NIH Blue Ribbon Panel to
Advise on Risk Assessment for the BU
National Emerging Infectious Diseases Laboratory

Findings and Recommendations

Phase I: Risk Assessment

Advisory Committee to Director, NIH
June 6, 2008

Background

- In 2003, following a peer-review process, Boston University Medical Center (BUMC) was awarded a grant from the National Institute of Allergy and Infectious Diseases (NIAID) for the construction of a national biocontainment laboratory (NBL), known as the National Emerging Infectious Diseases Laboratories (NEIDL)
- The NBL would provide essential infrastructure for congressionally mandated programs of biodefense research
    - Including comprehensive, state-of-the-art biosafety level 2, 3, and critically needed biosafety 4 (BSL-4) research space
- Purpose of the NBL:
  - To assist national, state and local public health efforts in the event of an infectious disease emergency or an act of bioterrorism
  - To serve as a national resource for conducting biodefense research

Background

- Prerequisites to the facility's construction
  - BU prepared a Final Environmental Impact Report (FEIR) in accordance with the Massachusetts Environmental Policy Act (MEPA)
  - NIH completed a Final Environmental Impact Statement (FEIS) for the NEIDL (December 05) and published a Record of Decision (February 06) in accordance with the National Environmental Policy Act (NEPA)
- Law suits filed in State court (July 05) and Federal court (May 06) to stop construction and operation of the NEIDL

Background

- In July 06, the Massachusetts Superior Court held that the BU FEIR failed to:
  - Consider any "worst case" scenario "involving accidental or malevolent release of a highly contagious pathogen"
  - Analyze whether the "worst case" scenario would be materially less catastrophic if NEIDL located in a less densely populated area
- Judge voided the State Agency's approval of the FEIR and the State Agency required BU to submit a supplemental FEIR to address these shortcomings

Background

- Federal court requested that the agency address: "Public health consequences of the accidental release of communicable Category-A [including BSL-4] pathogens"
- In response to concerns raised by the court and public comments, NIH published for public comment Draft Supplementary Risk Assessment and Site Suitability Analysis (DSRASSA) of the NEIDL (July 07)
  - Focused primarily on potential impacts of the release of several BSL-4 agents into the community under various scenarios
- Viewing the DSRASSA as potentially relevant to its decision-making process, the State Agency asked the NRC to analyze the draft report
- In November 2007, NRC issued a report highly critical of the analytic approach used in the DSRASSA

Establishment of Blue Ribbon Panel

- To guide the agency in responding comprehensively to the judicial requests and public concerns, NIH established the Blue Ribbon Panel in March 2008 as a Working Group of the ACD:
  - 16 members
  - Expertise in ID, public health and epidemiology, risk assessment, environmental justice, risk communications, biodefense, biosafety, and ID modeling
- Panel's Two-fold charge:
  - The scope of any additional risk assessments that might be necessary (Phase I)
  - Ways to enhance community relations and effective risk communication (Phase II)

See Appendices 1 and 2

Phase I Tasks

- Determine what additional studies are needed to assess potential risks and public health consequences of:
  - Accidental and malevolent releases of infectious agents
  - Exposure to infectious agents in urban versus less populated locations
  - Define the key elements of studies:
    - Infectious agents
    - Scenarios
    - Methodologies
- Review of strategies to minimize chances of release and to mitigate potential public health consequences
- Address concept of "worst case"
  - Define term
  - Develop and analyze cases

See Appendix 3

Panel's Approach

- Reviewed background materials:
  - Previous studies
  - Judicial materials
  - Safety and emergency preparedness plans
  - Epidemiologic and demographic data
  - Public input
- Explored analytic approaches with the National Research Council Committee

NIH Asks for Input from NRC

- To further inform the Panel's analysis, the NIH commissioned the NRC committee that reviewed the DSRASSA to suggest approaches to risk assessment
- April 2008 NRC report noted that:
  - BSL-4 facilities have been operated safely in both urban and rural settings
  - Selection of sites for high-containment labs should be supported by detailed analyses and transparent communication of information regarding possible risks
- Panel and NRC met May 2nd to discuss NRC report
  - NRC specific conclusions similar to the Panel's, validating its emerging findings

