Final Supplementary Risk Assessment for the Boston University National Emerging Infectious Diseases Laboratories (NEIDL)

Reader's Guide

National Emerging Infectious Diseases Laboratories

NATIONAL INSTITUTES OF HEALTH

DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Note to the Reader

This Reader's Guide was developed by NIH as an aid to the reader. Its purpose is to provide a synopsis of the Final Supplementary Risk Assessment for the National Emerging Infectious Diseases Laboratories at Boston University. It is written to be brief and more accessible than the full risk assessment, which is more than 2,700 pages long. It is not meant to replace the risk assessment as a source of analysis and information.

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Table of Contents

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History of the Risk Assessment Process for the Boston University National Emerging Infectious Diseases Laboratories

Responsibility for protecting the health of the American people lies primarily with the Department of Health and Human Services. Within the Department, the National Institutes of Health (NIH) is the key agency for conducting and supporting biomedical research. The National Institute of Allergy and Infectious Diseases (NIAID) is the lead organization within the NIH that conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. For more than 60 years, NIAID research has led to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people in the United States and around the world.

Following the terrorist attacks on the United States in the fall of 2001 and the mailing of letters containing anthrax, the federal government amplified focus on funding research related to developing vaccines, diagnostics, and therapeutics against naturally occurring or deliberately released biological agents. By February 2002, NIAID had convened an expert panel composed of distinguished infectious disease scientists to provide objective guidance on the Institute's future biodefense research agenda. The expert panel determined that the capacity of Biological Safety Level (BSL)-3 and -4 laboratory space was insufficient and that this deficiency was, in fact, a barrier to progress in protecting the United States from further bioterrorist attacks.

Additionally, concerns about naturally occurring emerging and reemerging infectious disease threats heightened in the fall of 2002 when a new viral illness called Severe Acute Respiratory Syndrome (SARS) emerged. Around the same time, it became apparent that a form of avian influenza, H5N1, had moved from birds to humans and was causing illness among some people who had close contact with infected poultry. The potential for H5N1 influenza to spark a human pandemic is still being monitored closely.

Responding to these ongoing threats from new and emerging pathogens, Congress and the Administration in 2002 mandated a major expansion of research on such biological agents with an emphasis on the development of vaccines, therapeutics, and diagnostics to address these public health threats. This expansion of federally sponsored research recognized that, regardless of whether the sources of unexpected infectious disease outbreaks were natural or deliberate, the nation must be better prepared to control epidemics and protect the American public against such health threats.

As part of its response to the Congressional mandate, on September 30, 2003, NIAID awarded grant funding to 11 US academic research institutions for the construction of biocontainment facilities to enhance the nation's capability to do research on biological agents. Specifically, awards were made for the construction of nine Regional Biocontainment Laboratories (RBLs) which provide BSL-2 and BSL-3 capacity and two National Biocontainment Laboratories (NBLs) containing BSL-2, BSL-3, and BSL-4 laboratories. These comprehensive, state-of-the-art biocontainment facilities were selected through a competitive peer review process on the basis of multiple factors but primarily on the scientific and technical merit of the applicants' applications. The NBLs and RBLs were to be constructed to support

development of improved diagnostics, therapeutics, and vaccines for protecting the public from emerging and reemerging infectious diseases.

Trustees of Boston University, the Boston University Medical Campus (BUMC), received one of two NBL construction grants. The Boston University NBL, later to be named the National Emerging Infectious Diseases Laboratories (NEIDL), was proposed to be located in BioSquare, a biomedical research and business park adjacent to BUMC in Boston, Massachusetts. The NEIDL stands today as a 192,000 square foot, seven-story building that includes BSL-2, BSL-3, and BSL-4 capacities. The containment area (the specially designed areas where work with pathogens can be conducted safely) includes specialized research facilities and support spaces. In addition, the facility houses a BSL-4 training simulator to provide hands-on training for research staff, faculty, and support personnel. The NEIDL's design employs state-of-the-art technologies to enable the conduct of research in safe and secure environments.

During the design phase of the NEIDL and prior to the start of construction, both NIH and Boston University performed environmental reviews that examined the potential impacts of the NEIDL on the environment and the public. As part of the Federal Environmental Impact Statement (EIS), prepared pursuant to the National Environmental Policy Act, a risk assessment was conducted involving the theoretical release of an infectious agent from the NEIDL into the community as a result of the complete failure of containment systems in the BSL-4 laboratory. The EIS concluded that the risk to the community arising from the potential release of an infectious agent from the NEIDL was negligible. Boston University also prepared an Environmental Impact Report (EIR) as required under Massachusetts state law. The EIR was approved by the appropriate state agency.

