with a low infectious dose that is transmissible by the aerosol route might have a greater risk than culturing another biological agent with a high infectious dose that is only transmissible by the oral route. Or, performing research on a biological agent that is not prevalent in the local community will pose a greater risk than performing the work in a region where it is endemic.

It is important to remember that gathering information should also include defining the attributes of the laboratory environment, such as the condition of the building and laboratory areas where the work will be conducted. Improperly maintained structures can contribute to increased risks by increasing the probability of breakages or failures of features such as waste disposal or ventilation systems. Cracks in flooring and bench tops make disinfecting laboratory surfaces difficult, and can contribute to slips, trips, falls and dropped items containing biological agents.

Finally, information on human factors should also be considered, because the competence of laboratory personnel and their ability to follow established biosafety practice and procedure (in particular GMPP) are likely to have the greatest influence on the likelihood of incidents. Even the best designed and constructed facility or the most sophisticated equipment can only confer safety to its user if he/she is able to operate it correctly through proper training and proficiency practices.

### 2.1.1 Information on new or unknown biological agents

Where new biological agents are being used, or there are specimens for which detailed data are unknown, the information available may be insufficient to be able to carry out a comprehensive risk assessment. This applies to clinical specimens collected in the field during potential outbreak investigations. In such cases, it is sensible to take a cautious approach to specimen manipulation and handle all materials as potentially infectious. More information about biosafety in outbreak situations can be found in *Monograph: outbreak preparedness and resilience (23)*.

Certain information should be requested, where possible, to assist in determining the risks associated with handling such specimens including:

- medical data on the patient from whom the specimen was taken,
- epidemiological data (severity and mortality data, suspected route of transmission, other outbreak investigation data), and
- information on the geographical origin of the specimen.

In the case of an outbreak of a disease of unknown etiology, appropriate ad hoc guidelines can be produced and posted by competent national authorities and/or WHO to indicate how specimens are to be handled safely. This may include how specimens should be prepared for shipment as well as specific risk control measures that should be implemented.

## 2.2 Evaluate the risks

After gathering all available information on the circumstances of the work to be performed, it is necessary to use that information to identify and evaluate any risks that exist. The goal of the risk evaluation step is to:

- determine the likelihood of an exposure to and/or release of a biological agent occurring and the severity of the consequences of such an event,
- establish how the likelihood and consequence contribute to the initial risk of the work to be performed,
- decide, based on the gathered information of the risk assessment, whether these risks are acceptable or not; this decision must be justified and documented comprehensively.

If the evaluated risks are not acceptable, those performing the risk assessment should proceed to step 3 of the risk assessment framework and develop an appropriate risk control strategy, unless it is decided not to undertake the work at all. The primary considerations required during this risk evaluation step are outlined in the subsections below.

### 2.2.1 Determine the likelihood and consequences

Evaluation of the information gathered should first include the determination of likelihood of an exposure to and/or release of a biological agent occurring, and of the severity of the associated consequences. It is these factors, when considered together, that will ultimately determine the overall, or initial, risk of the situation for which the information has been gathered. This is illustrated in Box 2.2.

**BOX 2.2** EXAMPLE OF HOW LIKELIHOOD AND CONSEQUENCE INFLUENCE RISK

Cigarette smoke is a common hazard.

The likelihood of exposure to cigarette smoke will differ depending on the situation. It will be greatest for an individual smoking a cigarette, moderate for those exposed to a smoker's second-hand smoke, and lowest for someone with respiratory protection or in smoke-free zones.

The consequences of exposure to cigarette smoke will range from mild nausea and respiratory irritation to various cardiac and pulmonary diseases to cancer and even death depending on the toxicity of the cigarette, frequency and duration of exposure and other factors related to human susceptibility.

Both likelihood and consequence must be considered when evaluating the risks associated with cigarette smoke. This example also shows how individuals evaluate and accept risk differently, given how prevalent smoking is despite the potential negative consequences. A similar risk assessment process for working with biological agents in the laboratory, weighing likelihood and consequence, is outlined in this section.

Examples of factors that can elevate the likelihood of an exposure to and/or release of biological agents during work in the laboratory, and/or escalate its associated consequences are given in Tables 2.2 to 2.4.