Phase I: Overarching Recommendation from Blue Ribbon Panel

- **Additional studies should be performed to address judicial requests and public concerns:**
  - **Use proven methods and reflect known epidemiologic data**
  - **Clearly describe methods, sensitivity of methods, assumptions, final results, and interpretation of results**
  - **Take into account characteristics of the surrounding communities**

See Appendix 4

Agents for Study

Agents for Study: Key Attributes

- **Intrinsic agent attributes:**
  - Infectivity (primary infection rate, primary routes of human infection)
  - Transmissibility (including secondary and tertiary transmission)
  - Incubation period
  - Infection period
  - Pathogenicity
  - Mortality rate
  - Reservoirs (if known)
  - Vectors (if known)
  - Availability and efficacy of treatments

Agents for Study: Key Attributes

- **Extrinsic attributes:**
  - Relevance to the site locations (actual and alternatives), especially in terms of reservoirs and vectors
  - Extent of epidemiologic data
  - Availability of sound models for a given infectious disease
  - Degree to which an agent is recognized as a public health concern
    - For example, designation as
      - BSL-3 Agent
      - BSL-4 Agent
      - Category A Agent
      - Select Agent

Recommendation: Agents for Study

- **Agents to be studied should include those that are:**
  - **Highly transmissible, highly pathogenic, and higher case fatality rate**
  - **Highly transmissible, pathogenic, and lower case fatality rate**
  - **Poorly transmissible but highly pathogenic, and higher case fatality rate**
  - **Vector-borne and relevant to the sites to be assessed**
- **Sufficient epidemiologic data should be available**
- **Agents should be recognized public health threats**
  - **i.e., designated as a select agent or category A agent, likely to be studied in the NEIDL, and/or otherwise recognized by the public as an agent of concern.**

See Appendices 5, 6, and 8

Recommendation: Agents for Study

(See Appendices 5 , 6 and 8)

- **Risk assessments should be done for the following agents:**
  - **1918 pandemic influenza virus**
  - ***Yersinia pestis***
  - ***Francisella tularensis***
  - ***Bacillus anthracis***
  - **SARS-associated coronavirus**
  - **Rift Valley fever virus**

  BSL 3

  - **Andes hantavirus** — **BSL 3 or 4**

  - **Junin haemorrhagic fever virus**
  - **Tick-borne encephalitis complex (Russian spring-summer encephalitis) virus**
  - **Lassa fever virus**
  - **Marburg virus**
  - **Ebola virus**

  BSL 4

NOTE: Agents in RED are CDC and/or NIH Category A Agents and/or Select Agents

Scenarios for Study

Recommendation: Scenarios

- Scenarios should:
  - Be scientifically accurate and credible
  - Be realistic
    - Relate to a real case if possible
    - Include agents that are recognized as a public health concern
  - Include releases of infectious agents into the community that are representative of what could occur through:
    - Accidental release
    - Malevolent action

See Appendices 7

Recommendation: "Worst Case" Scenarios

- State court requested evaluation of "worst case" scenario that involves "risk of contagion arising from accidental or malevolent release of a contagious pathogen."
  - Concept of "worst case"
    - Intuitively understood but highly subjective notion
      - Therefore "worst case" is a discredited term in the field of risk assessment (e.g., nuclear reactor safety)*
  - Variations of the scenarios will address underlying concept: "highly unlikely but still credible high consequence event" *

