THE NATIONAL ACADEMIES
Advisers to the Nation on Science, Engineering, and Medicine

April 29, 2008

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Dear Dr. Zerhouni,

At your request, the National Research Council[1] reconvened its Committee on Technical Input on the NIH's Draft Supplementary Risk Assessment and Site Suitability Analyses [DSRASSA][2] to provide you and your blue ribbon panel with further technical input on the scope and design of any additional studies that may be needed to assess risk associated with the siting and operation of the National Emerging Infectious Diseases Laboratory (NEIDL) at Boston University. This new committee is referred to as the Committee on Technical Input on Any Additional Studies to Assess Risk Associated with Operation of the National Emerging Infectious Diseases Laboratory, Boston University.

In particular, you asked the committee to prepare a brief letter report summarizing its views on the scope (e.g., worst case scenarios, alternative sites, biosafety level-3 and -4 facilities, and selection of agents) and methodological approaches to be taken to improve any additional risk assessment studies that NIH prepares. The committee's full statement of task, as developed with your office, is provided in the main body of the report.

To clarify, in responding to this charge from NIH, the committee did not review the content of previous documents (such as the original environmental impact statement or environmental impact report) or the scope of what has already been done to address risk and community concerns. This committee restricted its comments to suggestions based only on its review of the DSRASSA and on improving the risk assessments presented therein as input to any additional studies that may be needed to assess risk associated with the siting and operation of the NEIDL.

The committee has largely refrained from prescribing specific methods and other details, electing instead to structure its suggestions for the blue ribbon panel around a

[1]The principal operating arm of the National Academy of Sciences and the National Academy of Engineering.
[2]A list of committee members and their biographies is included as Attachment A.

small number of overarching questions about the risks associated with operating the NEIDL:

> What could go wrong? That is, what might be the sequence of events that could cause an infectious agent to escape the laboratory, set up a chain of transmission, and cause infectious disease in the surrounding community?
> What are the probabilities of such a sequence of events?
> What would be the consequences of such a sequence of events?

The committee briefly summarizes its advice on these questions below. More detailed discussions are provided in the main body of this report, starting on page 6.

What Could Go Wrong? Scenarios of Release of an Infectious Agent. The committee suggests a two-phase analysis. The first phase is risk assessment based on a variety of plausible scenarios designed to allow a realistic assessment of risks associated with the NEIDL in general and to illuminate the comparative risks to the communities at the three sites evaluated in the DSRASSA. In a second phase, a highly unlikely but still credible high-consequence event could be analyzed. In addition, the committee recommends that discussions of potential agent release include procedural or work-practice failures, including those which lead to worker exposures and infections; biocontainment-system and equipment failures; and an appropriate array of malevolent actions.

What Could Go Wrong? Agents to Consider for Risk Assessment. The committee recommends that for any future assessments NIH select a variety of agents with appropriately diverse transmission characteristics (bloodborne, transmitted on fomites, spread by aerosol, and/or requiring vectors and the potential for maintenance in existing reservoir species). In addition to portal of entry into the host, such aspects of transmission as high or low R_0, latency, and incubation periods should be thoroughly addressed. The committee also believes that it may be helpful for NIH to clarify for the public and the courts what agents and forms of agents will *not* be researched at the NEIDL for reasons that are likely to apply in the future. Examples may include the virus that causes smallpox and dry, powdered agents that are more easily spread in the air.

What Are the Probabilities? The committee recommends that discussions of potential agent release include probabilistic statements regarding the three categories of release mentioned above. NIH could update previously generated quantitative measurements of safety records for its own and other contemporary BSL-3 and BSL-4 laboratories over the last 20 years, including consideration of recent accidents and exposures, to inform the process.

An infectious agent release could have a variety of consequences, and an assessment should account for them. The committee has described four possible scenarios that are points along the continuum of possible consequences: no subsequent transmission, following a small initial pool of infection; little or no subsequent transmission, following multiple exposures; limited transmission that is contained by public health measures; and amplified transmission. A basic risk assessment should begin

with these four possible outcomes and assess how the characteristics of agents that might be studied in the NEIDL influence the likelihood of each outcome in the event of a release. Even a qualitative analysis of potential outcome should consider impact of the local characteristics (for example, population density, vector availability, and public health infrastructure) on the probability of the various outcomes.

What Would Be the Consequences? If NIH decides that there is a compelling rationale for the use of mathematical modeling in any future risk assessments, the modeling must be done credibly, transparently, and to professional standards by an experienced team of epidemiological modelers and microbial risk assessors. The results should be interpreted in light of the strength of the data used to develop them. Independently of the type of approach used, the model-building procedure and the procedure for assigning values to parameters need to be clearly laid out and justified. For example, which parameter values are supported by the literature, which are estimated from empirical data, and how estimates were derived need to be transparent and clearly presented. The level of detail in a model should be defended with appropriate empirical data and reference to appropriate scientific literature, and any modeling exercise should be accompanied by thorough uncertainty and sensitivity analyses.

Finally, the committee recommends that NIH use the accumulated wisdom in the published literature on how to achieve effective risk communication.

This report reflects the consensus of the committee and has been reviewed in accordance with standard National Research Council procedures (see Attachment B). The work was supported by staff of the National Research Council's Board on Life Sciences: Marilee Shelton-Davenport (study director) and Frances Sharples (director, Board on Life Sciences).

The committee thanks the NIH for seeking its input as the NIH works to develop resources for advancing the national capacity to protect and improve health. The committee hopes that its suggestions will be useful in this regard. We look forward to discussing this report with you and the blue ribbon panel on May 2.

