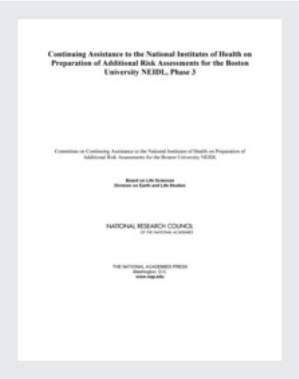

Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University NEIDL, Phase 3

DETAILS

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Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University NEIDL, Phase 3

Committee on Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University NEIDL

Board on Life Sciences
Division on Earth and Life Studies

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December 6, 2011

Francis Collins, M.D., Ph.D.
Director
National Institutes of Health
Building 1
9000 Rockville Pike
Bethesda, Maryland 20892

Dear Dr. Collins:

At your request, the National Research Council (NRC)[1] reconvened its Committee on Technical Input on Any Additional Studies to Assess Risk Associated with Operation of the National Emerging Infectious Diseases Laboratory (NEIDL), Boston University[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 the risks associated with the siting and operation of the NEIDL.

In particular, you asked the NRC Committee to meet with the NIH Blue Ribbon Panel in public at key milestones in the development of the draft risk assessment. To this end, the NRC Committee met in open session with the Blue Ribbon Panel on November 2, 2011. The purpose of this meeting was to discuss the NRC Committee's comments and questions on a "90 percent" draft of the revised risk assessment. This Phase 3 letter report provides the NRC Committee's written comments in response to that November 2 meeting. The NRC Committee's full statement of task, as developed with your office, is provided in the main body of this report.

The Committee found that the "90 percent," or penultimate, draft of the risk assessment is a substantial improvement over past documents we have reviewed. What follows is intended to present some areas in which the Committee on Continuing Assistance to NIH sees elements that might be used to improve the version prepared for public comment.

We hope that the comments provided in this letter report will be helpful to you and the Blue Ribbon Panel as you consider how the remainder of the work to be performed is carried out. It is the Committee's consensus that the advice and assistance we have provided to NIH should

[1] The principal operating arm of the National Academy of Sciences and the National Academy of Engineering.
[2] The Committee is now known as the Committee on Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University NEIDL. A list of Committee members and their biographies is included as Attachment A.

now be at an end. The Committee thanks NIH for seeking its input as it 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.

This report reflects the consensus of the Committee and has been reviewed in accordance with standard NRC procedures. The work was supported by Frances Sharples, Director of the NRC's Board on Life Sciences and Orin Luke of the Board on Life Sciences.

Sincerely,

John F. Ahearne, Chair
Committee on Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University NEIDL

cc: Amy Patterson, M.D.

ACKNOWLEDGMENTS

This report has been reviewed in draft form by individuals 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 this 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 for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this report:

John S. Applegate, University of Indiana School of Law, Bloomington, IN
John C. Bailar, III (Emeritus), University of Chicago, IL
Kenneth I. Berns, University of Florida, Gainesville, FL
Charles N. Haas, Drexel University, Philadelphia, PA
Marc Lipsitch, Harvard University School of Public Health, Boston, MA
Stephen Ostroff, Pennsylvania Department of Health, Harrisburg, PA
Catherine Wilhelmsen, U.S. Army Medical Research Institute for Infectious Diseases, Frederick, MD

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 this report was overseen by Edward B. Perrin, University of Washington, Seattle, WA. Appointed by the National Research Council, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring Committee and the institution.

BACKGROUND AND INTRODUCTION

In 2003, the Boston University Medical Center (BUMC) was awarded a $128 million grant from the National Institutes of Health (NIH) to build one of two national maximum-containment laboratory facilities for pathogen research. The National Emerging Infectious Diseases Laboratories (NEIDL) are meant to support the National Institute of Allergy and Infectious Diseases' biodefense research agenda, conducting research to develop new approaches to treating, preventing, and diagnosing a variety of bacterial and viral diseases. Diseases and pathogens to be studied include viruses (e.g., Ebola, Marburg, dengue fever, Lassa fever, and highly pathogenic influenza) and bacteria (e.g., *Shigella* and plague) that occur naturally and cause infections or that could be used in deliberate attacks. The facility includes a biosafety level 4 (BSL-4) containment laboratory housed in a 192,000 square foot building. Although the NEIDL BSL-4 laboratory accounts for only 13 percent of the building's total space, it has been the source of virtually all of the community concern surrounding this project. The location of the facility on Albany Street in Boston's South End, which is an environmental justice community, (Boston Region Metropolitan Planning Organization, Journey to 2030; Loh, et al., 2002) has been controversial, and there have been numerous public meetings over the plans for the facility as well as three legal actions challenging the project. Construction of the laboratory building is now finished although commissioning of the laboratory facilities has not been completed. A remaining issue is whether the BSL-4 component will become operational.