BIOSAFETY LEVEL DESIGNATION

BSL 2: for work involving agents that pose moderate hazards to personnel and the environment

BSL 3: for work involving indigenous or exotic agents which may cause serious or potentially lethal disease as a result of exposure by the inhalation route

BSL 4: for work involving dangerous and exotic agents which pose a high individual risk of aerosol-transmitted laboratory infections and life-threatening disease

Concern was expressed by local residents of the Roxbury neighborhood and other Boston residents, who opposed the location of the NEIDL. After the EIR was approved, lawsuits were filed by local citizens in 2005 at the state level and by local citizens and public interest groups in 2006 at the federal level claiming that the environmental reviews inadequately assessed the risks that the NEIDL posed to the community. The lawsuits also alleged that the reviews failed to consider reasonable alternative locations for the NEIDL. The lawsuits raised specific questions about the most stringent high-containment laboratory within the NEIDL, designated BSL-4, which is a small component of the overall facility. A Massachusetts state court held that the state agency's approval of the state EIR was arbitrary and capricious and vacated the approval. That decision was upheld by the Supreme Judicial Court of Massachusetts.

In response to the concerns brought to the federal court by the plaintiffs and at the request of the federal judge for additional risk analyses, the NIH embarked upon what has become an unprecedented effort to perform a supplementary risk assessment to further analyze and determine what, if any, adverse human health effects would occur from an accidental or malevolent release of a pathogen from

the NEIDL. This supplementary risk assessment is also intended to address the issues raised in the state lawsuits.

In March 2008, the NIH established an expert Blue Ribbon Panel (BRP) to provide scientific and technical advice to aid the agency as it responded to the comments and concerns voiced by state and federal courts, the local community, the National Research Council (NRC) of the National Academies, and the general public regarding the construction and operation of a national biocontainment laboratory at BUMC. The BRP included 16 members with expertise in a broad range of fields, including infectious diseases and modeling of those diseases, public health and epidemiology, risk assessment, environmental justice, risk communication, bioethics, biodefense, and biosafety. The BRP has provided the NIH with independent scientific advice on the supplementary risk assessment, including questions to be addressed, possible scenarios, specific infectious agents to consider as well as guidance on processes, methods, and modeling techniques that would result in a comprehensive, sound, and credible risk analysis.

Additionally, NIH requested the services of the National Academies to reconvene the independent NRC committee involved in the review of a prior risk assessment in order to provide technical input and make recommendations regarding the characteristics of the supplementary risk assessment. Throughout the process, the NRC committee performed multiple technical reviews at key milestones and provided valuable recommendations and advice in order to help the NIH prepare a comprehensive, sound, and scientifically credible analysis.

This supplementary risk assessment contains a detailed analysis of potential health and environmental risks associated with the NEIDL. Carefully designed to be realistic and to consider input from the Boston community, the BRP, and the NRC, this analysis examines a series of scenarios describing the likely fates of specific pathogens that might be involved in plausible procedural failures, containment system failures, and malevolent actions. The report also compares the potential public health consequences of biocontainment failures at three separate, proposed sites, each with different population characteristics corresponding to urban (the current Boston site), suburban (Tyngsborough, MA), and rural (Peterborough, NH) settings. Although some of this analysis is highly technical, the goal in preparing the report was to follow objective and well established methods and to make the basis for the risk assessment findings as thorough and transparent as possible.

This companion synopsis is intended to provide an overview of the 2,717 page risk assessment as well as to highlight the key points of the methods, approach, and conclusions contained in the risk assessment.

Definition of Risk Assessment Terms and Process Overview

Definitions and Technical Issues

In order to fully understand the risk assessment, it is necessary to appreciate some technical issues that have a substantial influence on both the way the risk assessment was conducted and the results obtained.

The principles of risk assessment include transparency, clarity, consistency, and reasonableness. Every effort has been made to follow these principles throughout the risk assessment process. Existing guidance for conducting risk assessments (from such agencies as the Environmental Protection Agency and the Department of Energy) was followed throughout the risk assessment process as well. When qualitative and quantitative analyses were performed, scientifically validated peer-reviewed methods were used.

Data sources and quality: Central to the risk assessment is the data used for the analyses. To the extent possible, real data from peer-reviewed sources and real-world experience were used. For example, the risk of a 1918 H1N1 influenza outbreak in the community that might occur in the event of a loss of containment at the NEIDL was estimated based on data available from actual outbreaks of this disease. For other diseases, no appropriate studies have been published, or the diseases are so rare that data does not exist. Where such information is unavailable, estimates, reasonable assumptions, and expert opinion were used. Throughout the report, the sources of data and any data limitations are clearly indicated.

In instances where no definitive information to estimate potential risk exists, the analysis used estimates at the higher end of values that are available, which generally results in an over-estimation of risk. This is known as conservatism. However, the use of broad data estimates leads to uncertainty and impacts the precision of results. In the risk assessment, such results are generally expressed as ranges of values to account for this uncertainty. Range of values may also account for variability, where, because of random chance, the same event may yield different outcomes should that event occur a number of times. Considerable effort, therefore, was devoted in the risk assessment to understand the impact of uncertainty and variability associated with the results of the analysis.

Qualitative and quantitative analysis: The analysis of data in a risk assessment may be *quantitative*, where measurements or other numerical data are analyzed using mathematical approaches, or *qualitative*, where characteristics that are not numerical or directly countable are assessed with non-mathematical methods. For 4 of the 13 pathogens, sufficient numerical data was available, and the analyses were performed quantitatively. Qualitative analysis was also performed on these 4 pathogens as well as the other 9 pathogens for which numerical data was insufficient.