Sincerely

John Ahearne
Chair, Committee on Technical Input on Any Additional Studies to Assess Risk Associated with Operation of the National Emerging Infectious Diseases Laboratory, Boston University

BACKGROUND

In 2003, the Boston University (BU) Medical Center was awarded a $128 million grant from the National Institutes of Health (NIH) to build one of two national maximum-containment laboratories for research on biological pathogens. The National Emerging Infectious Diseases Laboratory (NEIDL) is part of the National Institute of Allergy and Infectious Diseases efforts to provide physical infrastructure for the conduct of biodefense and emerging-infectious-disease research to develop new and improved approaches to treating, preventing, and diagnosing a variety of bacterial and viral diseases. Diseases to be studied include biothreat agents and emerging novel pathogens, such as those which cause Ebola, Marburg, plague, dengue fever, Lassa fever, shigellosis, and unusual virulent influenzas. The facility will include a biosafety level-4 (BSL-4) and several BSL-3 containment laboratories housed in a 223,000-ft^2 building. Under the National Environmental Policy Act (NEPA), NIH reviewed the potential impacts of the NEIDL at its location[3] in Boston's South End. The review concluded that the facility would not pose a risk to the community. However, the location of the facility on Albany Street in Boston's South End, which includes environmental justice communities with large low-income and minority populations, is controversial, and there have been numerous contentious public meetings about the plans for the facility. Three legal actions have been filed to stop the funding and construction of the NEIDL.

NIH prepared a document, “Draft Supplementary Risk Assessment and Site Suitability Analyses” (DSRASSA), regarding the siting and operation of the BU NEIDL in response to comments from the federal court presiding over a NEPA lawsuit. The DSRASSA was prepared to supplement NIH's previous assessments of the potential risks posed by the NEIDL at its current location in Boston.

In 2007, the Massachusetts Executive Office of Energy and Environmental Affairs (MEOEEA) asked the National Research Council to establish a committee to provide technical input on the NIH DSRASSA to the MEOEEA. Although the DSRASSA was prepared in response to comments that arose in federal litigation pursuant to the NEPA process, the MEOEEA requested a review because it expected the DSRASSA to be an integral part of the material that would be submitted to it by BU in fulfillment of Massachusetts Environmental Policy Act (MEPA) requirements.

The National Research Council Committee on Technical Input on the NIH's Draft Supplementary Risk Assessment and Site Suitability Analyses reviewed the DSRASSA and discussed its methods and analyses to address the specific questions posed by the MEOEEA (see below). In November 2007, the committee released its letter report answering these questions. The committee's letter report was critical of the DSRASSA, finding that it was not sound and credible, did not adequately identify and thoroughly develop worst-case scenarios, and did not contain the appropriate level of information to compare the risks associated with alternative locations. The letter report also raised specific concerns about agent selection, scenario development, modeling methodology, consideration of environmental justice issues, and risk communication.

[3]Construction of the laboratory building is nearly complete. The remaining issue is whether the BSL-4 component will become operational.

In March 2008, NIH announced that additional steps would be taken to address judicial requests and public comments on risks associated with the siting and operation of the NEIDL (see http://nihblueribbonpanel-bumc-neidl.od.nih.gov/roster.htm for a list of blue ribbon panel members.) Specifically, NIH established a blue ribbon panel of outside experts to advise NIH on how to respond to comments by the courts and the public regarding possible risks associated with the siting and operation of the NEIDL. An early task of the panel will be to advise NIH on the development of a statement of work for any risk analyses that may be necessary later. Given prior National Research Council comments on the DSRASSA, NIH also asked the Research Council to reconvene the Committee on Technical Input on the NIH's Draft Supplementary Risk Assessment and Site Suitability Analyses to obtain additional insights on scope and methodologies for future risk analyses from the NRC Committee.

INTRODUCTION AND COMMITTEE'S CHARGE

The report prepared by the committee and released for publication on November 29, 2007, was a review of a document prepared by NIH (now called the DSRASSA but also called the NIH study and the DSER in the November 2007 report) for the MEOEEA. The committee was asked by Massachusetts to carry out a technical review of the scientific adequacy of the DSRASSA and to address three specific questions:

- Are the scientific analyses in the DSER sound and credible?
- Has the NIH identified representative worst case scenarios?
- Based on comparison of risk associated with alternative locations, is there a greater risk to public health and safety from the location of the facility in one or another proposed location?

These three questions were not developed by the committee but rather were negotiated as part of the statement of task agreed on between the National Research Council and Massachusetts to guide the committee's work.

In its November 2007 report, the committee addressed the three questions and concluded that the DSRASSA had significant deficiencies in scientific adequacy. The committee described the deficiencies in relation to the three questions. It did not focus attention on how the deficiencies might be remedied, whether they were limited to the single work product it reviewed, or whether they reflected problems in previous NIH work products to assess the potential impacts of the NEIDL.

