Report of Pneumonic Tularemia in Three Boston University Researchers

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Forward

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This report gives a comprehensive overview of the 2004 tularemia outbreak at Boston University. The issues contained in this report highlight the need for additional City-wide safety measures to prevent the recurrence of such an event. The growth in the number of laboratories in the City working with potentially hazardous organisms and substances, including the increase in the amount of research involving Select Agents, requires new and expanded governmental oversight at multiple levels.

Discussion about how best to achieve the proper level of monitoring and oversight must involve officials at the local, state and federal level. However, even while such discussions are proceeding, BPHC believes that positive action steps should be undertaken at a local level to insure the health and safety of microbiology research laboratory workers and the greater Boston community. In the coming weeks and months the Commission will do the following:

1. Develop and implement new mandatory guidelines on the monitoring and reporting of occupationally acquired infectious disease illness among microbiology research laboratory workers.
2. Develop and implement mandatory procedures for the public health response to reported occupationally acquired infectious diseases.
3. Identify a public health worker to monitor practices in microbiology research laboratories, particularly those working with the most dangerous organisms and toxins.
4. Develop and offer a mandatory educational training for Institutional Biosafety Committees, Human Resources, and Occupation Health personnel responsible for ID research laboratories
5. Solicit the input of laboratory science and infectious disease experts to consider specific policy and regulatory changes regarding laboratory operations, including but not limited to the criteria for specimen acceptance, periodic verification of the organism's virulence, storage, chain of custody, and sharing of specimens with other research labs.
6. Closely monitor the internal progress made at BU to strengthen infection control practices in its laboratories.

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Summary

In November 2004, three cases of tularemia (1 confirmed, 2 probable) were reported to the Boston Public Health Commission (BPHC). All three cases occurred in laboratory researchers who believed they were working with the Live Vaccine Strain (LVS) of *Francisella tularensis*, the organism that causes tularemia. The LVS strain of *F. tularensis* is an attenuated form of the bacterium not previously associated with human illness. The first two cases became ill in May; the third in September, 2004. Laboratory testing by the Centers for Disease Control and Prevention (CDC) in late November, 2004 showed that the LVS stock used by the BU researchers was contaminated with Type A tularemia, a wild-type, virulent form of the organism. Because of their potential for use as bioterrorism agents, Type A and B tularemia are classified as Category A agents by the CDC, and their use is restricted to CDC - approved select agent programs. These programs must have facilities with appropriate safeguards and security in place. An investigation was conducted by the BPHC, the Massachusetts Department of Public Health (MDPH), and the CDC. Review of the BSL2 laboratory where research was conducted and interviews with research personnel revealed inconsistencies in laboratory safety practices, but the source of the Type A tularemia has not been identified to date. Outside Boston, the investigation into the source of the wild type tularemia is ongoing, and results of additional CDC tests and investigations are pending.

I. Introduction

Tularemia is a zoonotic bacterial disease, caused by the bacterium *Francisella tularensis*, a small, gram-negative coccobacillus. Tularemia can have various clinical manifestations depending on the route of introduction and the virulence of the organism. Primary pneumonic tularemia results from inhalational exposure and though uncommon, is considered the most severe form of disease with mortality rates as high as 30-60% if untreated. Disease onset is abrupt, characterized by fever, chills, malaise, low back pain, myalgias, and pleuritic chest pain. The incubation period is 1-14 days, averaging 3-5 days. Human to human transmission has not been documented.[1]

There are two types of *F. tularensis*: Type A and Type B, distinguished by virulence and other biochemical properties. Type A is more virulent than Type B. The live vaccine strain (LVS) of *F. tularensis* is a Type B, further attenuated strain of *F. tularensis* not previously associated with human disease. Type A and B *F. tularensis* are classified as select agents by the CDC, which regulates the possession of biological agents and toxins that have the potential to pose a severe threat to public health and safety. The exception to that is the LVS strain of *F. tularensis* which is not a select agent. Recommendations differ regarding the level of laboratory safety practices required when working with cultures of LVS. However, biosafety guidelines mandate that any laboratory work involving manipulation of Type A or Type B tularemia be performed using BSL3 level precautions.