The building, including the BSL-4 laboratory, is part of the BioSquare Phase II project. Under the Massachusetts Environmental Policy Act (MEPA), the Secretary of the Commonwealth of Massachusetts's Executive Office of Environmental Affairs issued a certificate stating that the BioSquare II project required the preparation of an Environmental Impact Report (EIR). Although the Massachusetts Secretary of Environmental Affairs in 2004 found that the final Environmental Impact Report adequately and properly complied with MEPA, this determination was challenged in court. In July 2006 the Superior Court of Massachusetts vacated Massachusetts' certification of the EIR and remanded the matter to the Secretary of Environmental Affairs.

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

At the request of the State of Massachusetts, in November 2007 the NRC Committee authoring the current report released the first in a series of letter reports assessing the DSRASSA.[3] The Committee's assessment 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 report also raised specific concerns about agent selection, scenario development, modeling methodology, environmental justice issues, and risk communication.

In March 2008, NIH established its Blue Ribbon Panel (BRP) to provide scientific and technical advice to the NIH Director through recommendations made to the Advisory Committee

[3] NRC. Technical Input on the National Institutes of Health's Draft Supplemental Risk Assessments and Site Suitability Analyses for the National Emerging Infectious Diseases Laboratory, Boston University: A Letter Report (2007). Available at: http://www.nap.edu/catalog/12073.html.

to the Director. The panel members were charged with providing ongoing, expert input to guide the development of any necessary additional risk assessment analyses. Also in 2008, the same NRC Committee reconvened at the request of NIH. The NRC Committee has been meeting with the BRP periodically as milestones were reached in the preparation of additional risk assessment materials. The NRC released its second letter report in April 2008.[4] The Committee restricted its comments in that report to suggestions based only on its previous review of the DSRASSA and 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. As noted in its 2007 report, the Committee acknowledged and emphasized the need for biocontainment laboratories, including BSL-4 laboratories. However, the Committee's view remained 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.

In its 2008 report, the Committee refrained from prescribing specific methods and other details, electing instead to structure its suggestions to the NIH BRP around the following overarching questions that should be addressed in future reports about the risks associated with operating the NEIDL:

- What could go wrong?
  - — Release scenarios for infectious agents
  - — Agents to consider for risk assessment
- What are the probabilities that these scenarios will occur?
- What would be the consequences if they did occur?

The Committee also recommended that NIH make greater use of the accumulated wisdom in the published literature on how to achieve effective risk communication.

In 2009 NIH asked the NRC to convene the NRC Committee again to provide input at key milestones in the development of the supplementary risk assessment through a series of letter reports (see full Statement of Task, below). The first milestone for which input from the NRC was requested was the development of plans for the supplemental risk assessment. On March 19, 2010 at a joint meeting of the NIH BRP and the NRC Committee, the two contractor groups selected by NIH to complete the supplemental risk assessment—Tetra Tech and its subcontractors from the University of Utah—made presentations on the proposed plans for the supplemental risk assessment. At NIH's request, the NRC Committee focused its discussions of the proposed approaches on the following questions:

1. Is the range of agents being studied appropriate?
2. Is the approach to event sequence analysis appropriate?
   - — Will the method result in an adequate range of scenarios being considered and selected for analysis?
   - — Are the plans for analysis and expression of results appropriate?
3. Is the modeling approach appropriate?
   - — Is the approach to initial infection sound?
   - — Are the criteria for and selection of models sound?
   - — Are the uses of the hybrid branching-compartment models and the extreme values analysis sound?

[4] Technical Input on Any Additional Studies to Assess Risk Associated with Operation of the National Emerging Infectious Diseases Laboratory, Boston University: A Letter Report (2008). Available at: http://www.nap.edu/catalog/12208.html.

On the basis of this meeting, in April 2010 the NRC Committee delivered its third letter report.[5] In that report, the Committee noted that it had heard about plans, but not yet results. In general, the NRC Committee found the proposed approaches to conducting the risk assessment suitable and well planned. The agents selected for analysis were appropriate and comprehensive, and the expertise available on and to the assessment team seemed strong. NIH and Tetra Tech appeared to recognize data limitations and the need for flexibility in study design. The Committee encouraged NIH and Tetra Tech to develop qualitative analyses (an explanation of the safety and risk profile) of all 13 pathogens on the list in a manner that is clear and accessible to the public. The Committee also suggested that the qualitative analyses in the body of the assessment be supplemented with results of quantitative modeling planned for five pathogens, with details provided in appendices. Further, the Committee encouraged NIH and Tetra Tech to rely on data that are available from existing case studies, public health surveillance of the surrounding communities, and release incidents, not only to support its models but also to provide a complete and understandable picture for the public. The NRC Committee again emphasized that the final risk assessment be able to serve as an effective risk communication tool.