In the present report, the same committee is responding to a request from NIH to provide input and assistance on the scope and design of any additional studies that may be needed to assess the risks associated with the siting and operation of the NEIDL. The committee's new statement of task is as follows:

The NRC Committee on Technical Input on the NIH's Draft Supplementary Risk Assessments and Site Suitability Analyses (DSRASSA) for the Boston University (BU) National Emerging Infectious Diseases Laboratories (NEIDL) will be reconvened to provide input on the scope and design of any additional studies that may be needed to assess risk associated with the siting and operation of the NEIDL. The original NRC Committee was appointed to provide technical input on the DSRASSA as requested by the

Massachusetts Executive Office of Energy and Environmental Affairs. The Committee's letter report, which was released in November 2007, was critical of the NIH's draft document, with specific concerns raised about agent selection, scenario development, modeling methodology, consideration of environmental justice issues, and risk communication. The NIH has now appointed a Blue Ribbon Panel to advise NIH on responding to judicial and public concerns about the siting and operation of the BU NEIDL and to recommend any additional risk assessment studies that may be needed. Given prior NRC comments on the DSRASSA, the NIH is asking the NRC Committee for input on any further supplementary risk assessments that NIH might undertake. The reconvened NRC committee will prepare a brief letter report summarizing its views on the scope (e.g., worst case scenarios, alternative sites, BSL-3 and BSL-4 facilities, selection of agents, etc.) and methodological approaches to be taken to improve any additional risk assessment studies NIH prepares and will discuss these views with the Blue Ribbon Panel in a meeting or conference call after the letter report is delivered to the NIH.

As in its first report, in addressing this charge from NIH, the committee did not review the content of previous documents (such as the original environmental impact statement or environmental impact report) or the scope of what has already been done to address risk and community concerns. The committee restricted its comments to suggestions based only on its review of the DSRASSA and on improving the risk assessments presented therein as input to any additional studies that may be needed to assess risk associated with the siting and operation of the NEIDL.

The committee prepared this report largely on the basis of the analysis and discussions that went into the preparation of its November 2007 report, discussions that were expanded on in a series of conference calls held in April 2008. Additional input from outside the committee was not solicited beyond the standard National Research Council review process.

As noted in its previous report, the committee acknowledges here—and wishes to emphasize—the need for biocontainment laboratories, including BSL-4 laboratories. These laboratories can conduct valuable scientific research. The committee also recognizes that BSL-4 facilities are being operated safely in both urban and rural areas. However, the committee's view remains that the selection of sites for high-containment laboratories should be supported by detailed analyses and transparent communication of the available scientific information regarding possible risks.

COMMITTEE'S SUGGESTIONS AND RECOMMENDATIONS

Risk assessment can and should be used to address both the probability and the consequences of adverse events, such as the release of human or animal pathogens from a biocontainment facility that leads to morbidity and mortality. Risk assessment is generally an appropriate approach for characterizing risk and, when performed well and directed at answering the right questions, can assist in decision-making (such as siting decisions) and in addressing public concerns. It provides a framework for organizing information about a situation that may be highly complex and involve uncertainties with respect to matters on which experimental data are sparse or absent. Risk assessment does not generally produce a precise quantitative risk value, but it can be used to summarize

whatever information is available and provide insights to improve understanding and suggest new research that is needed. Such understanding, in turn, can be used to design appropriate mitigation and response strategies. The risk assessment process should be transparent, and it should inform the parties who have decision responsibility so that they are better able to make decisions, in this case, about measures to ensure the safe siting, design, and operation of the laboratory. The communities of professionals in risk analysis and infectious disease, working together, can provide specific guidance in these fields, and NIH should seek to use the best knowledge and talent available in the two communities in any future risk assessments.

Scientifically sound documents can help NIH address the public's concerns and provide information requested by the courts about site comparisons. Reviewing the scope and content of previous project documents is not within the committee's scope of work, but the committee is pleased to make suggestions about approaches for the blue ribbon panel to consider. The committee cannot comment on the cost of such measures or on what resources are needed.

The committee has elected to structure its suggestions for the blue ribbon panel around a small number of overarching questions (Kaplan and Garrick, 1981) about the risks associated with operating the NEIDL:

- What could go wrong? That is, what might be the sequence of events that could cause an infectious agent to escape the laboratory, set up a chain of transmission, and cause infectious disease in the surrounding community?
- What are the probabilities of such a sequence of events?
- What would be the consequences of such a sequence of events?

What Could Go Wrong? Scenarios of Release of an Infectious Agent

The committee is aware that the courts asked for a description and evaluation of "worst-case scenarios" and reiterates that the question of whether NIH had provided representative worst-case scenarios in the DSRASSA was specifically posed to the committee by the MEOEEA. However, the committee does not endorse an exclusive focus on the development of worst-case scenarios as an appropriate procedure for carrying out risk assessments for the NEIDL or for other facilities of this type. **Rather, the committee suggests two phases of analysis**. **The first phase is risk assessment based on a variety of plausible scenarios designed to allow a realistic assessment of risks associated with the NEIDL in general and to illuminate the comparative risks to the communities at the three sites evaluated in the DSRASSA.** This analysis would not represent worst-case scenarios; rather, it could lay out realistic situations, such as protective features in place, public health mitigation strategies in place, and training and standard operating procedures followed. **In a second phase, a highly unlikely but still credible high-consequence event could be analyzed.** This might be referred to as a worst-case scenario, although the committee encourages NIH to define clearly what it means if it uses this term. This phase of the analysis could examine possible sequences of post-release events to explore the magnitude of the possible consequences of a release,

perhaps by considering such details as highly effective transmission (large R_0[4]) and a long latent period during which infectious symptoms are nonspecific or not evident. The effects of limitations in the public health and emergency response systems could also be analyzed. Any future risk assessments should incorporate sufficient meaningful biological data in the scenarios to make it possible to understand how the results of the analyses were reached.