*Note: NRC Report, May 2008

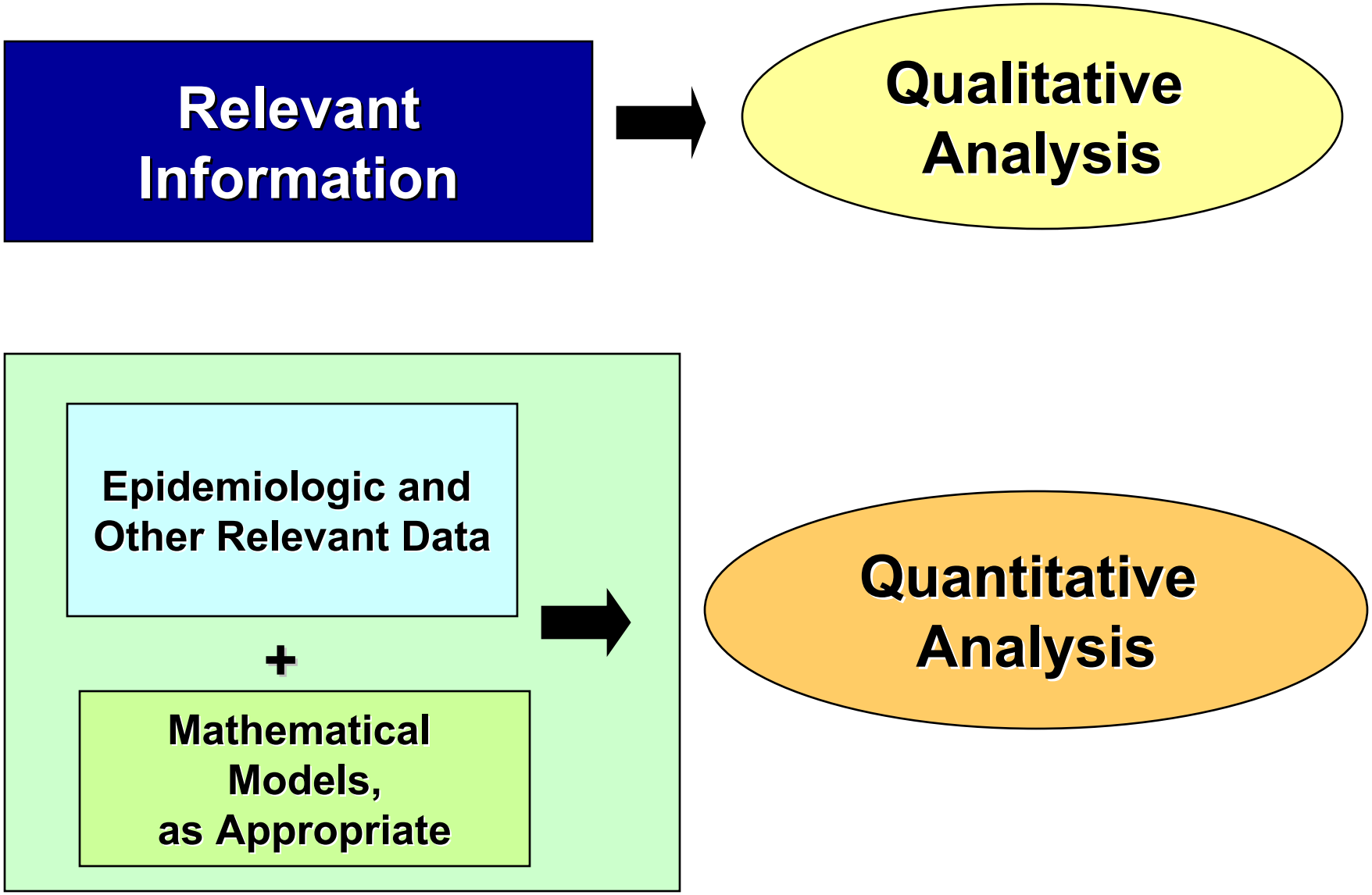
Type of Scenario	Examples	Sources
Mechanical or Power Failure	Lab Equipment failure	NRC
	Loss of power	Public
	Malfunction of solid and liquid waste disposal systems	Public
Transportation Accident	Transportation Accident	Federal Court
Security Failure	Site security failure	NRC
	Personnel security failure	NRC
Exposure via Fomites or release of Vectors	Fomites bearing transmissible agents	Public
	Vector-borne agent release	NRC, Public
Human Errors	Procedural errors resulting in inadvertent infection (e.g., mislabeled tubes)	NRC, Public
	Infection not diagnosed early and spreads in community, esp. via public transportation	Public
Malevolent Actions	Malevolent actions	NRC, State Court
	Suicide bomber/airplane attack/truck with explosives/fire	Public
	Disgruntled or deranged lab worker spreads agents in	Public

Methodology and Analyses

Recommendation: Analyses

- **Qualitative analyses:**
  - Should be conducted for all agents and scenarios
- **Quantitative analyses:**
  - Should also be performed in all cases for which sufficient epidemiologic data and validated mathematical models are available
- **Analyses should:**
  - Use proven methods and reflect known epidemiologic data
  - Take into account characteristics of the surrounding community
  - Be transparent regarding any assumptions made and sensitivity of analyses