A low infectious dose is associated with a greater consequence from an exposure as the amount of the biological agent needed to cause a laboratory-associated infection is small. However, a low infectious dose does not affect the likelihood that an exposure occurs; this relies on factors associated with the work (Table 2.2).

**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.<br>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.<br>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 HIGHER LIKELIHOOD AND GREATER CONSEQUENCE | 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.<br>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 airborne 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.<br>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. |

## 2.2.2 Determine the initial risk

The information gathered must then be used to establish how much risk a particular situation presents (for example, how likely and how severe). Table 2.5 shows a risk assessment matrix which provides a simplified example of how to assess the relationship between likelihood and consequence in order to determine the initial risk of exposure to and/or release of a biological agent. In reality, the relationship comparison may include a broader or more complex range of values for determining likelihood and consequence than that which is shown in Table 2.5, but it is a useful tool to demonstrate how the initial risk can change relative to these independent factors. In addition to the method described here, there are further methods to determine initial risk and prioritize risks for the implementation of risk control measures. Institutions should employ a risk prioritization strategy that best meets their unique needs while acknowledging the limitations of the selected strategy and ensuring that professional judgement remains a critical part of the risk prioritization process.

**Table 2.5** Risk assessment matrix

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

### 2.2.3 Establish an acceptable risk

Once the initial risk has been evaluated, it is necessary to determine whether this risk is acceptable to allow work to proceed. If it is not, a risk control strategy will be required to reduce and sustainably control those risks appropriately as described in the next step of the risk assessment framework.

It is important to acknowledge that there will never be zero risk, unless the work is not conducted at all, so a balance must be carefully managed between conducting the work and ensuring that personnel and the community are as safe as possible from inadvertent exposure to and/or release of biological agents. It is also important to recognize that the work being performed in the laboratory offers considerable benefits to both health care and global health security that justifies a certain degree of risk. Determining the acceptable risk is essential in providing a benchmark below which the initial risk must be reduced in order for work to be considered safe enough to proceed.

*It is important to note that risk can never be completely eliminated unless the work is not performed at all. Therefore, determining if the initial and/or residual risks are acceptable, controllable or unacceptable is a vital part of the risk evaluation process.*

Beyond what is regulated by national legislation and policies *(27)*, the acceptable risk must be established by an organization itself so that it is proportionate to the organization's situation and resources. Consideration must be given to organizational risks such as compliance risk (legal action, fines, citations), security risk (theft or loss), environmental risk (socioeconomic impact on community health and agriculture), and even perceived risk (subjective judgements or uncertainty about the severity of risk). Perceived risks of the personnel should be taken seriously. Self-introduced risk control measures by the personnel should be avoided.

Taking into consideration the risk perceptions of relevant stakeholders (for example, government departments, donors, audit/oversight agencies, the general public and the local community), especially where high actual risks are involved, may be useful to allay the fears of those stakeholders who might otherwise be resistant (for example, politically or administratively) to the laboratory performing its usual functions.

## 2.3 Develop a risk control strategy

Once an acceptable risk has been established, a risk control strategy must be developed to reduce any initial risks to an acceptable risk and allow the work to proceed safely. As previously mentioned, because elimination of risk is not generally possible in practice, careful selection of a risk control strategy is required to ensure that risks are prioritized against the available resources with the understanding that a low acceptable risk will require many more resources to implement and maintain the relevant risk control measures needed to reduce the risk. Acceptable risk, however, must not be raised unnecessarily as a substitute for making resources available to fulfil the necessary risk control strategy and provide the appropriate protection. Resources must be made available or work should not proceed.

There are a number of different strategies that may be used to reduce and control risks. Often, more than one risk control strategy may need to be applied in order to reduce the risks effectively. Table 2.6 provides an overview of some of the most common strategies employed for risk control and examples of the risk control measures.

A good risk control strategy will:

- provide an overall direction of the nature of the risk control measures that may be required to reduce unacceptable risks, without stipulating necessarily the types of risk control measures that can be used to achieve this reduction,
- be achievable using the available resources in the context of the local conditions,
- help minimize any resistance to the work being performed (for example, addresses the risk perceptions of relevant stakeholders) and secure support (for example, approvals from national/international regulatory authorities),
- align with the overall goals, objectives and mission of the organization and facilitate success (that is improves public health and/or health security).