Although engineering and design—and hence safety—of high-containment biological laboratories have undoubtedly improved greatly with contemporary practices, accidental releases due to human error or maintenance failures certainly can still occur. Recent such events include the infection of workers with *Brucella* at one of Texas A&M University's BSL-3 laboratories in 2006; a 1-hour power outage in 2007 at the new BSL-4 facility of the Centers for Disease Control and Prevention in Atlanta, before work with pathogens began, wherein the main and backup power systems both failed and the negative-air-pressure system, a key element of pathogen containment, shut down; and, also in 2007, a release of foot-and-mouth disease to livestock on farms near the Pirbright high-containment laboratory in the United Kingdom due to a damaged and leaking drainage system at the facility (GAO 2007). Scenarios for evaluating the risks posed by the NEIDL should systematically include potential realistic means of biological-agent escape and should describe the various safeguards to protect laboratory workers and the surrounding community. **The committee recommends that discussions of potential agent release include**

- **Procedural or work-practice failures, including those which lead to worker exposures and infections.**
- **Biocontainment-system and equipment failures.**
- **An appropriate array of malevolent actions.**

Within these categories, one could consider contamination of the waste stream from the laboratory, the effects of power outages, unintentional or malevolent infection of laboratory workers, and unintentional or malevolent release of laboratory animals or pests (such as insects capable of serving as disease vectors).

Designing scenarios in this way may also highlight where additional measures might prove useful for enhancing laboratory safety. The DSRASSA assumed, for purposes of providing an initial case for modeling, that a release occurred. Scientifically accurate scenarios that include probabilistic evaluation (see next section for discussion of probabilistic evaluation) of how a biological agent could be released could lead to enhanced preventive measures. For example, an assessment might highlight the importance of laboratory-worker training or of occupational health surveillance. Or it could lead to the recommendation of interventions instituted in other laboratories, such as working with vectorborne agents during seasons when the vectors are not circulating in the community.

[4]Theoretically, R_0, the basic reproduction number, is defined as the average number of secondary cases generated by a single primary case during its entire period of infectiousness in a completely susceptible population (Diekmann and Heesterbeek, 2000).

In addition to laboratory-related interventions to *minimize the occurrence* of such events (that is, prevention measures), risk assessments should address the capabilities of the medical and public health systems to *respond* to untoward events (that is, mitigating measures) at the South End and alternative sites. These measures are especially important to consider in the context of environmental justice, potentially unequal access to health care among the three sites, and other factors of importance to the communities. Without the discussion of preventive and mitigating measures, scenarios do not reflect how the laboratory is intended to be operated and managed, and risks are obscured to the detriment of decision-making. Basing scenarios on as much factual information as possible will make them more relevant and ensure that they portray more accurately the hazards associated with work in high-containment (BSL-3) and maximum-containment (BSL-4) laboratories.

What Could Go Wrong? Agents to Consider for Risk Assessment

The characteristics of a particular infectious agent may make it more or less likely that the agent could lend itself to the establishment of a chain of transmission that leads to the spread of infection in the community. The DSRASSA analyzed the potential for disease spread by four pathogens, but all four were of low transmissibility and not likely to spread beyond the persons initially infected. As noted by the committee in its November 2007 report, "Because the probability of transmission of disease from one person to another was set to be low, infections die out, rather than propagate. As a result, for all four of the agents considered, the risks calculated from the two models are small." The committee believes that many of the agents mentioned as expected to be studied at the NEIDL (Klempner, 2008) are candidate agents with higher transmission rates that could be addressed in risk assessments regardless of the biosafety level at which they will be studied.

Including both BSL-3 and BSL-4 agents in any future risk assessments is appropriate because the reasons for studying a biological agent under BSL-3 vs BSL-4 conditions include factors other than the risk associated with release of an agent (BMBL 2007). These factors include, for example, risk to laboratory workers and whether or not the agent is endemic. BSL-3 laboratories are used to study biological agents that are potentially lethal and that are transmissible by the aerosol route. It is thus possible that BSL-3 agents have greater transmissibility than some BSL-4 agents. BSL-4 agents may produce higher mortality and lack treatment options, but morbidity is also important in evaluating risk. In addition, engineered controls are greater in BSL-4 facilities, and it is possible that risks of human error are greater in BSL-3 laboratories.

The committee recommends that for any future assessments NIH select a variety of agents with appropriately diverse transmission characteristics (bloodborne, transmitted on fomites, spread by aerosol, and/or requiring vectors and the potential for maintenance in existing reservoir species). In addition to portal of entry into the host, such aspects of transmission as high or low R_0, latency, and incubation periods should be thoroughly addressed. Furthermore, NIH should describe why specific agents were ultimately selected for the analysis. The committee is aware of the degree of complexity involved in this task, but it is a cornerstone of assessing and communicating biological risk reliably and realistically.

The committee believes that it may be helpful for NIH to clarify for the public and the courts what agents and forms of agents will *not* be researched at the NEIDL for reasons that are likely to apply in the future. Examples may include the virus that causes smallpox and dry, powdered agents that are more easily spread in the air. A sound and well-documented rationale could be provided to substantiate why particular agents or forms of agents will not be studied. The rationale may include legal or treaty constraints and prohibitions, the fact that government agencies other than NIH are charged with missions involving work with particular agents and forms of agents, and circumstances surrounding the acquisition of agents. For example, NIH might clarify that no offensive biological weapons research will be conducted at the NEIDL, because it is prohibited by the biological weapons convention (Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction). This treaty prohibits signatories from developing, producing, stockpiling, or otherwise retaining microbial or other biological agents or toxins, whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective, or other peaceful purposes.

What Are the Probabilities?

Risk assessment addresses both the probability and the consequences of adverse events. The scenarios and agents discussed above should be used in any future risk assessments to analyze and communicate the probabilities of adverse events.