Methodologies to Assess Consequences of a Release/Exposure Event



Recommendation: Analyses

- Analyses should address:
  - Risk of agent release
  - Probability of occurrence
  - Any uncertainty in critical parameters used
  - For any value selected for use, the range of published values
  - Available public health interventions
  - Comparative risks at urban, suburban, and rural sites
  - What happens when safety measures and emergency plans do and don’t work

Next Steps

- Pending ACD recommendations and ultimate decision by the NIH Director, any additional risk assessment studies will be carried out in the latter half of 2008.
- Blue Ribbon Panel will:
  - Evaluate the progress of the risk assessment studies
  - Analyze risk mitigation and emergency preparedness strategies currently in place
  - Examine the scope and implications of Boston municipal restrictions on rDNA BSL-4 research
  - Identify strategies for enhancing community engagement and community relations, public trust, and risk communications
- The Panel will address these matters over the course of the summer and fall and will present to the ACD during its December 2008 meeting

Questions for Discussion

- Does the ACD agree with the Blue Ribbon Panel recommendations regarding:
  - Agents for Study?
  - Scenarios for Study?
  - Analytic Methodologies for Studies?

- Are there additional elements that should be included in these studies?

Appendix 5:
Overview of Agents Recommended for Study

Designations of Agents

- BSL-3 agents – Agents that must be worked with under Biosafety Level 3 containment conditions because they have a known potential for aerosol transmission, may cause serious and potentially lethal infections, and are indigenous or exotic in origin
- BSL-4 agents – Agents that must be worked with under Biosafety Level 4 (the highest) containment conditions because they are exotic agents that pose a high individual risk of life-threatening disease by infectious aerosols and for which no treatment is available
- Category A agents – Agents that, according to NIH or CDC classification, pose a risk to national security because they can be easily disseminated or transmitted from person to person; result in high mortality rates and have the potential for major public health impact; might cause public panic and social disruption; and require special action for public health preparedness
- Select Agents – Agents subject to CDC and/or USDA rules governing the transportation, possession, and use by virtue of having the potential to pose a severe threat to public health and safety

Agent	BSL	SA	Cat A	Attributes	R_0	R_X	Vector-borne Reservoir (rural/urban)
SARS-associated coronavirus	NIH Guideline: RG2 (corona viruses) BMBL: BSL-3 (propagation) BSL-2 (treated diagnostic samples) BSL-2+ (untreated diagnostic sample)	–	–	High transmissibility (respiratory) High morbidity High mortality (global CFR ~15%, 6.8% patients<60 yrs, 55% patients >60 yrs)	2-3 (excludes super-spreading events)	–	Not vector-borne Reservoir: closely-related coronaviruses in civet cats and bats: urban (animal markets in China)
Reconstructed 1918 influenza virus	NIH Guideline: RG2 (influenza viruses) BMBL: BSL-3+	√	–	High transmissibility (respiratory) High morbidity (~30% world population infected in 1918) High mortality (CFR>2.5%, [<0.1% for other flu pandemics[~50 million total deaths, peak death rates in young adults 20-40 yrs)	2-4 (community-based settings) 2-10 (confined settings)	√	Not vector-borne No reservoir

Agent	BSL	SA	Cat A	Attributes	R_0	R_X	Vector-borne Reservoir (rural/urban)
Bacillus anthracis	NIH Guideline: RG2 BMBL: BSL-2; BSL-3 practices for production quantities, high concentrations, powders	√	NIH CDC	No human-to-human transmission Transmissibility—Low 95%of cases are cutaneous Mortality—cutaneous form low with treatment, 20% if not treated; high mortality (45%) for pulmonary High morbidity	Not known (NK)	√	Not vector-borne Reservoir—rural; soil bacterium
Reconstructed 1918 influenza virus	NIH Guideline: RG2 (influenza viruses) BMBL: BSL-3+	√	–	High transmissibility (respiratory) High morbidity (~30% world population infected in 1918) High mortality (CFR>2.5%, [<0.1% for other flu pandemics[~50 million total deaths, peak death rates in young adults 20-40 yrs)	2-4 (commu-ity-based settings) 2-10 (confined settings)	√	Not vector-borne No reservoir