On September 22, 2010, the NRC Committee again met in open session with the Blue Ribbon Panel to hear presentations by NIH's contractors on the approaches they were taking to conduct the risk assessment. After reviewing the material presented at the meeting, the NRC Committee concluded that it could not endorse as scientifically and technically sound the illustrative analyses presented. At that time, the NRC Committee found that the analyses presented did not represent a thorough assessment of the public health concerns raised by the Committee in its previous reports. The Committee noted that the analytical results discussed were incomplete, work on additional analyses was still ongoing, and expressed the hope that the comments provided in that letter report[6] would be helpful to NIH and the Blue Ribbon Panel as the remainder of the work to be performed was carried out.

In October of 2011, NIH provided a 1700 page "90 percent" draft of the revised risk assessment (RA) for the NEIDL to the NRC Committee for its review. (This is the penultimate draft of the document before it is released for public comment.) The Committee met in closed session on November 1, 2011 to compile its questions and comments for a discussion with the Blue Ribbon Panel and the NIH contractor team the following day, November 2. This letter report contains the NRC Committee's written comments in response to that November 2 meeting.

Statement of Task for This Letter Report

As with the Committee's previous two letter report of the same title, the statement of task for this letter report is as follows:

> The NIH will engage the Committee on Technical Input on the NIH's DSRASSA for the Boston University NEIDL at key milestones during the development of a

[5] Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University NEIDL, Phase 1: A Letter Report (2010)

[6] Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University NEIDL, Phase 2 (2010)

draft supplementary risk assessment. The NRC and the NIH Blue Ribbon Panel (BRP) will meet together in public to discuss the developing draft report. Information contained in the draft risk assessment may include data on agents, models, and scenarios; preliminary modeling results; and quantitative and qualitative assessments. Documents reviewed and discussed at these meetings will be made available to the public. Following each meeting with the BRP, the NRC Committee in closed session will prepare brief letter reports on the preliminary results of the supplementary risk analyses, focusing on whether the analyses are scientifically and technically sound in general and whether they address the public health concerns previously raised by the NRC in its review of the July 2007 DSRASSA. These letter reports will be made available to the public. The Committee will also provide written comments on the draft supplementary risk assessment when that document is made available for formal public comment. The Committee will submit its findings in the form of a final letter report that will also be made available to the public.

COMMITTEE RESPONSE TO THE NOVEMBER 2, 2011 MEETING

General comments

The 90 percent Risk Assessment draft is a substantial improvement over past documents the Committee has reviewed. Given the document's already substantial length, the Committee's comments are not meant to suggest that it would be desirable to add a great deal more text or analysis. Rather our comments are intended to present some areas in which the Committee on Continuing Assistance to NIH sees elements that might be used to improve the version that is ultimately prepared for public comment. Following a few general comments, the Committee will provide its thoughts on the individual chapters of the report.

1. This draft report is an extremely large and technically complex document. The Committee strongly recommends that both an Executive Summary written for the lay audience and a summary of Chapter 11 that synthesizes and interprets the major findings of the RA in plain language be developed to facilitate public understanding. Several of the other expansive chapters could also benefit from the addition of plain language summaries.

2. The document would be improved by including as one of its key messages a clear commitment by NIH and Boston University to encouraging and maintaining a culture of safety at the NEIDL. In addition, NIH or Boston University should periodically review the RA as new agents are introduced into the NEIDL or other significant changes are made in operating procedures. Of course the BU Institutional Biosafety Committee (IBC) and Institutional Animal Care and Use Committee (IACUC) will also review and oversee changes involving new organisms or toxins, procedures, or increased volumes of materials.

3. The Committee has reservations about the omission of a fomite "carry out" scenario in the quantitative modeling. The rationale for why this scenario is not included should, at the very least, be discussed and justified.

4. While the Committee recognizes that there are many areas for which there simply are no data to analyze for a number of the pathogens assessed, it is important that assumptions and conclusions that rely on "expert opinion" be distinguished from those that derive from data from the literature. The report would also benefit from being more transparent about what was done and for what reasons throughout.

5. The document is very difficult to navigate due to its structure and length as well as to inconsistencies in style and the use of terminology. It will be important to include many cross references so that conclusions presented in one section can be traced back to analytical discussions in previous chapters, etc.

Chapter 1: Introduction

Some of the statements included in Chapter 1 on "environmental justice" seem to imply that the major concern in this area is differences in population density among sites. It might be helpful to craft a paragraph for this chapter describing how environmental justice seeks to compare population characteristics, not just density. Other differences in environmental justice communities might include variations in host population susceptibilities to infectious agents and access to appropriate health care. The relevant factor is how much environmental justice communities differ in their ability to react if infection occurred.

Chapter 2 and Appendices A and B: Facility Design, Operation, and Site Descriptions

This chapter is readable for regulators as well as the general public. The illustrations help communicate the technology. The design as described is state-of-the-art by 2011 standards and construction appears to be compliant with all relevant standards and guidance, e.g., BMBL and Massachusetts State requirements. Oversight is described as being provided by the Institutional Biosafety Committee, which is standard. Additional oversight by the Institutional Animal Care and Use Committee, the NIH Office of Biotechnology Activities (RAC), and the NIH Office of Laboratory Animal Welfare should be mentioned, as these are important for animal and recombinant work.