The committee recommends that discussions of potential agent release include probabilistic statements regarding the three categories of release discussed above:

- **Procedural or work-practice failures, including those which lead to worker exposures and infections.**
- **Biocontainment-system and equipment failures.**
- **An appropriate array of malevolent actions.**

The development of these probabilistic statements should draw on information that already exists (for example, Johnson, 2003a, 2003b, 2004) and other risk assessment documents despite the fact that inherently the information is not comprehensive. NIH could also update previously generated quantitative measurements of safety records for its own and other contemporary BSL-3 and BSL-4 laboratories over the last 20 years, including consideration of recent accidents and exposures to inform the process. Such a quantitative analysis could include estimates of person-hours worked, numbers of laboratory-acquired infections, outcomes of infections in workers and the community, biological agents involved, and other measures relevant to biocontainment work. The historical experience of biocontainment facilities—both those associated with NIH activities and the many similar facilities around the world—is that releases of disease pathogens have been rare. There have been laboratory-acquired infections, but the resulting diseases have mostly been confined to the facilities' workers and, in a few cases, members of their immediate families or health care providers (Harding and Byers, 2006). As noted above, contemporary BSL-3 and BSL- 4 facilities minimize the probability that a release will occur with extensive equipment and design features,

laboratory protocols for safety, and rigorous occupational health programs. In addition, specialized patient isolation facilities are generally available at local hospitals in the event that workers become ill after an inadvertent exposure.

An infectious agent release could have a variety of consequences, and an assessment should account for them. These consequences can be conceptualized as a continuum that ranges from few or no adverse outcomes (requiring minimal or no public health response) to amplified disease transmission resulting in a public health emergency. To illustrate the continuum in more detail, the committee has described four possible scenarios that are points along it. The committee has provided examples for each scenario. Although the examples represent public health events that have been documented in the literature, the committee emphasizes that they are *not* based on releases from BSL-4 laboratories.

- *No subsequent transmission, following a small initial pool of infection.* The agent may fail to establish a productive chain of transmission after only a few people are initially infected. An example is the 2003 monkeypox outbreak in the United States, which is thought to have been related to contact with pet rodents.

- *Little or no subsequent transmission, following multiple exposures.* The agent may fail to establish a productive chain of transmission after multiple initial exposures. An example is the intentional contamination of food with *Salmonella* that infected hundreds of consumers but failed to spread in the community.

- *Limited transmission that is contained by public health measures.* The agent may establish a successful chain of transmission but be controllable by public health measures (tens to perhaps hundreds or thousands of people infected). An example is the SARS outbreak observed in 2003 (Lipsitch et al., 2003).

- *Amplified transmission.* The agent may establish a chain of transmission that amplifies rapidly and is not controlled by public health measures, which may be ineffective or overwhelmed (say, 10,000 people infected). Examples are the outbreaks of influenza, smallpox, and poliomyelitis *before* the availability of effective vaccines for these agents.

A basic risk assessment should begin with these four possible outcomes and assess how the characteristics of agents that might be studied in the NEIDL influence the likelihood of each outcome in the event of a release. This basic approach should be a minimal requirement for risk assessment. A qualitative approach to this assessment might consider actual events, taking into consideration important differences, such as metropolitan settings and circumstances, and qualitative consideration of transmissibility (R_0) and the proportion of transmission that occurs before onset of symptoms. R_0 is a key quantity in estimating transmissibility of infectious diseases, and the proportion of

transmission that occurs before the onset of overt clinical symptoms can affect the success of public health measures (Fraser et al., 2004).

Even a qualitative analysis of potential outcomes should consider impact of local characteristics (for example, population density, vector availability, and public health infrastructure) on the probability of the various outcomes.

More complex approaches to predicting outcome, such as modeling, if pursued, should be rigorously justified and should be designed to build on this basic analysis (see next section).

What Would Be the Consequences?

The consequences of a release of an infectious agent from a high-containment laboratory depend on numerous factors, such as the characteristics of the agent, the pathway by which it is spread, and the size and characteristics of the population that is exposed to it. The major concern is the potential for community outbreaks of disease, taking into account both morbidity and mortality.

The previous section discussed the need for an assessment of agents and the probability of different outcomes in the event of a release. This section discusses modeling, which is of course, another way of assessing how the disease caused by an agent may spread. Modeling may also be an important tool in devising appropriate mitigating strategies.

Calculating the outcome of a release of a biological agent with models is extraordinarily difficult. The basic test of a model is whether it can replicate the various types of outcomes that are known to happen, but our understanding of any individual agent is incomplete, to say the least. Furthermore, the biology of agents *within* experimentally infected animals or infected humans is much better understood than the process of *transmission*, about which relatively little is known although it is a major parameter in determining the results of a release. For example, the observation that there are “superspreaders”, a small proportion of hosts that account for a large portion of the amplification of an epidemic, makes estimates of average transmission rates highly questionable. Likewise, it is difficult to estimate the number of contacts between people although recent estimates of age-specific contact rates from surveys that are relevant for respiratory spread of infectious diseases have become available for some populations (Mossong et al., 2008). The ability of a single model to simulate accurately both the transmission of an aerosol-transmissible agent and that of a fomite-transmitted agent is questionable. These uncertainties and complexities compound as the number of model parameters increases.

There is no consensus on an approach to model all, or even many, infectious diseases. In the absence of an accepted approach, simplicity has advantages: the behavior of simple models is relatively well understood, and the effects of changing inputs are relatively transparent. More complexity and detail may not add to confidence or accuracy of model results, particularly if the data used to develop input are scant and there are many uncertainties.