Measures of likelihood, ranges of values: An event may be possible, but knowing how likely (or probable) it is to occur is of more value when calculating or estimating risk. If an event is very unlikely, the overall risk is less. Generally, likelihood (probability) is expressed in the risk assessment in one of two ways: first, as a frequency (the number of times a specified periodic phenomenon occurs within a specified interval; for example, 0.01 per year, which is equivalent to once in 100 years), or second, in this case 100 years is known as the return period, which is an estimate of the interval of time between the occurrence of events like an earthquake or flood of a certain intensity or size. Therefore, on average the event would occur once every 100 years but could happen more or less often (next year or 99 years from now). Likelihoods are expressed this way throughout the report, or as a probability of occurring during the facility lifetime (estimated to be 50 years). Since the values are not precise, ranges are usually presented when performing risk assessments.

Exposure and risk categories: Because of the uncertainty associated with the results of the risk assessment, results are sometimes presented as categories of exposure, infection, or risk. In this risk assessment, we have identified Category A events as having a frequency range of once a year to once in a 100 years. Category B events have a frequency range of once in 100–10,000 years. Additional categories are similarly measured in increasingly longer durations. According to federal guidance, analyzing events that occur once in 10 million years or greater is considered sufficient and was applied throughout this study.

Biosafety levels: When working with infectious pathogens, specialized facilities, procedures, precautions, and practices are used that are appropriate for the potential danger associated with the particular pathogen. In the guidance *Biosafety in Microbiological and Biomedical Laboratories*, the Centers for Disease Control and Prevention and the NIH have defined the four biosafety levels and recommend facilities, procedures, precautions, and practices for each of the four levels of increasing risk. Agents with a greater potential to cause serious disease and death are studied under BSL-3 or BSL-4 conditions. The pathogens analyzed in this risk assessment are all BSL-3 and BSL-4 agents.

Dose-response curves: Dose-response is the relationship between the amount of a pathogen (the dose) received (e.g., inhaled, ingested) by an individual and how likely it is that an infection would result from the exposure (response). This relationship is typically represented by a graph curve. Ideally, risk analysis would use real-world, quantitative information from well-documented human infections to develop dose-response curves. However, for many of the pathogens included in the NEIDL risk assessment, such data does not exist because the required studies cannot ethically be performed on humans. As a substitute, data from animal studies, data from other human infectious diseases and real world events, or estimates from experts have to be used. This leads to some uncertainty, which has also been analyzed. Two sets of dose-response relationships are used in the risk assessment, the first based on information drawn from the scientific literature and the second based on advice from subject-matter experts who followed a widely used consensus approach to provide estimates. The expert opinions were used only when appropriate estimates were not available from the scientific literature, as is the case for some of these rare pathogens.

Modeling and Delphi Method: Modeling is the process of using mathematical approaches or formulas to predict the range of possible outcomes from an event. This method was used to analyze secondary infections and to estimate whether outbreaks are likely and what size they might be. In some cases, there is no human data or any way to accurately quantify probabilities using available information in the scientific literature. In those instances, a technique called the Delphi Method is used to develop estimates based on opinions from subject matter experts.

Mitigation: Many of the possible events or circumstances that might lead to release of pathogens and subsequent problems are known or predictable. Thus, a variety of precautions and steps can be taken to reduce the possible risks. This is known as mitigation. Mitigation may be accomplished through the use of specialized building design features, personnel protective equipment, personnel training, and administrative procedures. Generally, system failures or personnel failures cause events that lead to loss of containment. However, at the NEIDL filtration systems prevent release of pathogens from the

laboratories. Workers wear masks or negative-pressure suits to avoid inhaling pathogens (respiratory protection). In addition, a "culture of safety" that involves detailed, on-going training, prompt reporting of possible problems before there are adverse consequences, and shared responsibility for safety has been developed and implemented at Boston University to reduce the risk of accidents and to ensure prompt and appropriate responses to any accidents that do occur.

Risk Assessment Process

To guide the supplemental risk assessment process, the following questions were posed:

1) What could go wrong? What is the likelihood of each kind of potential incident or accident? What would the consequences be should something go wrong?
2) What are the risks to the workers at the NEIDL and to the public?
3) Would the risks be different if the NEIDL were to be located at a suburban or rural site?

A major objective of the analysis was to estimate how many primary and secondary infections and possible fatalities might occur in lab workers or in the public were any of the studied pathogens accidentally released. Primary infections result from direct exposure to a pathogen that is released during an event; secondary infections occur when a person with a primary infection transmits the disease to others. A further objective of the assessment was to evaluate the possibility that pathogens released from the NEIDL could persist in the environment. The risk assessment process is explained in further detail below.

In general, a risk assessment involves

- Identifying possible hazards;
- Analyzing their likelihood;
- Evaluating the resulting consequences should a hazard occur.

In the case of the NEIDL, where the concern is infections or fatalities resulting from loss of containment, the risk assessment process involved the following steps:

- Identify pathogens;
- Identify and analyze events;
- Estimate Initial infections;
- Assess and model secondary infections;
- Characterize risk.

Each of these steps is outlined in further detail below.

Identify pathogens: The pathogens chosen for study in the risk assessment were based on agents that are

- Expected to be studied at NEIDL;
- Of concern to the public and the courts;

- A representative sample of the range of pathogens requiring BSL-3 and BSL-4 containment.