**Table 2.6** Strategies for risk reduction

| STRATEGY | EXAMPLE |
|---|---|
| **Elimination** | Eliminate the hazard:<br>▪ use an inactivated biological agent,<br>▪ use a harmless surrogate. |
| **Reduction and substitution** | Reduce the risk:<br>▪ substitute with an attenuated or less infectious biological agent,<br>▪ reduce the volume/titre being used,<br>▪ change the procedure for one that is less hazardous, such as polymerase chain reaction rather than culture. |
| **Isolation** | Isolate the hazard:<br>▪ elimination and reduction might not be possible, particularly in a clinical setting, therefore isolate the biological agent(s) (for example, in a primary containment device). |
| **Protection** | Protect personnel/the environment:<br>▪ use engineering controls (for example, BSC),<br>▪ use PPE,<br>▪ vaccinate personnel. |
| **Compliance** | Have administrative controls and effective biosafety programme management in place such as:<br>▪ GMPP observed by personnel,<br>▪ good communication of hazards, risks and risk control measures,<br>▪ appropriate training,<br>▪ clear SOPs,<br>▪ an established safety culture. |

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

## 2.4 Select and implement risk control measures

Once a risk control strategy has been developed, risk control measures must be selected and then implemented in order to fulfil the risk control strategy. In some cases, the nature of the risk control measures required will be predetermined, prescribed by a set of minimum standards for risk control (for example, by internationally accepted best practice, national/international regulations).

However, for some cases, a variety of risk control measures will be available to appropriately achieve the risk control strategy depending upon the nature of the risk identified, the available resources, and other local conditions.

It must be remembered that even after a risk control measure is selected for your risk strategy, a certain degree of risk will still remain. If that risk, known as the residual risk, is still unacceptable, additional and/or more effective risk control measures may need to be used to fulfil the risk control strategy and bring the risk to an acceptable risk. Usually, the higher the initial risk, the greater the number of risk control measures needed to reduce the residual risk to an acceptable risk for work to continue.

However, the relative effectiveness of each available risk control measure to reduce the evaluated risks will also affect how many risk control measures are needed to close the gap between the residual risk and the acceptable risk. Furthermore, the use of multiple risk control measures in combination to reduce the residual risk may have further benefits in building redundancy in case of failure of one or more of the selected risk control measures.

The following subsections provide an overview of the key considerations required for the selection and implementation of risk control measures in order to fulfil the risk control strategy.

### 2.4.1 Select risk control measures

When selecting laboratory risk control measures, national regulations and guidelines must always be considered first to ensure compliance. These may be verified through inspections, certifications, audits and assessments, and be overseen by nationally appointed authorities.

The remainder of this subsection describes the selection of risk control measures at the laboratory level, outside those required by any national regulations that may be in place.

For most laboratory activities, the likelihood of exposure and/or release is unlikely, with a negligible to moderate severity of consequences. This means the initial risk is very low or low and is often near or below the acceptable risk even before risk control measures are applied. International guidance and accepted best practice for biosafety recommend the adoption of a basic set of biosafety principles, technologies and practices to act as risk control measures to ensure that all work remains below the accepted risk. For this reason, this manual provides a minimum set of risk control measures to be implemented during any work with biological agents. This combination of risk control measures is known collectively as the core requirements and include tools, training, and physical and operational controls considered necessary to work safely in most laboratory situations. These requirements are described in more detail in section 3 core requirements. However, it is important to note that despite the low risk, GMPP still needs to be promoted and laboratory activities needs to be reviewed periodically to ensure that GMPP and all the core requirements are effectively implemented to complete the risk assessment framework.

*The majority of clinical and diagnostic laboratory work will require only the prescribed core requirements to effectively control risks.*

For cases where initial risks fall into higher categories, a selection of additional risk control measures will be required in addition to the core requirements. Examples of factors associated with a likely or possible likelihood of and/or severe consequence of an incident occurring are shown in Tables 2.2 to 2.4. Under such circumstances, the additional risk control measures selected to reduce the residual risk to an acceptable risk are considered heightened control measures.