In short, although mathematical models of infectious diseases at the population level may provide results that can give us perspective and insight as to how and why infectious diseases cause epidemics, there is great complexity in using them and in interpreting their results. The use of models cannot make up for what is often a deficiency

of biological and other data, so it is essential that the judgment of epidemiologists, infectious disease specialists, and microbial risk assessors be applied to the interpretation of model results. **If NIH decides that there is a compelling rationale for the use of mathematical modeling in any future risk assessments, the modeling must be done credibly, transparently, and to professional standards by an experienced team of epidemiological modelers and microbial risk assessors. The results should be interpreted in light of the strength of the data used to develop them.**

If modeling is deemed necessary to study the effects of an infectious agent release into a community, the type of model used should be considered case by case. If the objective is to evaluate epidemic characteristics—such as size, peak, and duration—dynamic compartmental epidemic models based on differential equations can be useful (Anderson and May, 1991). Most mathematical models used in the literature to date are simple compartmental models of various levels of complexity, such as those used to study the SARS epidemic (see, for example, Lipsitch et al., 2003). Dynamic models based on differential equations are tractable for systematic uncertainty and sensitivity analyses. In contrast, large-scale agent-based models are increasingly used to assess the role of specific control interventions in specific settings. However, these large-scale agent-based models are typically difficult to calibrate and require large-scale computing resources.

Independently of the type of approach used, the model-building procedure and the procedure for assigning values to parameters need to be clearly laid out and justified. For example, **which parameter values are supported by the literature, which are estimated from empirical data, and how estimates were derived need to be transparent and clearly presented.** The level of detail in a model should be defended with appropriate empirical data and reference to appropriate scientific literature.

The infectious disease transmission potential and uncertainty of transmission must be quantified to determine the disease related impact on the population of a release of an infectious agent. **Any modeling exercise should be accompanied by thorough uncertainty and sensitivity analyses**. As pointed out in the committee's November 2007 report, assessing the uncertainty of parameter values and the sensitivity of model outputs to them is crucial. Uncertainty analysis includes assessment of the uncertainty in epidemic size, peak, and duration as parameter values vary within plausible ranges. It is especially important to consider the impact of values used for infectious disease transmission potential. Because each set of plausible model values is not equally likely, values can be drawn from appropriate probability distributions with simple random sampling or Latin hypercube sampling (see, for example, Blower and Dowlatabadi, 1994; Chowell et al., 2004). Similarly, sensitivity analysis should be conducted to assess the effects of changes in parameter values on specific model outputs, such as those described above. A sensitivity analysis will help to rank parameter values according to the size of their effect on model output.

As discussed in the qualitative description above, modeling approaches should also consider the impact of local conditions (for example, population density, vector availability, and public health infrastructure) on the consequences. It would be useful to consider the possibility that different disease spread outcomes have different implications for the population immediately surrounding the laboratory (see the next section).

Including Community Characteristics

The characteristics of the surrounding community—such as its racial, ethnic, and socioeconomic composition; its access to health care and health services; and the environmental stressors it faces—should be taken into account in the risk assessment and analysis. Urban communities often face environmental and other stressors that wealthier communities do not face. These factors are important because communities, such as the South Boston neighborhoods that surround the NEIDL, face challenges that could affect, among other things, the transmission of infectious disease, the health consequences, and the scope and deployment of public health resources required for response. It is also important to include these factors in an analysis because they form the basis of many community and environmental justice concerns about the siting of the NEIDL. Site selection can contribute to the probability of various possible outcomes. The potential for various outcomes to have different effects on sites is noted above on page 13.

If modeling is used, these factors could be incorporated into the modeling exercise (see, for example, Halloran et al., 2008). If another approach is chosen, or if a modeling approach that does not accommodate the inclusion of environmental justice concerns is used, the risk assessment should adopt another quantitative or qualitative technique that reflects the community's attributes.

Improving Communication of Risk

In its November 2007 report, the committee discussed risk communication aspects of the DSRASSA. The report noted that particularly in cases where there is strong public interest, such as this siting decision, it is important to develop presentations and documents that are transparent and complete and that clearly address the concerns of affected and other interested parties. There are many information resources on risk assessment and risk communication, and NIH should use the wisdom accumulated in the published literature on effective communication of risk. Although the committee has not described the specifics of risk communication in this report, it notes that a recent article by Race (2008) analyzes public review processes and risk communication with respect to a number of high-containment laboratories recently built or under construction. Many of the laboratories that generated serious controversies had key issues in common, including concerns about trust, transparency, and the reporting of accidents. Lofstedt (2002) and Fell and Bailey (2005) also discuss risk communication in connection with laboratory siting. Finally, the committee refers the blue ribbon panel to the risk communication concepts discussed in the National Research Council reports *Improving Risk Communication* (1989) and *Understanding Risk: Informing Decisions in a Democratic Society* (1996).