Chapter 2 might be the right place for adding the recommended statement (see General Comments, above) on committing to a "culture of safety."

Training: Demonstration of competency should be instituted as a requirement for independent work in the BSL-3 or BSL-4 suites. In addition, periodic retraining and retraining after incidents such as accidents should be required. The BSL-4 simulator training is a positive aspect.

The fact that Boston University is working with the Boston Public Health Commission (BPHC, p. B-4) is a change for the better. Sustaining this partnership over the life of the facility would

be far preferable to relying on it only for establishing the ability to operate the BSL-3 and BSL-4 laboratories.

A positive note with regard to the NEIDL's current location is its affiliation with the Boston Medical Center, which has ample isolation space and provides an ability to bring point-of-care to the patient and minimize patient movement through the hospital.

Attachment B contains a number of editorial comments and minor questions from this chapter.

Chapter 3 and Appendix C: Pathogen Characteristics

This chapter and the lengthy Appendix C contain a wealth of valuable information on what is known about the pathogens assessed. But perhaps because of this great length (Appendix C is 300 pages) there is a certain lack of cohesion. The material would benefit from a clearer explanation of the state of the science and its relevance for the risk assessment. A brief introduction ("primer") to the chapter that explained the relevance of the major categories of information could be included for each pathogen. For example, an explanation of dose-response assessment that describes what is known about dose-response relationships relevant to predicting the likelihood and severity of human disease would be helpful. A common language description of principles and limitations of dose-response assessment could also help the less technically oriented reader understand the reason for the inclusion of this information in the chapter.

In addition, the epidemiological "case control" literature that refines our ideas about transmission routes and the likelihood and severity of resulting disease for some of the pathogens is not adequately incorporated into the analyses and referenced. This would enable "plausible inference" about routes of transmission rather than simply making statements such as "person to person transmission does not happen." In general, statements like this one occur throughout the document and should be softened to suggest that likelihood is small.

Again, in this chapter and throughout the document, it is important to distinguish carefully and clearly between what is based on expert opinion and what is based on data from animal models or other scientific evidence. It is also important to make clear where data do not exist and what assumptions have consequently been made and why. For example, on p. 3-71, lines 16-17, a statement is made that the RA will make probabilistic estimates of initial infection for those exposed to model-generated amounts of Tick-borne Encephalitis virus. However, there are no human dose response data for this virus, so an explanation of how such estimates can be made and what is assumed to make them is needed.

Chapter 4 and Appendices D, E, and F: Event Sequence Analysis

This chapter contains numerous tables of information about event and exposure scenarios. However, because the basis for assigning frequencies to the various exposure categories (e.g., Table 4-5 on pp. 4-10-4-11) is not clear, the Committee is not confident that we can agree with the values assigned. In several cases, the Committee definitely disagrees with the frequencies assigned. As noted above, the Committee would like to see the rationale for the exclusion of a

fomite "carry out" scenario, as this kind of event has been shown to be the source of significant problems at real labs.

Second, it is the Committee's view that real world experience would seem to indicate that the frequency of unreported punctures due to needle sticks may be much higher than the "low" category (once in 1 to 100 years) assigned (Table 4-5). Furthermore, because reporting of such an event is dependent on worker compliance, the Committee is concerned that the likelihood of a non-reporting lab worker spreading an infection may be somewhat underestimated. There is already a quote on page D-2 on why laboratory-related exposures may not be reported: "hampered by an indifference to and, frequently, an unwillingness to report these incidents" [in part] "due to fear of reprisal and the stigma associated with such events." Using a more realistic estimate of frequency and/or expansions of sensitivity analyses for this scenario could potentially strengthen this analysis.

Third, the assignment of frequency category C (1 in 10,000 to 1 million years) to the high consequence earthquake scenario, given the paucity of actual data on occurrences of large magnitude quakes on the eastern seaboard of the US, is a concern. (Note that a magnitude 5.8 quake occurred in 2011 in Virginia, where such earthquakes are conventionally thought to be highly unlikely.) The Committee recommends that the contractor at least investigate whether categorizing the latter frequency as a B (I in 100 to 10,000 years) makes a difference in the outcome.

Finally, the analysis of the probability that one or more infected animals might survive an earthquake and escape if the building collapses was not entirely convincing. This possibility is mentioned briefly at the bottom of page 4-31, and again on page 4-41 and in the appendices. Chapter 7 also suggests that infected animals could lead to pathogens becoming endemic in the local area. Could the probability that even if building containment fails catastrophically, all infected arthropods and lab animals will die rather than escape be discussed? At the very least, this and some of the other "highly unlikely" scenarios that are excluded from further consideration should at least receive attention in the form of sensitivity analyses.

Chapter 5: Transportation and Appendix G

The committee believes that the chapter on transportation is thorough and has no concerns with the content. The Committee is persuaded that following federal, state and local requirements should provide adequate means for addressing transportation issues if such should arise.