From this step of the process, a total of 13 bacteria and viruses were selected for inclusion in the risk assessment study. They were characterized based on how likely they are to make people ill; how likely they are to be fatal; and how easily and by what means they are transmitted.

Of these 13 pathogens, 7 require BSL-3 containment (the name of the disease each causes is shown in parentheses):

- *Bacillus anthracis* (anthrax)
- *Francisella tularensis* (tularemia)
- *Yersinia pestis* (plague)
- 1918 H1N1 influenza virus (influenza)
- SARS-associated coronavirus (severe acute respiratory syndrome)
- Rift Valley fever virus (Rift Valley fever)
- Andes virus (hantavirus cardiopulmonary syndrome)

The remaining 6 pathogens require BSL-4 containment:

- Ebola virus (Ebola hemorrhagic fever)
- Marburg virus (Marburg hemorrhagic fever)
- Lassa virus (Lassa fever)
- Junin virus (Argentine hemorrhagic fever)
- Tick-borne encephalitis virus (tick-borne encephalitis)
- Nipah virus (viral encephalitis)

It is important to note that only small quantities of each pathogen will be used in studies at the NEIDL. This is a key point in determining risk because the overall risk of an infection is a function of both the characteristics of the pathogen and how much of that pathogen is present in the lab.

Identify and analyze events: Next, the risk assessment process involves identifying, selecting, and analyzing events that might cause the release of a pathogen and result in the exposure of laboratory workers or members of the public. Several hundred possible events were considered, evaluated, and grouped into categories. Events were chosen based on several factors including real world operating experience in existing BSL-3 and BSL-4 labs, knowledge of NEIDL operations, and predictions based on the nature of the work that will be conducted. From this comprehensive list of events, four event categories representing the overall range of what might possibly happen were selected for detailed analysis. The events included

- a needlestick accident in which a lab worker breaks his or her skin with a hypodermic needle or other contaminated sharp object so that a pathogen enters the body;
- a centrifuge aerosol release in which a centrifuge tube breaks and a pathogen is released into the air when the centrifuge is opened (centrifuges are commonly used in microbiology laboratories to separate materials based on their density);

- an earthquake; and
- a transportation mishap.

It is important to note that events not chosen for detailed analysis were either similar to the events listed above or were considered less likely to pose more risk relative to those chosen for further analysis. For example, a hurricane event was considered but not included in the risk assessment because it is similar to an earthquake in the structural damage it could cause to the building; furthermore, analysis shows that a severe earthquake is more likely to have greater consequences than a hurricane.

Analysis was then performed to estimate how often the chosen events would occur. These events were analyzed in situations involving both BSL-3 and BSL-4 operations. Finally, exposure could be approximated using these estimates as well as taking into account the quantities of pathogens on hand, the number of people exposed, and the amount of pathogen units (a unit is one bacterial cell or virus particle or a small clump of them).

Estimate initial infections: Not all exposures to a pathogen lead to infection and disease. Estimating the number of initial infections involves considering the type of event that led to the exposure, then estimating the amount of the pathogen a person would be exposed to following the event. Whether an infection occurs depends on several factors, including the amount of the pathogen the person was exposed to, the dose-response relationship for that pathogen, and mitigating features. Higher exposure doses are more likely to cause infection, but this relationship varies by pathogen and the circumstances of the exposure. The number of people exposed as a result of an accident can range from zero to many. However, most laboratory incidents have the potential to expose only one or a few laboratory workers. In contrast, events such as a major earthquake might result directly in initial infections in members of the public.

Assess and model secondary infections: An infected person (either a laboratory worker or member of the public) may in some cases transmit the infection to other people, leading to a secondary infection. This aspect of the risk assessment involves, first, determining whether each of the 13 pathogens can be transmitted from person-to-person, and, second—for those that are transmissible—assessing the size and scope of outbreaks that might result. In some cases, there is sufficient existing information to allow detailed quantitative mathematical modeling of transmission. In other cases, only qualitative (or descriptive) assessment is possible.

Characterize risk: This last phase of risk assessment provides a summary of the number of possible exposures, infections, and fatalities that could potentially result from each event. It also synthesizes the key findings and interprets them.

In addition, the following issues were of interest and concern to the Boston community and were considered and analyzed.

Site differences and population differences: A major concern of some members of the public is whether potential risks resulting from the operation of the NEIDL would differ significantly if the NEIDL were located in a suburban or rural area instead of in the South End of Boston. This portion of the risk

assessment considered these issues from the standpoint of population density and other population characteristics. In addition, the issue of environmental justice was analyzed. Environmental justice is defined as the fair treatment and meaningful involvement of all people regardless of race, color, sex, national origin, or income with respect to the development, implementation and enforcement of environmental laws, regulations, and policies.

Threat assessment: The risk of infections or fatalities as a result of malevolent actions is the focus of a threat assessment. Because of the sensitive nature of the analysis and its results, only the general methodology is reported in a summary contained in the risk assessment released for public comment. The results of the threat assessment were vital as a means to implement important mitigation strategies and contributed to the data for the risk assessment.