ATTACHMENT A: BIOGRAPHICAL SKETCHES OF COMMITTEE MEMBERS

John Ahearne (*Chair*) is executive director emeritus of Sigma Xi, the Scientific Research Society, and director emeritus of the Sigma Xi Ethics Program. Before working at Sigma Xi, Dr. Ahearne served as vice president and senior fellow at Resources for the Future and as commissioner and chair of the US Nuclear Regulatory Commission. He worked in the White House Energy Office and as deputy assistant secretary of energy. He also worked on weapons-systems analysis, force structure, and personnel policy as deputy and principal deputy assistant secretary of defense. Serving in the US Air Force (USAF), he worked on nuclear-weapons effects and taught at the USAF Academy. Dr. Ahearne's research interests include risk analysis, risk communication, energy analysis, reactor safety, radioactive waste, nuclear weapons, materials disposition, science policy, and environmental management. He was elected to the National Academy of Engineering in 1996 for his leadership in energy policy and in the safety and regulation of nuclear power. Dr. Ahearne has served on many National Research Council committees in the last 20 years and has chaired a number of them, including the current Committee on Evaluation of Quantification of Margins and Uncertainty Methodology Applied to the Certification of the Nation's Nuclear Weapons Stockpile and the Committee on the Internationalization of the Civil Nuclear Fuel Cycle. In 1966, Dr. Ahearne earned his PhD in physics from Princeton University.

Thomas W. Armstrong recently retired from his position as senior scientific associate in the Exposure Sciences Section of ExxonMobil Biomedical Sciences, Inc., where he had worked since 1989. Dr. Armstrong is working with the University of Colorado Health Sciences Center as the lead investigator in exposure assessment for epidemiological investigations of potentially benzene-related hematopoietic diseases in Shanghai, China. Dr. Armstrong spent 9 years working for the Linde Group as the manager of loss control in the gases division and a manager of safety and industrial hygiene. He recently conducted research on quantitative risk-assessment models related to inhalation exposure to *Legionella*. He is a member of the Society for Risk Analysis and the American Industrial Hygiene Association, and he has been certified as an industrial hygienist by the American Board of Industrial Hygiene. Dr. Armstrong has an MS in environmental health and a PhD in environmental engineering from Drexel University.

Gerardo Chowell is an assistant professor at the Arizona State University (ASU) School of Human Evolution and Social Change. Before joining ASU, Dr. Chowell was a director's postdoctoral fellow with the Mathematical Modeling and Analysis group (Theoretical Division) at the Los Alamos National Laboratory. He performs mathematical modeling of emergent and re-emergent infectious diseases (including SARS, influenza, Ebola, and foot-and-mouth disease) with an emphasis on quantifying the effects of public-health interventions. His research interests include agent-based modeling, model validation, and social-network analysis. Dr. Chowell received his PhD in biometry from Cornell University and his engineering degree in telematics from the Universidad de Colima, Mexico.

Margaret E. Coleman is a senior microbiologist at Syracuse Research Corporation (SRC) in the Environmental Science Center, an independent not-for-profit research and development organization. Ms. Coleman leads multidisciplinary teams in SRC's Microbial Risk Assessment Center of Excellence (M-RACE) and is a founding member and councilor of the new Upstate New York Chapter of the Society for Risk Analysis (SRA). Since 1996, she has served in various leadership roles in SRA: chairing symposia and workshops in quantitative microbial risk assessment (QMRA), being a member of program committees for domestic and international conferences, and holding offices in the Biostressors Specialty Group and the Dose-Response Specialty Group. An active member of the American Society for Microbiology (ASM), she recently contributed an article to ASM's *Microbe* magazine ("Microbial Risk Assessment Scenarios, Causality, and Uncertainty"). Ms. Coleman contributes to peer-review processes in QMRA for several journals, including SRA's journal *Risk Analysis*. She served as a reviewer for the National Research Council report *Reopening Public Facilities After a Biological Attack* and as a committee member for *Review of Testing and Evaluation Methodology for Biological Point Detectors*. Before her work in SRC, Ms. Coleman contributed to development of QMRA methodology for foodborne and waterborne hazards at the US Department of Agriculture and member agencies of the federal Risk Assessment Consortium. Ms. Coleman earned her BS from the State University of New York at Syracuse College of Environmental Science and Forestry and MSs from Utah State University and the University of Georgia in biology and biochemistry and in medical microbiology.

Gigi Kwik Gronvall is a senior associate at the Center for Biosecurity of the University of Pittsburgh Medical Center (UPMC) and assistant professor of medicine at the University of Pittsburgh. Dr. Gronvall is an immunologist by training. Her work addresses how scientists can diminish the threat of biological weapons and how they can contribute to an effective response against biological weapons and natural epidemics. She is a term member of the Council on Foreign Relations and also serves on the American Association for the Advancement of Science Committee on Scientific Freedom and Responsibility. Dr. Gronvall is a founding member of the Center for Biosecurity of UPMC and, before joining the faculty in 2003, worked at the Johns Hopkins University Center for Civilian Biodefense Strategies. From 2000 to 2001, she was a National Research Council postdoctoral associate at the US Army Medical Research Institute of Infectious Diseases (USAMRIID) in Fort Detrick, Maryland. Dr. Gronvall earned a PhD from Johns Hopkins University for her work on T-cell receptor/MHC I interactions.

Eric Harvill is an associate professor of microbiology and infectious diseases at the Pennsylvania State University. His primary research interest is in the interactions between bacterial pathogens and the host immune system, and his group investigates bacterial virulence factors and host immune functions at the molecular level, using the tools of bacterial genetics and mouse molecular immunology. The studies investigate the possible effects of these molecular-level activities on the population-level behavior of infectious diseases. Dr. Harvill has served on several National Research Council

committees, including the Committee on Methodological Improvements to the Department of Homeland Security's Biological Agent Risk Analysis. He has reviewed for more than 20 scientific journals and serves on the Editorial Board of *Infection and Immunity*. Dr. Harvill has reviewed proposals for six National Institutes of Health study sections, the US Department of Agriculture, and multiple international funding organizations. He has organized international and local meetings and chaired sessions at annual meetings of the American Association of Immunologists and the American Society for Microbiology. He earned his PhD at the University of California, Los Angeles.