Chapter 6: Threat Assessment

The Committee is sympathetic to the difficulties of presenting a threat assessment but is concerned that this chapter will not alleviate public concern in its current form. It is frustrating to read because conclusions are not presented at the end. The chapter would benefit if it were to state clearly up front that the results of some calculations cannot be reported because of security concerns. This would at least spare the reader the frustration of finding no bottom line at the end of the chapter.

Chapter 7 and Appendix H: Environmental Persistence

The Committee agrees with the conclusions drawn about which pathogens have the potential to become established in the environment.

A "cleaned up" version of the Delphi report (Appendix H and attachments) would be valuable and should include explanations of how the information was used. Some of the data tables in the report (e.g., Attachment H-4, p.99) are not clearly labeled and their meaning is not apparent. As noted above, it is important that assumptions and conclusions that rely on "expert opinion" be distinguished from those based on data from the literature.

Chapter 8 and Appendices I, J, and K: Health Effects Following Exposure

Table 3-2B on p. 8-14: It is not clear whether the stated frequencies are for individual workers vs. workforce risk for needle stick. It appears that the risk of a needle stick event should go up with number of workers and perhaps with numbers of injections required.

The committee believes that the numbers presented in the table on p. I-10 (differential susceptibility) are optimistic and underestimate potential differences among vulnerable groups, particularly when categories are combined. For example, it is not unusual to find obesity and diabetes in the elderly, and the combination of these three factors in individual patients might dramatically change the estimates of increased vulnerability in some members of the population. It is also plausible that a pregnant woman could be both diabetic and HIV infected. Addressing the vulnerability factors one at a time may drastically underestimate susceptibility and co-morbidity. The Committee recognizes that data on such factors may be scarce. Given this, it is important that the document be completely transparent about how rigorous the estimates presented can be.

Some of the numbers in Table 5-2a on p. 8-23 are an example of false precision, e.g., $1.5X10^{-47}$, particularly when so many of the parameters have had to be estimated. Similarly, the dose response tables in appendix J (p. J-21) contain detail that may not be biologically meaningful.

Chapter 9 and Appendix L: Secondary Transmission

In general, the committee finds the modeling on secondary transmission to be satisfactory and the assumptions made in the chapter are transparent. There are, however, a number of editorial issues that it would help to address:

- There are about five different definitions of R_0 presented in this chapter and elsewhere; all are different and some are incorrect.
- The definition of "latency period" used in the document is usually what is referred to as "incubation period" elsewhere. These two parameters are not the same and only coincide when the onset of infectiousness coincides with the onset of symptoms.
- p. I-13, line 25: The assumptions that underpin the modeling methodology are clearly described. Some of these assumptions, though, are convenient approximations (e.g., the assumption that contact rates between medically vulnerable subpopulations and others are

directly and simply related to their abundance). The report would be improved if there were some discussion about how the approximations can be expected to alter (if at all) model conclusions.

- The equations in this chapter did not reproduce into the pdf version, and this must clearly be corrected before the document goes public.

Chapter 10 and Appendix M: Environmental Justice

The Committee believes that the RA team has made substantial progress in addressing environmental justice and Chapter 10 and Appendix M set out a credible and thoughtful approach to environmental justice based largely on federal and state environmental justice executive orders and policies. There is still, however, one significant short-coming in the environmental justice analysis, which is captured in lines 23 to 26 on page 10-22.

"If a member of the environmental justice community is exposed to a pathogen, there are no published data or guidance to inform the analysis of increased susceptibility to any of the 13 pathogens considered in the RA."

It is essential that the RA make a good faith effort to assess increased susceptibility to these pathogens. As noted earlier in this same chapter (page 10-19, lines 13 – 26), there is some evidence that minority communities have higher rates of hospitalization, morbidity and mortality from infectious diseases. Second, equal accessibility to health services and medical care – which would be available if the Massachusetts law is implemented – is not the same as equal utilization of health services and medical care. It is likely that environmental justice communities could have utilization barriers to medical care and health services. Third, the secondary transmission rate among environmental justice community members is a key question for community members. Citizens and the public are likely to ask about it. Questions of increased morbidity and mortality, accessibility and utilization of health services, and secondary transmission in minority communities should at least be explored in a philosophical discussion, even if current, hard data do not exist.

In the absence of data or guidance, the RA team should use the qualitative information that is available to it and, at a minimum, provide a discussion of the effects of health disparities and what these might mean in terms of transmission among, and impact to, the community. On such an important question, it is not enough to terminate all further examination in the way that lines 23 to 26 (page 10-22) now do.

Chapter 11: Risk Characterization

In general and as noted above, the Committee finds this chapter long on numerical information and short on explanations about what it all means. A summary written in plain language for the non-technical reader would improve the chapter and the report overall.