Transportation analysis: As agents are transferred to and from the NEIDL, there is the possibility of infections or fatalities resulting from transportation accidents. This part of the RA analyzed the risks associated with such transportation-related events.

Environmental persistence: This aspect of the risk assessment deals with the possible retention in the environment (in the bodies of animals or insects or in the soil, or water) of a pathogen that had escaped containment. The analysis was based on known pathogen characteristics and the features of the three sites.

Organization of the Risk Assessment

Following an introductory overview in **Chapter 1**, the RA is divided into a series of chapters that present background information and then describe in-depth the specific stages of the analysis outlined briefly above. Many chapters also have appendices that provide additional details about methods, relevant secondary information, references, and explanations about assumptions made in the analysis. This section is intended to provide the reader a "map" of the full risk assessment, so that parts of interest may be found more easily.

Chapter 2, "Facility Design, Operations, and Site Description," describes the design of the NEIDL facility, how it will be operated, and the kinds of research activities that are expected to be conducted there. This chapter includes an overview of each of the three sites, including the downtown area that surrounds the NEIDL at its urban site, as well as the alternate suburban and rural sites.

Chapter 3, "Pathogen Characteristics," discusses each of the 13 pathogens that were analyzed and provides an overview about why they were chosen for this analysis, details about their biology, and the kinds of infections that each causes. It also describes the limits of the availability of information for each of them. The material in this chapter was summarized from information published in scientific journals.

Chapter 4, "Event Sequence Analysis," explains the overall process of identifying, selecting, and analyzing risk-related events that might occur at the NEIDL. The results of the analysis are the potential consequences of various events, expressed in terms of how many lab workers or members of the public

might be exposed to one of the pathogens following an accident or the failure of equipment; also predicted is the amount of exposure in terms of units of pathogen.

Chapter 5, "Transportation Analysis," deals in detail with risks associated with shipments of pathogens to and from the NEIDL facility. A traffic accident involving these shipments, in which packages containing pathogens might be damaged, may pose a risk to the surrounding community due to the risk of exposing members of the public to infectious materials. The results describe the probability and consequences of such events.

Chapter 6, "Threat Assessment Summary," is concerned with threats to the public that originate within the NEIDL, particularly those that might stem from deliberate efforts to expose personnel at the NEIDL or members of the public to the pathogens being studied there. The chapter describes the process used to develop the threat analysis. Because of the sensitive nature of the threat assessment, only an overview of the findings is available for public review and comment. The results of the threat assessment were used in the analyses included in the risk assessment.

Chapter 7, "Potential for Released Pathogens to Become Established in the Environment," considers whether, as a result of loss of biocontainment, a pathogen could find its way into the environment and become established in the environment (in animals, insects, soil, or water). This chapter considers all 13 pathogens to evaluate whether any have potential to become established in the environments near the sites under evaluation.

Chapter 8, "Health Effects, Initial Infection," and **Chapter 9**, "Health Effects, Secondary Transmission," together examine what might happen if any of the 13 pathogens escaped biocontainment. The first of the two chapters looks at the probability of an infection or fatality occurring as a result of direct exposure from an accident in the research facility. It focuses on personnel at the laboratory who routinely work with pathogens and are, thus, at greatest risk in an accidental exposure. Also considered are accidents that could potentially lead to direct exposures of the public to the pathogens. This chapter also describes the analytic approaches taken for estimating how likely it is that a particular exposure to a pathogen, or dose, is likely to result in an infection.

Chapter 9, considers the likelihood of an initial infection (either in a laboratory worker or member of the public) subsequently being transmitted to others. This chapter also describes mathematical approaches for quantitatively assessing the likelihood of infections being transmitted from one person to others and the likely size of such outbreaks, an approach known as modeling. Mathematical modeling was applied to four pathogens for which adequate information from the published scientific literature is available. These are pathogens that can generally be spread directly from one person to another through close contact.

Chapter 10, "Environmental Justice," is concerned with the requirement for fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income in significant actions taken by the federal government. The final supplementary risk assessment must evaluate whether events associated with the NEIDL might have a disproportionate negative effect on minority or low-income populations residing near the NEIDL. In addition to minority and low-income populations,

Massachusetts also requires consideration of foreign-born populations and populations with limited English skills. The report examines in detail the populations in the vicinity of the three sites and looks at whether the inadvertent release of pathogens from the NEIDL facility would affect members of such communities in a different way than other neighboring communities.

Chapter 11, "Risk Characterization," presents key findings of the overall report. Those findings are highlighted in the next section.

Results of the Final Supplementary Risk Assessment

Chapter 11, "Risk Characterization," summarizes the results of the supplementary risk assessment and answers these questions:

1) What could go wrong? What is the likelihood of each kind of potential incident or accident? What would the consequences be should something go wrong?
2) What are the risks to the workers at the NEIDL and to the public?
3) Would the risks be different if the NEIDL were to be located at a suburban or rural site?

The majority of the results provide likelihoods for primary and secondary infections and fatalities that could occur in lab workers or the public if various events occurred.