On November 10, 2004 the Boston Public Health Commission was notified that three Boston University researchers working with tularemia had been ill in 2004, with symptoms consistent with pneumonic tularemia. Two became ill in May, and the third in September. All three had worked with what they believed to be the live vaccine strain (LVS) of tularemia in conjunction with vaccine development research. Subsequent serologic testing by the Massachusetts State Laboratory Institute (SLI) confirmed the presence of antibodies to tularemia in the three cases, a key step in diagnosis. BPHC investigated the implicated laboratory, interviewed laboratory personnel, and reviewed research documents and practices related to *F. tularensis* at the Boston University laboratory to determine the source of illness and introduce appropriate control measures.

II. Initial Plan for Investigation and Control

A collaborative investigation was conducted by the Boston Public Health Commission (BPHC), Massachusetts Department of Public Health (MDPH) and the Bacterial Zoonoses Branch of the Division of Vector-borne Infectious Diseases, Centers for Disease Control and Prevention (CDC). On November 12, a conference call with representatives from Boston University (BU), BPHC, MDPH, the CDC, and the Boston

[1] Tularemia as a Biological Weapon: Medical and Public Health Management. JAMA 2001 285: 2763-2773

field office of the Federal Bureau of Investigation (FBI) agreed on initial response measures, including the following:

(1) immediate stoppage of all work conducted using tularemia;
(2) review of research protocols and safety measures in place at the BU laboratory where the workers had become ill;
(3) tularemia specimen submission to CDC for further testing and analysis;
(4) survey of all available personnel working in the vicinity of the implicated tularemia laboratory regarding laboratory practices, illness, and other risk factors for tularemia; and
(5) voluntary serologic testing among laboratory personnel for evidence of tularemia infection.

III. Case Investigation and Surveillance for Other Cases

Methods

A BPHC public health nurse interviewed the three reported tularemia cases. Medical records for the three cases were obtained and reviewed for clinical information. Information collected included presentation of illness, duration of illness, treatment, and outcomes.

To identify any other potential cases among laboratory workers, BPHC requested that BU provide records of absenteeism among workers in the implicated infectious disease laboratory. In addition, the Boston University Occupational Health Center monitored laboratory workers for any subsequent reports of illness.

In this investigation, a case was defined according to CDC guidelines:

- a case is *probable* if the case is clinically compatible with laboratory results indicative of presumptive infection

- a case is *confirmed* if it is a clinically compatible case with confirmatory laboratory results

Results

All three cases reported working directly with tularemia. Clinical information describing disease progression was obtained from health providers, and symptomology was similar among cases. All three were treated with antibiotics and recovered. Tularemia infection was not diagnosed by any of the treating physicians, none of whom were associated with the BU Occupational Health Center. Since tularemia is not transmitted person-to-person, secondary cases in laboratory or non-laboratory contacts of the cases were not expected and were not found.

IV. Epidemiologic Survey

Methods

From November 23 to December 9, 2004, all available laboratory researchers and personnel working in the vicinity of the 6th floor laboratory where tularemia research was conducted were interviewed by the BPHC using a standardized survey. The survey included questions on health history, including previous pneumonia and symptom history during the time period when tularemia was being manipulated in the laboratory. Specifically, personnel were asked if they had developed symptoms consistent with tularemia infection for a period of 72 hours or greater between May 1st and November 15th, 2004. Respondents were also asked about possible environmental exposures, travel history, including visits to Martha's Vineyard and other areas known to have endemic tularemia. Information was also collected on laboratory practices and safety procedures when working with *F. tularensis*, and general laboratory safety measures for all laboratory activities.