Biological agents and procedures that require heightened control measures may vary, ranging from culture and propagation of biological agents in small volumes with a medium risk to large-scale work with drug-resistant strains or animal studies with aerosol-transmissible, zoonotic agents, which are considered high risk. The heightened control measures should be appropriate and proportionate to address the specific factor(s) that contributes to the likelihood and/or consequence of an exposure and/or release; for example, a procedure with an aerosol risk should have a risk control measure that is effective at capturing aerosols. For this reason, the most appropriate heightened control measure will also vary considerably depending on the biological agents being handled, procedures being performed and potential transmission routes. All heightened control measures will have advantages and disadvantages that must be carefully considered when selecting the appropriate ones to close the gap between the residual risk and the acceptable risk.

Where the evaluated risks are considered high on the risk spectrum, cost–benefit analyses should be undertaken to assess options such as outsourcing the work (to a suitable facility that has the appropriate risk control measures and resources in place), as well as a detailed evaluation of heightened control measures that could be implemented to enhance the laboratory facility. The risk control measures chosen will be most effective when they are selected to meet local needs.

*It is important to note that while a hierarchy of risk control measures has been defined by many countries, it cannot be assumed that one risk control measure is always preferable to another (such as engineering controls versus personal protective equipment).*

Usually, heightened control measures should be selected based on available evidence of their effectiveness, either through peer-reviewed studies or other reliable sources of information. Where reliable information does not exist, in-house validation of risk control measures may be required. Where applicable, publishing in-house validation in peer-reviewed journals should be considered so that others can benefit from the conclusions of such studies. This includes new information, previous incidents and the effectiveness of and the protection afforded by the risk control measures. Such studies may also help highlight the likelihood of exposure associated with specific equipment or procedures, which can be included in future information-gathering activities and be used to inform the risk evaluation step in the risk assessment framework.

Some of the most commonly used heightened control measures are discussed in more detail in section 4 heightened control measures, including their relative effectiveness when used in different local conditions.

Where heightened control measures are applied, it is important to recalculate the residual risk after a risk control measure is selected and estimate whether this has effectively brought the residual risk to the acceptable risk. This requires a re-evaluation of the residual risk, guided by questions such as:

- Has the possibility of an exposure/release become less likely to happen?
- Have the consequences become less severe?
- Have the likelihood and consequences been reduced such that the residual risk is acceptable?
- If no, are additional risk control measures available?
- Should work proceed, with or without which risk control measures?
- Who has the authority to accept the residual risk and approve the work to go ahead?
- How should the selected risk control measures and subsequent approval for work to proceed be documented?

In very rare situations, there may be a very high likelihood of exposure and/or release. However, more important is the possibility of severe consequences from any exposure and/or release if it were to occur. Such cases include work with globally eradicated pathogens, or with highly transmissible animal pathogens that could spread rapidly in susceptible populations upon release and cause widespread panic, and decimation of species and/or livelihoods. The risk would be further increased if the agent were propagated in liquid media, particularly if in large volumes, and if infectious aerosols were produced (for example, in vaccine development studies). In such cases, a very high initial risk of exposure to and/or release of a biological agent exists which will likely require a highly specialized, highly effective set of risk control measures to reach an acceptable risk, if the work is to be performed at all. This includes a large set of strict and complicated operational practices, safety equipment and facility design criteria which can be referred to as maximum containment measures; these are described in more detail in section 5 maximum containment measures. As maximum containment measures are necessary to provide the highest protection against the most severe consequences of an exposure or release, evaluating the feasibility of effectively implementing and maintaining maximum containment measures is an extremely important and necessary exercise. This would require frequent and rigorous verification of procedures, equipment and laboratory facilities. Periodic review must also include analysis of ongoing studies to ensure they are adequately justified with the scientific benefits outweighing the biosafety risks.

While an overview of the commonly employed maximum containment measures are presented in this manual, the specialized and complex facilities and expertise required to implement maximum containment measures are only available in a very few laboratories worldwide.

Implementing risk control measures of this complexity requires careful individual consideration by experienced international experts as well as coordination by many sectors, normally including government. For this reason, it is not possible to provide a specific set of requirements applicable to each situation that is considered to require maximum containment measures.

The following schematic (Figure 2.2) summarizes the risk outlined in Table 2.5 (the risk assessment matrix) and associates the risks with the types of risk control measures likely to be required. It highlights the following:

- Most laboratory activities can be safely executed using core requirements, where the risks are very low to low,
- Some laboratory activities will require heightened control measures to safely control the associated risks, which may be medium to high, and
- A very small amount of laboratory work will require maximum containment measures due to very high risks, particularly those risks associated with catastrophic consequences.