In keeping with comments made above in Chapters 4 and 8, the Committee is concerned that failure of protective equipment and failure to follow procedures on the part of personnel are underestimated in the analyses. For example, the categorization of various categories of human

error as "B" (one per 100 years or even less frequently) does not align with much of what we know about human error rates and the ability of human beings to defeat sophisticated engineering solutions. As another example, the Committee does not believe that the assumptions made about PAPR (powered air purifying respirator) failure rates on p. 11-8 are realistic. This could be addressed using a sensitivity analysis to see whether an increase has any effect on the overall assessment.

The statement on p. 11-9, lines 24-26 that an undetected needle stick would affect only one worker and is "estimated to be in frequency category B (one in 100 to 10,000 years)" is a strong statement that should be explained. (See also discussion under Chapters 4 and 8, above.) Similarly, on p. 11-27, line 31, the statement that there is "no risk of person-to-person transmission" is overly strong and in fact contradicts cases sited in chapter 3 of person to person transmission (e.g., for cutaneous anthrax). It would also be helpful to point readers to the source (in the report) of analysis and information on which conclusions about "operational information" are based (p. 11-29, line 5).

SUMMARY

As noted earlier, the Committee finds that this penultimate draft of the RA is a substantial improvement over past documents we have reviewed. In the terms in which our Statement of Task is written, the RA is now closer to reaching its goal of being "scientifically and technically sound" and, in general, addresses the concerns raised in the original NRC review of the "DSRASSA" document in 2007. While there are many approaches to preparing a risk assessment and in some aspects the Committee would have used approaches other than those found in this draft, this is no reason to fault the document. It is clear that NIH and the Blue Ribbon Panel have gone to unprecedented lengths to improve the risk assessment for the NIEDL and have made substantial advances. It is the Committee's hope that the comments in this letter report will be taken as suggestions for improving the final draft report further. We wish NIH well as it moves into the next phases of this complex process and prepares for the solicitation of public comments on the final draft. It is the Committee's view that no further advice from this group would be useful nor should it be required.

Attachment A: Committee Roster and Biographies

Committee on Continuing Assistance to the National Institutes of Health on Preparation of Additional Risk Assessments for the Boston University NEIDL

JOHN AHEARNE *(Chair)*, The Scientific Research Society, Research Triangle Park, NC
THOMAS ARMSTRONG, TWA8HR Occupational Hygiene Consulting, LLC, Branchburg, NJ
GERARDO CHOWELL, Arizona State University, Tempe, AZ
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FRANCES SHARPLES, Project Director
ORIN LUKE, Senior Program Assistant

Committee Biographies

John Ahearne (chair) is Executive Director Emeritus of Sigma Xi, the Scientific Research Society, and Emeritus Director of the Sigma Xi Ethics Program. Prior to 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 U.S. 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 U.S. 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 the safety and regulation of nuclear power. Dr. Ahearne has served on many NRC Committees in the past twenty years, and has chaired a number of these, 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. He is a Fellow of the American Academy of Arts and Sciences, the

American Physical Society, the Society for Risk Analysis, and the AAAS. In 1966, Dr. Ahearne earned his Ph.D. in Physics from Princeton University.

Thomas W. Armstrong retired in 2008 from his position as Senior Scientific Associate in the Exposure Sciences Section of ExxonMobil Biomedical Sciences, Inc., where he worked since 1989. Dr. Armstrong also worked with the University of Colorado Health Sciences Center as the lead investigator on exposure assessment for epidemiological investigations of potentially benzene-related or other occupational exposure-related hematopoietic diseases in Shanghai, China. Dr. Armstrong also spent nine years working for the Linde Group, as both the manager of loss control in the gases division and as a manager of safety and industrial hygiene. Dr. Armstrong conducted research on quantitative risk assessment models for inhalation exposure to Legionella, and remains professionally active on that topic. He has recently contributed to publications on mathematical models to estimate exposures to hazardous materials, and methods for exposure reconstruction. He was a member of the Society for Risk Analysis and remains an active member of the American Industrial Hygiene Association. The American Board of Industrial Hygiene certifies him as an Industrial Hygienist. Dr. Armstrong has an M.S. in Environmental Health and a Ph.D. in Environmental Engineering from Drexel University.

Gerardo Chowell is an Assistant Professor at the School of Human Evolution and Social Change at Arizona State University. Prior to 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 in quantifying the effects of public health interventions. His research interests include agent-based modeling, model validation, and social network analysis. Dr. Chowell received his Ph.D. in Biometry from Cornell University and his engineering degree in telematics from the Universidad de Colima, Mexico.