Barbara Johnson has over 15 years of experience in biosafety, biocontainment, and biosecurity for the US government and owns the consulting company Barbara Johnson & Associates, LLC. Dr. Johnson has managed the design, construction, and commissioning of a biosafety level-3 aerosol pathogen test facility, and she launched the US government's first chemical and biological counterterrorism training facility. Her research interests include biological risk assessment and mitigation, testing of the efficiency of respiratory protective devices, and testing of novel decontamination methods against biological threat agents. In the private sector, she pioneered the development of the first joint biosafety and biosecurity programs between the United States and institutes in the former Soviet Union, and she founded and directed a center for biosecurity in association with this work. She has served as the president of the American Biological Safety Association and is the coeditor of the journal *Applied Biosafety*.

Paul A. Locke is an associate professor in the Department of Environmental Health Sciences at the Johns Hopkins Bloomberg School of Public Health. He is a public-health scientist and attorney with expertise in risk assessment and risk management, radiation-protection law and policy, and alternatives to animals in biomedical testing. Dr. Locke serves on the Environmental Protection Agency's Clean Air Act Advisory Committee and is a member of the Board of Councilors of the National Council on Radiation Protection and Measurements. Since 2004, he has been a member of the National Research Council Nuclear and Radiation Studies Board, and he has participated on two Research Council committees that evaluated the risks associated with the disposal of high-level radioactive waste. Dr. Locke has received several awards, including the Yale School of Public Health Alumni Service Award and the American Public Health Association Environment Section Distinguished Service Award. He holds an MPH from Yale University School of Medicine, a JD from Vanderbilt University School of Law, and a DrPH from the Johns Hopkins Bloomberg School of Public Health.

Warner North is president of NorthWorks, Inc., a consulting firm in Belmont, California. He is also a consulting professor in the Department of Management Science and Engineering at Stanford University. Over the last 30 years, Dr. North has carried out applications of decision analysis and risk analysis for electric utilities in the United States and Mexico, for petroleum and chemical industries, and for government agencies with responsibility for energy and environmental protection. He has served as a member and consultant to the Environmental Protection Agency Science Advisory Board since 1978 and as a presidentially appointed member of the US Nuclear Waste Technical Review

Board. Dr. North is a member of the National Research Council Panel on Public Participation in Environmental Assessment and Decision Making and has chaired Research Council committees. He is a past president of the Society for Risk Analysis (SRA), a recipient of SRA's Outstanding Risk Practitioner Award, and a recipient of the Frank P. Ramsey Medal from the Decision Analysis Society for lifetime contributions to the field of decision analysis.

Jonathan Richmond is CEO of Jonathan Richmond and Associates, a biosafety consulting firm with a global clientele. Before starting his own firm, Dr. Richmond was the director of the Office of Health and Safety at the Centers for Disease Control and Prevention in Atlanta, Georgia. He is an international authority on biosafety and laboratory-containment design. Dr. Richmond was trained as a geneticist, worked for 10 years as a research virologist, and has been involved in biosafety for the last 25 years. He is the author of many scientific publications in microbiology and has edited numerous books, has chaired many national symposia, and is an international consultant to ministries of health on laboratory safety and training. He served as president of the American Biological Safety Association.

Gary Smith is chief of the Section of Epidemiology and Public Health in the University of Pennsylvania School of Veterinary Medicine. He has a secondary appointment in the Department of Biostatistics and Epidemiology of the university's School of Medicine and is an associate scholar in the Center for Clinical Epidemiology and Biostatistics. He is also an affiliated faculty member of the university's Institute for Strategic Threat Analysis and Response. His research deals with the epidemiology and population dynamics of infectious disease in humans and in wild and domestic animals. He has extensive experience in mathematical modeling in the context of infectious and parasitic disease control strategies (including the evolution of drug resistance) and has published case-control studies of various infectious diseases of animals and humans. Dr. Smith served on a Food and Agriculture Organization–World Health Organization expert committee on the implementation of farm models in the developing world, served on the Pennsylvania Food Quality Assurance Committee, and was a member of a European Union expert committee on the risk of bovine spongiform encephalopathy. He has served on the editorial boards of *Parasitology Today*, the *International Journal of Parasitology*, the *Veterinary Quarterly*, and *Frontiers in Ecology and the Environment*. Dr. Smith earned bachelor's degrees in zoology and education from the University of Oxford and the University of Cambridge, respectively, and a DPhil in ecology from the University of York.

ATTACHMENT B: ACKNOWLEDGMENTS

The chair thanks the committee members for working extremely hard on a very tight schedule to produce this report and for their willingness to adjust personal schedules to do this work on short notice. He also thanks the staff of the Board on Life Sciences for handling logistics and coordinating the production of the committee's report. Once again, the chair notes that the most valuable contribution was made by the study director, Marilee Shelton-Davenport, whose knowledge and patient leadership were instrumental in producing a high-quality report.

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of the independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We thank the following for their review of this report:

John Applegate, Indiana University
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David Franz, Midwest Research Institute
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Bailus Walker, Howard University
Catherine Wilhelmsen, The United States Army Medical Research Institute for Infectious Diseases

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of the report was overseen by Ed Perrin, University of Washington, and John Samet, Johns Hopkins University. Appointed by the National Research Council, they were responsible for making certain that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of the report rests entirely with the authoring committee and the institution.

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