Results

The Infectious Disease Laboratory on the 6th floor of the Evans Biomedical Research Building is a site for research conducted by Boston University students, employees, and Boston Medical Center clinicians. At the time of the investigation, BU reported that a total of 77 people worked on the floor in some capacity. BPHC interviewed 62 researchers and administrative staff, including all seven of the researchers directly involved in the tularemia research. Of the 62 people, 57 voluntarily provided serum for tularemia antibody testing. Five individuals declined testing, citing for "no exposure" or "personal" reasons.

None of the seven tularemia researchers had traveled to endemic areas between May and November 2004, compared to 17% of those who did not work with tularemia. Four researchers working directly with tularemia reported symptoms. Fever and fatigue/ malaise were the most common symptoms. Of the four researchers reporting these symptoms, three had pneumonic tularemia. The other researcher had a febrile illness with serology negative for tularemia.

Researchers reported performing laboratory activities with a wide range of frequencies. Centrifuging was performed more than 16 times per month by 42.6% of the researchers. In contrast, 80.9% never lyophilized.

Survey participants performed various laboratory procedures. Hand tightening or loosening screw caps (n=42), centrifuging (n=41) and vortexing (n=40) were the most commonly reported activities by the 47 people who worked in the laboratory. The objectives of various research projects and the experience of the researcher determined specific laboratory activities. There was wide variability in the use of protective

equipment and infection control measures. Of the 25 researchers who reported counting bacterial colonies, only eight (32%) reported always using a biosafety cabinet to do so.

The tularemia researchers reported a wide variety of laboratory activities. Eight laboratory procedures were performed by all the cases. Due to the small numbers involved, illness could not be statistically associated with a specific laboratory procedure. However, activities that may have resulted in aerosolization of bacteria were identified and performance of these activities prior to onset of illness was reviewed. All three cases performed multiple laboratory activities during the course of routine research that may have resulted in exposure, including preparation of cultures in broth and on agar, counting bacterial colonies on open agar plates, capsule preparation, centrifugation, and lyophilization. Chamberlain's media, believed to enhance the virulence of tularemia in culture, was used on several occasions. The first two cases became ill in late May, and at that time worked with large quantities of *F. tularensis* in liquid broth. Both cases reported numerous laboratory activities using infectious material at that time, but did not recall any specific laboratory accident or spill. The third case, with illness onset in late September, reported performing similar activities. This case also reported the use of a colony counter examining open plates of *F. tularensis* cultures outside a biosafety cabinet or fume hood.

V. Serologic Survey

Methods

Survey participants were asked to voluntarily provide a blood specimen to assess whether they had been infected with tularemia. Blood specimens were collected at the time of the surveys and were submitted to the Massachusetts SLI to test for antibody against *F. tularensis*.

Laboratory criteria for interpreting test results followed CDC guidelines, as follows:

- Results are *presumptive positive* if an elevated serum antibody titer(s) (≥1:128) to *F. tularensis* antigen (without documented fourfold or greater change) is observed in a patient with no history of tularemia vaccination OR detection of *F. tularensis* in a clinical specimen by fluorescent assay.

- Results are *confirmatory* when there is isolation of *F. tularensis* in a clinical specimen OR a fourfold or greater change in serum antibody titer to *F. tularensis* antigen is observed

Results

Two laboratory workers were identified as probable cases; both had paired convalescent serum titers >1:128 and symptomology consistent with pneumonic tularemia. No blood samples were available prior to illness for these two cases. One laboratory worker was identified as a confirmed case; this individual had blood drawn prior to onset of illness, and paired serum showed a four-fold increase in antibody titer, with subsequent samples showing titer levels >1:128.

Fifty-one non-cases were presumptive negative based on a single serum sample, drawn at least two weeks after all tularemia related work in the laboratory was stopped. Two additional individuals became ill during the course of the investigation; blood specimens for both were negative for tularemia antibody.

Finally, two researchers in a separate laboratory on another floor in the same building were tested because they were identified as having low levels of antibodies to LVS *F. tularensis* using a research assay conducted in August, 2004. This research assay was not an approved diagnostic test. Both tested negative for tularemia antibodies at the SLI, and reported no exposure, having only briefly visited the implicated laboratory to have blood drawn. Neither researcher had ever worked with *F. tularensis*.