Margaret E. Coleman is a medical microbiologist, risk analyst, and sole proprietor of Coleman Scientific Consulting. She serves as president of the Upstate NY Society for Risk Analysis (SRA) and in other leadership roles, including her appointment to the Editorial Board for the journal *Risk Analysis*. Also an active member of the American Society for Microbiology (ASM), she contributed an article to ASM's *Microbe* (*Microbial Risk Assessment Scenarios, Causality, and Uncertainty*). Ms. Coleman contributes to peer review processes for several journals, including SRA's journal *Risk Analysis*. She was selected as an invited expert at three recent workshops on microbial dose-response assessment and served as a reviewer for two NRC Reports (*Reopening Public Facilities After a Biological Attack; Evaluation of the Health and Safety Risks of the New USAMRIID High Containment Facilities)* and as a Committee member on the *Review of Testing and Evaluation Methodology for Biological Point Detectors*. Her recent consulting work includes qualitative and quantitative risk assessments for biothreat agents and related non-pathogenic species by inhalation, dermal, and oral exposure routes. Ms. Coleman earned her B.S. degree from the SUNY College of Environmental Science and Forestry/ Syracuse University and M.S. degrees from Utah State University and the University of Georgia in Biology/Biochemistry and Medical Microbiology.

Gigi Kwik Gronvall is a Senior Associate at the Center for Biosecurity of University of Pittsburgh Medical Center (UPMC) and Assistant Professor of Medicine at the University of Pittsburgh. An immunologist by training, Dr. Gronvall's work addresses how scientists can diminish the threat of biological weapons and how they can contribute to an effective response against a biological weapon or a natural epidemic. She is a term member of the Council on Foreign Relations and also serves on the American Association for the Advancement of Science (AAAS) Committee on Scientific Freedom and Responsibility. Dr. Gronvall is a founding member of the Center for Biosecurity of UPMC and, prior to joining the faculty in 2003, she worked at the Johns Hopkins University Center for Civilian Biodefense Strategies. From 2000-2001 she was a National Research Council Postdoctoral Associate at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Fort Detrick, Maryland. Dr. Gronvall earned a Ph.D. 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 both bacterial virulence factors and host immune functions at the molecular level using the tools of bacterial genetics and mouse molecular immunology. These studies investigate the effects these molecular-level activities may have on the population-level behavior of infectious diseases. Dr. Harvill has served on several NRC 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 for *Infection and Immunity*. Dr. Harvill has reviewed proposals for six different National Institutes of Health study sections, the U.S. Department of Agriculture and multiple international funding organizations. He has organized international and local meetings and chaired sessions at annual meetings of both the American Association of Immunologists and the American Society for Microbiology. He earned his Ph.D. at the University of California, Los Angeles.

Barbara Johnson has over 15 years of experience in the U.S. Government in the area of biosafety, biocontainment and biosecurity, and currently owns the consulting company Barbara Johnson & Associates, LLC. Dr. Johnson has managed the design, construction and commissioning of a BSL-3 Aerosol Pathogen Test Facility, and she launched the U.S. Government's first chemical and biological counterterrorism training facility. Research areas include biological risk assessment and mitigation, testing the efficiency of respiratory protective devices, and testing 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 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 Co-editor of the journal Applied Biosafety.

Paul A. Locke is an Associate Professor in the Department of Environmental Health Sciences (EHS) 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 is a member of the Board of Directors of the National Council on Radiation Protection and Measurements (NCRP) and

chaired the NCRP's 2010 annual meeting program Committee. From 2004 until 2009 he was a member of the NRC Nuclear and Radiation Study Board, and has participated on two NRC 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 M.P.H. from Yale University School of Medicine, a J.D. from Vanderbilt University School of Law, and a Dr.P.H .from the Johns Hopkins Bloomberg School of Public Health. He directs the EHS doctoral program in Public Health.

Warner North is President of NorthWorks, Inc., a consulting firm in Belmont, California. Dr. North is also a consulting professor in the Department of Management Science and Engineering at Stanford University. Over the past 40 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 Science Advisory Board of the Environmental Protection Agency since 1978, and as a presidentially appointed member of the U.S. Nuclear Waste Technical Review Board. Dr. North has served as a member of the NRC's Panel on Public Participation in Environmental Assessment and Decision Making and on numerous NRC Boards and Committees, twice as Committee Chair. Dr. North is a past president of the International Society for Risk Analysis, a recipient of the Frank P. Ramsey Medal from the Decision Analysis Society for lifetime contributions to the field of decision analysis, and a recipient of the Outstanding Risk Practitioner Award from the Society for Risk Analysis.

Jonathan Richmond is CEO of Jonathan Richmond and Associates, a biosafety consulting firm with a global clientele. Prior to 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 ten years as a research virologist, and has been involved in the field of biosafety for the past 25 years. He has authored many scientific publications in microbiology, chaired many national symposia, edited numerous books, 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 School of Veterinary Medicine at University of Pennsylvania. He has a secondary appointment in the Department of Biostatistics and Epidemiology at the University of Pennsylvania'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 Penn's Institute for Strategic Threat Analysis and Response. His research deals with the epidemiology and population dynamics of infectious disease in humans as well as wild and domestic animal species. He has extensive experience of mathematical modeling in the context of infectious and parasitic disease control strategies (including the evolution of drug resistance) and has published case-control studies on a range of infectious diseases of animals and humans. Dr. Smith served on an FAO/WHO Expert Committee on the implementation of farm models in the developing world; he served on the Pennsylvania Food Quality Assurance Committee, and he was a member of a European Union

Expert Committee on Bovine Spongiform Encephalopathy risk. 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 Bachelors degrees in Zoology and Education from the Universities of Oxford and Cambridge respectively and a D.Phil. in Ecology from the University of York.