### 2.4.2 Implement risk control measures

Once the appropriate combination of risk control measures has been selected, necessary approvals should be obtained. A proper review of cost, availability of funding, installation, maintenance, and security and safety criteria should be undertaken to ensure that the risk control measure(s) can be effectively used as part of the risk control strategy and can be sustained by the available laboratory resources. Each person operating laboratory equipment must be trained on the correct operating procedures required for each and every risk control measure in the laboratory, which may require SOPs to be written or updated. Consideration should also be given to ensuring that the risk control measures selected will not introduce their own risks to the work. For example, multiple layers of PPE might increase the likelihood of mistakes occurring because of reduced dexterity or increase the likelihood of contamination if it is difficult to remove, thereby increasing the overall risk of exposure. Non-biological risk factors of the selected risk control measures should also be considered; for example, specialized design features of furniture or equipment should not introduce ergonomic problems for personnel.

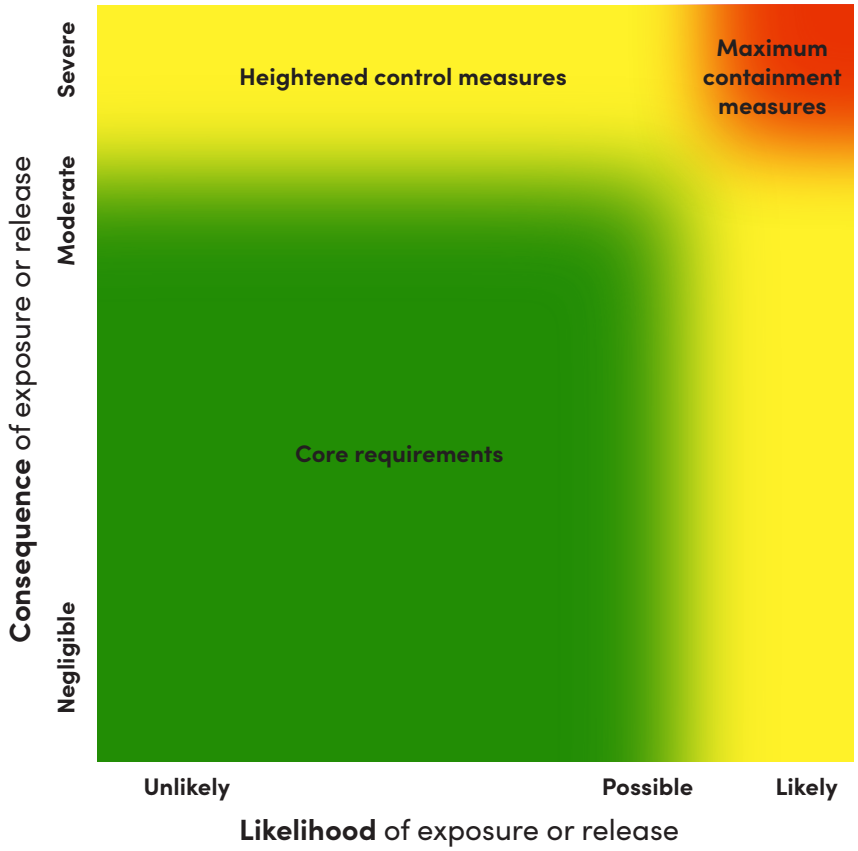


**Figure 2.2** Risk control measures needed based on the likelihood and consequence of exposure or release

Finally, once risk control measures have been selected, approved and acquired, information about their purpose, function and use must be communicated to all applicable personnel if they are to be implemented correctly and be effective. Communication is a vital part of biosafety and risk assessment. Without it, it is unlikely that the risk control measures will reduce residual risk. All those working in the laboratory are responsible for following the appropriate practices and procedures of any risk reduction strategy that applies to them and for providing feedback on their effectiveness. To achieve the appropriate level of awareness, training and competency for implementation of risk control measures and safe laboratory operation requires, at a minimum, communication of the hazards (biological agents) present, communication of the risks associated with the procedures being performed and communication of exactly how the risk control measures used can most effectively reduce those risks. Strategies for communication and outreach beyond traditional biosafety training include laboratory-specific SOPs, interactive team discussions, job aids and posters, generic awareness-raising through short publications (for example, pamphlets, handouts), briefings and email notifications.