Identify and analyze events: Approximately 300 events that could lead to loss of containment were identified, examined, and grouped initially into 30 categories of related events. Based on their likely risk, a small number was selected to represent the overall group. The selected events include higher- and lower-risk events that occur in a variety of ways and expose different groups of people or the environment. The included events encompass the anticipated range of possible severe events. Selected for further analysis were a needlestick accident, a centrifuge aerosol release, an earthquake, transportation accidents, and malevolent acts. The results are estimates of the number of people who would be exposed as a result of an event and the level of exposure in terms of units of pathogen.

A variety of building design features, standard operating procedures, and training are in place at the NEIDL and other BSL-3 and BSL-4 laboratories to prevent possible system failures from occurring or to reduce their impact. This is known as mitigation. When all mitigation strategies are in place and working properly, release event frequencies are often extremely low, and/or procedures are in place to prevent exposures and consequences if they do occur. For example, reporting accidents and confining an exposed worker greatly reduces the possibility of secondary transmission. Working in a biological safety cabinet and having standard operating procedures for conducting centrifuge work substantially reduce the possibility of initial exposures due to the escape of aerosols. To examine the consequences of the most negative possible outcomes, assumptions were made that increase the risk by posing failures without taking into account mitigating features. For example, for purposes of the risk assessment, it was assumed that a needlestick would not be recognized and reported. In reality, lab personnel are trained to recognize and report needlesticks, thus mitigating the consequences should such a lab accident occur.

Similarly, the risk assessment considered what would happen if a centrifuge release went undetected and unreported.

First examined are common lab accidents that might expose lab workers. Needlestick accidents or accidents that almost result in a needlestick are common in both BSL-3 and BSL-4 laboratories, typically occurring once or more per year. However, these incidents only involve a single lab worker; the public cannot be exposed directly to pathogens this way. In addition, needlesticks are likely to be detected and reported, thus preventing secondary infections. An undetected and unreported needlestick is estimated to occur and expose the lab worker to infection about once in 100–10,000 years. An undetected or unreported needlestick has the possibility of leading to a secondary transmission of infection. Whether this worker would become infected (i.e., have enough of an exposure to get the disease) or might subsequently infect others is discussed below.

Similarly, the results of the centrifuge accident analysis show that an undetected and unreported event is likely to occur about once in 1–100 years. No scenarios were found that would result in exposure of workers in a BSL-4 lab from a centrifuge release because of the positive pressure suits they wear. BSL-3 lab workers wear respiratory protective equipment (masks or hoods that filter entering air) that greatly reduces exposure if there is a release. The results of the centrifuge accident analysis indicate that one to four laboratory workers would be exposed with exposures in the range of 0–9 units of pathogen depending on the pathogen (a unit of pathogen is one bacterial cell or virus particle, or in some cases a clump of cells or viruses), with Rift Valley fever virus giving the greatest exposures. If a worker's respiratory protection is not functioning properly, the exposure would be greater, but such a potential greater exposure would be predicted to occur less frequently, since a centrifuge accident and respiratory equipment failure would have to occur at the same time. The analyses estimate a frequency of once per 100–10,000 years for a centrifuge accident concurrently with respiratory protection failure with worker exposures in the range of 0–900 pathogen units, with again RVFV being the greatest.

At the other extreme, a very rare event, like a severe earthquake, has the potential for substantial impact. In addition, an event of this sort could expose the public directly to pathogens. Based on known seismic data for the region, an earthquake of sufficient magnitude to destroy the NEIDL building and release all of the pathogens in the BSL-3 and BSL-4 labs might occur once in 10,000–1 million years. Because a fence surrounds the building site, the closest members of the public are about 100 feet away. Depending on the pathogen, one would predict that members of the public would be exposed to no more than one unit of Rift Valley Fever virus and far less than one on average for the other pathogens. People further away would receive even less exposure. Lab workers are not likely to survive the building collapse, but any who might are assumed to be exposed to levels similar to the public. Whether any of these people would be infected or might subsequently infect others is discussed below.

Estimate initial infections: To determine whether the exposures estimated above in the event analysis would actually result in infections or fatalities, dose-response curves were developed for the 13 pathogens. These curves allow one to estimate the likelihood of infection or fatality from a given dose of pathogen. Since available data from human cases was limited, data from animal experiments and expert opinions were used; the latter was generated by a Delphi expert panel process. The Delphi process

results are presented in the risk assessment. The results from the two methods were fairly similar, considering the overall uncertainty. Lab workers who are exposed via needlestick are assumed to get infected. This is not always the case, but data to estimate the likely dose received is not readily available. Making this conservative assumption, the results show that infections would occur on average about once per 100–10,000 years for an undetected and unreported event; fatalities to laboratory workers from the 13 agents due to the same event would occur once in 200–1 million years. The large range of frequencies for fatalities are due to differences in case fatality rates for the pathogens, with Ebola and Marburg being the greatest for BSL-4 agents; *B. anthracis*, *Y. pestis*, and Andes virus being greatest for BSL-3.