Agent	BSL	SA	Cat A	Attributes	R_0	R_X	Vector-borne Reservoir (rural/urban)
Rift Valley fever virus	3	√	NIH	No human-human transmission. Primarily of agricultural concern (high M&M in sheep and cattle) 1º transmission thru infected animal blood (contact and aerosol) and unpasteurized milk, 2º thru arthropods Low to moderate morbidity in humans (1ºrequires vertebrate reservoir, 2ºasymptomatic to mild infections Low mortality (overall <1%)	NK	(√) DoD vaccines (unavail.)	Vector: 1º mosquito, other arthropods possible Rural reservoir: vertebrates (herds--1º reservoir unknown).
Francisella tularensis	3	√	NIH CDC	No human-human transmission Low morbidity Low mortality (4% with trt)	NK	√	Rural vector: blood-feeding arthropods

Agent	BSL	Select Agent	Cat A	Attributes	R_0	R_X	Vector-borne Reservoir (rural/urban)
Yersinia pestis	3	√	NIH CDC	No human-human transmission. Low to moderate rodent-human transmission (flea-borne); direct contact with infected tissue or fluid, respiratory droplets High morbidity High mortality (50-90% untreated); low to moderate (15% treated)	2°= 1.3	√	Vector-borne Rural reservoir (wild rodents) Urban reservoir (commensal rats)
Andes hantavirus (bunyavirus)	RG3 BSL-2-4 Depending on work	–	NIH	Causative agent of hantavirus pulmonary syndrome & hemorrhagic fever with renal syndrome High transmissibility (aerosol) in lab & wild. Some evidence of human-human transmission. Moderate to high morbidity High mortality (30-50%)	NK	–	Not vector-borne Rural reservoir: many species new world mice. Transmitted in rat excreta or saliva. Can occur in urban areas bordering rural areas.

Agent	BSL	SA	Cat A	Attributes	R_0	R_X	Vector-borne Reservoir (rural/urban)
Lassa fever virus (arenavirus)	4	√	NIH CDC	High transmissibility in endemic areas (1º rodent-human) and 2º low transmissibility for human-human during viremia; requires close blood contact. Requires close contact with rats or ingestion of rat meat. Low to moderate morbidity (~80% mild, 20% severe) Low to moderate mortality (1-15% with trt, 12-23% without trt)	NK	√ Anti-viral	Not vector-borne Reservoir: single species of rat endemic to W. Africa (predominantly rural; virus transmitted in rat excreta)
Junin South American Haemorrhagic fever virus (arenavirus)	RG4 BMBL: BSL-4 (3 with vaccine)	√	NIH CDC	High transmissibility in endemic areas (1º rodent-human) and 2º low transmissibility for human-human during viremia; requires close blood contact. Low to moderate morbidity (90% mild, 10% severe) Low to moderate mortality (1-2% with trt, 15% without trt)	NK	√ Drugs Vacc. in trials	Rural reservoir: one genus of rodent endemic to Argentina. Transmitted in rat excreta, 1º occupational exposure (agricultural)

Agent	BSL	SA	Cat A	Attributes	R_0	R_X	Vector-borne Reservoir (rural/urban)
Tick-borne encephalitis virus (RSSE) (flavivirus)	RG4 BSL-4	√	–	1º transmitted by arthropods, 2ºunpasteurized milk from infected animals Low to moderate morbidity (5% severe) Low to high mortality (5-35% without trt, 1-2% with trt)	<1 (TBE, non-systemic trt) ~1.3 (systemic trt)	(√) Vacc.	Vector-borne: one genus of tick endemic to far eastern Russua, China, Japan Rural and urban reservoir (if near sylvatic areas): vertebrate (rodent?)
Marburg virus	RG4 BSL-4	√	NIH CDC	Poorly transmissible (direct contact with infected blood, bodily fluids) High morbidity High mortality (CFR 23% in 1967 Europem 83% 1998 DRC, 90% 2004 Angola), 55% Sudan EBOV)	NK	–	Not vector-borne Rural reservoir (suspected): fruitbats
Ebolavirus	RG4 BSL-4	√	NIH CDC	Poorly transmissible High morbidity High mortality (CFR 95% Zaire EBOV, 55% Sudan EBOV)	NK	–	Not vector-borne Rural reservoir: fruitbats suspected