Attachment B: List of Editorial Comments

Chapter 1

p. 1-17, line 30: "Reasonableness" may not be the best descriptor; wouldn't "rigor" be a better term?

p. 1-20, line 15: Are the worker populations at the respective sites truly "equal"? Is there any intent to pursue local hiring in preference to other approaches?

Chapter 2

p. 2-6, line 18: "*Biomolecule Production Core.* This operational service is responsible for developing SOPs for propagation and titration of all BSL-4 pathogens that will be used in the NEIDL."

Not clear why the Biomedical Production Core will develop SOPs for titration of BSL-4 pathogens. Is this not a normal practice for the researchers?

P.2-7, line 19: "*Specimen Processing Core.* This service supports NEIDL investigators in studying emerging infectious diseases by handling the collection and storage of animal specimens and cultures in the appropriate biocontainment setting (e.g., BSL-2, BSL-3)."

Who will be responsible for the storage of BSL-4 materials, and where will that be done?

p.2-8, line 11: "The BAS controls or monitors environmental and other 11 operational parameters (temperature, humidity, flow, and pressure values) for individual areas or 12 rooms, fire suppression, and liquid waste treatment."

Will the BAS also control the lighting in animal rooms?

P.2-10, line 7: "All electrical conduit, plumbing, piping, supply and exhaust ducts and miscellaneous 7 penetrations are sealed at the point of penetration into the high biocontainment laboratories (BSL-3 and BSL-4)."

"High containment" = BSL-3; "maximum containment" = BSL-4. This should be used throughout the report.

P.2-12, line 4: "In general, biological indicator vials are placed inside biocontainment bags containing the material to be processed in the autoclave. If the autoclave does not reach the programmed temperature, the spores will subsequently grow, and change the color of a pH-sensitive chemical in the growth medium."

Consider the following: In order to incubate the biological indicator, it has to be removed from the biohazard bag. If the spores should grow (indicating incomplete decontamination), then someone (plus the local area where the bag was opened outside of containment) will be

potentially contaminated. This is why the biological indicator is placed in "dummy" bags to mimic the contents of the biohazard bag.

p. 2-12, line 26: "A Class III BSC, is illustrated in Figure 2-4."

Figure 2-4 is a centrifuge; a Class III BSC is not shown. This figure is also referred to (appropriately) in the next section on centrifuges. The figure should be moved and a picture of a Class III BSC added at Figure 2-4.

P.2-14, line 10: "Ultra-low temperature freezers (Figure 2-5) provide long-term protection and storage for valuable samples of biohazardous materials."

An important feature (not mentioned in the draft report) is that such storage freezers need to be equipped with locks for biosecurity.

p. 2-16, line 29: "The IBC coordinates its application procedures with two other offices, Research Occupational Health Program (ROHP), to ensure that research personnel have adequate occupational health monitoring, training on safe work practices, exposure control emergencies, and use of PPE."

What is the second office? Only ROHP is listed.

p. 2-17, line 12: **2.1.4.3 Standard Operating Procedures and Training**

Generic question: Who reviews/approves SOPs?

p. 2-19, line 15: "Such materials are biological samples needing further analysis…"

What is the SOP for removing samples "for further analysis"? Where will that be done? Will they be irradiated? It would be helpful to describe this.

Appendix A

p. A-6, lines 4-8: Several of the items referenced are not "codes," but "guidelines" based on best practices and principles of biocontainment.

p. A-10, line 18: "… (e.g., an escape bottle air apparatus)."

Please describe.

p. A-18, line 8: "Work being performed within high-level biocontainment areas will be monitored by systems to ensure that at least two authorized persons are in each area at all times to ensure safety and minimize risk of an individual initiating a malevolent or unauthorized act."

Excellent procedure.

p. A-26, line11-12: “Gas decontamination will be considered for large pieces of equipment (e.g., penning, BSCs, carts) because gases pass between barriers of biocontainment.”

This does not make sense. Please clarify.

Chapter 3

p. 3-15, line 7- 8: “The disease occurs worldwide and in the US in animals. There are a significant number of naturally occurring cases reported in the US annually.”

The first sentence should be reworded as follows: “The disease occurs in animals worldwide and in the US.”

What does “significant” mean? Can a specific number or range be provided?

p. 3-17, line 24-25: “A vaccine was available for both military and civilian use that was offered to laboratory workers; however, currently, there are no FDA-approved vaccines available for *F. tularensis*.”

This sentence suggests that the vaccine for laboratory workers is no longer available, but this is not the case. A non-FDA approved tularemia vaccine is still available for lab workers from the special Immunizations Program at Fort Detrick, MD.

Chapter 9

Case fatality rate (CFR) should be used instead of mortality rate in the discussions in this chapter.