Using the exposure levels and event probabilities from the event sequence analysis, the dose-response curves were used to estimate infections and fatalities in lab workers as a result of a centrifuge accident. Since no plausible BSL-4 scenario could be identified that produced an exposure from a centrifuge accident, only BSL-3 pathogens were studied. In general, predicted exposures were in the lower range of the dose-response curves where the uncertainty is greatest. As a consequnce, the results include a wide range of values. The results for the seven BSL-3 pathogens show that the probability of one worker being infected ranges from once in 100–10,000 years for an event that is undetected and unreported. The large variation is due to differences in the amounts of the various pathogens expected to be on hand as well as differences in the amount of pathogen units that is needed to cause an infection. Rift Valley Fever Virus and *F. tularensis* had the greatest infection and fatality rates due to their low infectious doses. The range for fatalities was once per 5,000–2 million years. Some agents with high fatality rates were not as likely to cause fatalities because of the large infectious dose needed and thus produce a low number of estimated infections.

These results are consistent with real-world experience about laboratory-associated infections that show few infections or fatalities. Infections or fatalities resulting from an earthquake were not analyzed separately for lab workers. They are discussed in the results section relating to risk to the public.

The only event included in this risk assessment that can directly expose the public to infection is an earthquake. The probability of an infection for 12 of the 13 pathogens as a result of a severe earthquake was less than once in 10 million years or more. For Rift Valley Fever virus, the probability is in the range of once per 10,000–1 million years, which is due to the very low probability of such an event occurring and the very low exposures even for those members of the public closest to the building. Since the likelihood of initial infections is so low, the risk of secondary transmission is even lower, which is beyond what might reasonably be expected to occur. Of particular note is that this analysis only evaluated the likelihood of direct exposure and infection due to an earthquake and did not consider the potential injuries, trauma, and fatalities from the earthquake itself, which are likely to be more substantial.

Assess and model secondary infections: If an infected lab worker or infected member of the public interacts with other people, there is the possibility of secondary infections, and a number of additional infections or fatalities may occur. Most important in determining what could happen is whether the pathogen is transmissible from person-to-person. If it is, the probability and the number of secondary infections is dependent on several factors, including the number of additional people that an initially

infected person typically infects, how many contacts an infected person makes with other people, and the effect of instituting mitigating procedures like vaccines, drugs, and isolation. Information from the scientific literature about previous human infections and other relevant information were used to assess this outcome. Four pathogens had enough scientifically vetted, detailed information to model quantitatively. Secondary transmission was not analyzed separately for laboratory workers and others. For analyzing secondary infections, laboratory workers were considered members of the public.

All 13 pathogens were analyzed in a qualitative manner. Of the 13 pathogens, *B. anthracis, F. tularensis*, Rift Valley fever virus, and tick-borne encephalitis are not transmissible, so no further analysis was done. Andes, Lassa, Nipah and Junin viruses are probably transmissible, but available information suggests a low probability of transmission and, therefore, a low probability of secondary infections or fatalities. Modeling was not performed since existing data for these pathogens is very limited. Marburg virus is very similar to Ebola, so it was not analyzed separately. *Y. pestis*, SARS, 1918 H1N1 influenza, and Ebola were modeled quantitatively. Quantitative modeling consists of taking known information about the pathogen and its characteristics related to its transmission, and applying mathematical formulas to the data that can estimate the nature of transmission and possible outbreaks. The results of the analysis allow determination of several kinds of estimates, including 1) the probability of one or more subsequent infections resulting from an initial infection, and 2) the probability of outbreaks of various sizes, for example 10, 100, or 1,000 secondary infections. In addition, modeling results provide estimates of the uncertainty. For example, the probability of one or more secondary infections might be on average 1 in 500 years, but the range (resulting from uncertainty) might be 1 in 150–2,000 years.

The results for a *Y. pestis* exposure via a needlestick event show that the probability of one or more infections is in the range of once in 100–10,000 years; the probability of a fatality falls in the same range. The results for larger outbreaks, such as 10 cases, are between 1 in 10,000–1 million years. Larger outbreaks with of plague caused by *Y. pestis* are even less likely. Similar analyses were done for SARS, 1918 H1N1 influenza, and Ebola.

The results for SARS and Ebola are similar to plague and indicate that one to a few cases might possibly occur, but not likely over the anticipated lifetime of the facility (50 years). Larger outbreaks are unlikely even over 1 million years.

The results for 1918 H1N1 influenza are different and show higher probabilities for more infections, due to the fact that an infected person is more likely to infect many others. For influenza, the estimate for one or more infections is between 1 in 100–10,000 years. An outbreak of more than 1,000 cases might happen once in 10,000–1 million years. The risk to the public from centrifuge accidents is similar to that of needlesticks, so this event was not analyzed separately. The risk from an earthquake is beyond what might be expected even in 1 million years.

Transportation analysis: Shipments of pathogens into and out of the NEIDL are handled according to detailed Department of Transportation regulations with additional precautions specified by Boston University. Shipments arrive at the lab by truck from the sender's location or by truck after air shipment to Logan International Airport. The pathogens are encased in multiple layers of containers and

packaging to prevent release under virtually all conditions. The results of the analysis show that a truck accident that is sufficient to breach the packaging and release pathogens into the vicinity of the accident would occur rarely, certainly no more often than an accident that would cause fatalities to the occupants of the truck. A transportation related accident resulting in the breach of containment is estimated to occur less than once in 1 million years based on known transportation accident data. A similar analysis involving airplane crashes yielded similar results. The analysis determined that crash-related injuries and fatalities are more likely than public exposure to infectious pathogens. Finally, the risk from transportation accidents is less than that from an earthquake.