Table 2.7 provides some basic examples of laboratory activities and shows how the application of risk control measures affects the residual risk.

**Table 2.7** Examples of laboratory activities, their initial risk, and residual risk after application of appropriate risk control measures

| PROCEDURE | INITIAL RISK (LIKELIHOOD/ CONSEQUENCE) | RISK CONTROL MEASURE(S) | RESIDUAL RISK |
|---|---|---|---|
| **Polymerase chain reaction analysis of inactivated sputum specimen** | Very low (Unlikely/ Negligible) | CR | Very low |
| **Smear preparation and microscopy of sputum specimen** | Low (Unlikely/ Moderate) | CR | Very low |
| **Culture on solid media for antibiotic sensitivity testing** | Medium (Possible/ Moderate) | HCM (for example, CR plus respiratory protective equipment) | Low |
| **Culture in small quantities (< 50 mL) for strain characterization including antibiotic resistant strains** | High (Likely/ Moderate) | HCM (for example, CR plus biological safety cabinet) | Low/Medium |
| **Culture in large quantities (> 10 L) for animal challenge study via aerosol route** | High (Possible/ Severe) | HCM (for example, CR plus biological safety cabinet and respiratory protective equipment) | Medium |
| **Biological agent has been globally eradicated with studies ongoing with above procedures** | Very high (Likely/ Severe) | MCM | Medium |

**CR = Core requirements; HCM = Heightened control measures; MCM = Maximum containment measures. Note: Unless otherwise noted, the biological agent considered in the above scenarios has a low infectious dose, is transmitted via aerosol route and is susceptible to available treatments.**

The goal of risk communication is to help all stakeholders, including laboratory personnel, involved in the implementation of risk reduction strategies to understand the risk assessment method(s), results and risk control measure decisions. Risk communication is vital to allow laboratory personnel to make informed choices about how to perform their role in the laboratory and to establish a successful safety culture built around effective risk-reduction strategies.

Furthermore, strong communication practices will help establish good reporting mechanisms for any incidents, accidents or inefficiencies of the risk control measures. Risk communication also plays an important role in the laboratory's relationship with outside stakeholders, such as regulatory authorities and the general public. Maintaining open communication lines will also be beneficial when conducting future assessments. Written documents are essential to maintain an accurate and historical record of risk assessments and communicating the results to laboratory personnel.

## 2.5 Review risks and risk control measures

Once performed, risk assessments must be reviewed routinely and revised when necessary, taking into consideration new information about the biological agent, changes in laboratory activities or equipment and new risk control measures that may need to be applied. Suitable procedures must be put in place not only to ensure implementation and reliability of the risk control measures, but also to ensure that they are sustainable. Confirmation that measures are effective and that training has been carried out appropriately can be verified through inspection, review and audit of processes and documentation. This will also provide an opportunity for improvements to be made to the processes and associated safeguards. This will include a careful review of laboratory-associated infections, incidents, accidents as well as literature reviews and relevant references.

As was indicated for the initial risk assessment, recording the results of the reassessment is also important in order to document the decisions made, which will facilitate future reviews and performance evaluations.

A risk assessment must therefore be performed and reviewed periodically, at a frequency that corresponds to the risk of the laboratory work. Typically, an annual review is adequate; however, some situations may prompt an ad hoc review, such as a biosafety incident, or feedback from the laboratory personnel on the effectiveness and ease of use of the risk control measures that have been implemented.

*When laboratory activities, personnel, processes and technology change, so does the risk.*

Activities or events that affect the risk and will therefore trigger a risk reassessment include:

- changes to biological agents, or new information available on current biological agents,
- changes to personnel,
- changes to procedures and practices,
- changes to laboratory equipment,
- changes in international, national or regional regulations or guidelines,
- changes in national or regional disease status (endemicity of disease or eradication),
- introduction of new technology,
- laboratory relocation or renovation,
- an incident, accident, laboratory-associated infection, or any event where a potential for harm is identified,
- identification and/or implementation of corrective and/or preventive action,
- user feedback, and
- periodic review.

Whenever a reassessment is warranted, the next step is to return to the beginning of the risk assessment process where new information will be gathered relating to the change, risks will be re-evaluated and it will be determined whether new risk control measures need to be implemented. This ongoing cycle of risk assessment continues to apply throughout the duration of the laboratory work.