Environmental persistence: The possibility that pathogens might be released into the environment and remain there in an infectious form was examined. Based on known characteristics of the 13 pathogens, the analysis suggests that it is reasonable to conclude that five of the pathogens could possibly become established in animals, insects, or soil in the vicinity of the lab. These are *F. tularensis, Y. pestis*, 1918 H1N1 influenza, Rift Valley Fever virus, and tick-borne encephalitis virus. One, *F. tularensis,* occurs in the United States and may already be present in some areas near the proposed sites since cases of tularemia have been known occur in Massachusetts over the years. Whether the persistence of these pathogens in the environment would ever result in infections or other consequences cannot be determined due to lack of appropriate data.

Site differences: There are no differences in the risks of infections or fatalities to lab workers at the three different sites because the lab and its operations would be the same at all three sites and similar potential accidents are possible. There are differences in the three sites with regard to population density, and other features of the environment, such as availability of medical care. The possible effects of these differences on risks to the public were evaluated. The results show that, in most cases analyzed, there are slightly smaller risks at the suburban and rural sites (Peterborough and Tyngsborough) compared to the urban site (Boston). However, these differences are considered minimal, and the ranges of values in the estimates for the three sites overlap considerably.

Medically Vulnerable Populations and Environmental Justice: The risk assessment analyzed the potential impacts of the NEIDL's operation on environmental justice communities and medically vulnerable populations at each of the three sites.

The urban site (Boston), where the NEIDL is located, contains an environmental justice community in its vicinity. This community is defined as an environmental justice area due to the fact that it contains more than a 25% minority population. The suburban and rural sites do not contain any environmental justice communities. Nonetheless, the environmental justice community surrounding the NEIDL will not experience any disproportionate impacts from the operation of the NEIDL because the impacts on the three sites are very similar.

For the purposes of this risk assessment, medically vulnerable populations were defined as those individuals who are

- very young

- elderly
- asthmatic
- HIV positive or have AIDS
- diabetic

Full consideration was given to the possibility that medically vulnerable populations may be more susceptible to infections and could suffer more severe consequences, but the analysis did not show any significantly increased risk to these groups when analyzed as a group or individually.

Final Supplementary Risk Assessment: Major Findings and Overall Conclusions

Major findings

The final supplementary risk assessment examined a variety of possible situations—including those that posed the maximum realistically expected risk—that might expose laboratory workers and the general public to harm from disease-causing microbes that will be studied in the NEIDL. While there is no such thing as "no risk," the results of this analysis show that the risk of infections or deaths resulting from accidents or malevolent acts at the NEIDL are generally very low to only remotely possible. While evaluation of the NEIDL and proposed activities in it make up the bulk of the assessment, analyses were also conducted examining different geographic locations as well the impact to site-specific populations.

The greatest potential risk identified in the analysis is to the people conducting research in the laboratories. Laboratory workers have a risk of infection and potential fatalities, particularly with pathogens that can cause infection with a small number of pathogen units. Infections caused by 12 of the 13 pathogens are unlikely to occur in the lifetime of the facility (estimated to be 50 years), only Rift Valley Fever Virus infection has a reasonable chance of causing infection in a lab worker.

The risk to the public of direct infection resulting from an earthquake is beyond that reasonably expected to occur for all pathogens except Rift Valley Fever virus. Even that risk was found to be highly unlikely. The risk to the public is from secondary infections with a few agents. The probability of small outbreaks of one to a few infections or fatalities is unlikely in the facility lifetime, and large outbreaks (more than 100 infections) are beyond reasonably expected (unlikely in 1 million years) except for 1918 H1N1 influenza. Even for influenza, the probability of a large outbreak is only once in 100–10,000 years.

While there are some differences in the risks for the three different sites, they were small in comparison to the range of probabilities for each of the sites. Although medically vulnerable populations may be more susceptible to infections and perhaps suffer more severe consequences, the analysis did not show any significantly increased risk to these groups when analyzed as a group or individually. Environmental justice communities have been shown to not be affected disproportionately.

Environmental persistence is possible but the long-term impact cannot be evaluated due to lack of relevant data.

Transportation accidents are extremely unlikely to result in infections or deaths.

Overall Conclusions of the Final Supplementary Risk Assessment

This final supplementary risk assessment examined a variety of possible scenarios, including those that posed the maximum realistic risk that might result in laboratory workers or the general public having primary or secondary infections resulting from release of pathogens being studied in the NEIDL. While there can be no such thing as "no risk," the results of this analysis show that the risk of infections resulting from accidents or malevolent acts at the NEIDL are generally very low to only remotely possible. This is largely due to the safeguards built into the facility, the low amounts of pathogens that will be present, and the culture of biosafety and training that will be integrated into everyday practice at the NEIDL. The greatest risk is to individuals conducting research in the building. The risk to the general public is extremely low, or beyond reasonably foreseeable, with the exception of secondary infections involving 1918 H1N1 influenza and SARS. Infections from a release of 1918 H1N1 influenza or SARS might occur over 500–5,000 years of operation, far beyond the facility lifetime of 50 years.