VI. Environmental/Laboratory Inspection

Methods

All laboratory space where work with *F. tularensis* was conducted was inspected by BPHC and MDPH officials. On November 19, 2004, health officials inspected the laboratory and reviewed physical facilities to assess exposure risks. BPHC requested the results of all testing of ventilation, biosafety cabinets, and laboratory equipment. Interviews of laboratory staff were used to assess physical facilities, laboratory activities, and other environmental or procedural areas of concern. Finally, all records related to shipping, handling, and access to tularemia, as well as all research protocols and actions taken by laboratory staff were reviewed. Shipping and handling documents were verified when possible through the shipper or receiver, and access to tularemia reagents was confirmed using laboratory notebooks and a select agent logbook.

Results

Laboratory Overview

The 6th floor of the Evans Biomedical Research Building is a quadrant set-up, with a total of four BSL2 laboratories. Separate tissue culture, bacterial culture, and instrument rooms, as well as biosafety cabinets, were shared among the four laboratories. Tularemia research using animals was conducted on a separate floor in a BSL3 suite. Researchers and BU Environmental Health and Safety personnel reported that animals in that laboratory were not removed from the BSL3 room prior to euthanizing, and all necropsies

and tissue sampling was performed in the BSL3 room. All information regarding locations where tularemia research was conducted was verified through interviews with researchers and an internal BU investigative committee.

Ventilation and Biosafety Cabinets

BU reported no operating problems with the HVAC system, and submitted reports from an outside engineering contractor that measured air flow throughout the laboratory, verified air flow at each duct and fume hood, and assessed function of intake and exhaust systems. No problems were reported. The laboratory used a 100% fresh air supply, and had exhaust venting through the roof and an air exchange rate above recommended levels. In addition, BPHC Office of Environmental Health confirmed that air flow was adequate.

Environmental Risk

According to CDC, the LVS strain of *F. tularensis* presents only low-grade environmental risk for transmission. The bacterium is unlikely to survive for a long period in a laboratory outside of culture or stock. Despite the fact that the laboratory space was not thought to be contaminated or a source of ongoing exposure, BU reported that all equipment in the laboratory had been decontaminated by BU's Office of Environmental Health and Safety (OEHS) by November 19, 2004.

Facilities and Equipment

The appropriateness of facilities and equipment for laboratory activities being performed were reviewed. No specific failures of equipment were identified. However, availability of fume hoods and biosafety cabinets was very limited. Investigation of procedures that may have resulted in exposure was limited by a lack of specific research protocols detailing methodology.

VII. CDC Testing and Investigation

Methods

The *F. tularensis* materials used in research by BU were sent to the CDC for virulence testing and additional characterization. Initial testing was conducted during the week of November 15 to 19, 2004 on two vials of *F. tularensis* used by BU in research during the time period from April-November 2004. These included a sub-cultured stock vial grown from *F. tularensis* received from the University of Nebraska on April 15, 2004, and the original vial of *F. tularensis* received from the University of Iowa on June 3, 2004. Both LVS strains had the same American Type Culture Collection (ATCC) number. After initial results of testing by the CDC became available, the original vial received from Nebraska was sent to CDC from BU in late December 2004 and tested as well.

Between November 22, 2004 and January 6, 2005, BU sent and CDC tested all vials in BU's possession containing *F. tularensis* from either the University of Nebraska or the University of Iowa. Initial testing was done to assess whether the strain was Type A or

Type B, and if Type B, whether the strain was LVS. Mouse inoculation tests were performed to determine virulence, and additional testing was done to help further characterize the strains. Because many different strains of tularemia exist, CDC investigators employed pulse field gel electrophoresis (PFGE) and genomic sequencing to attempt to identify specific tularemia strains by comparing them with other known isolates. The tularemia strains isolated from BU samples were compared to known isolates from the East Coast and Midwest United States, an isolate from an outbreak in Martha's Vineyard in 2000, the SCHU-4 isolate, and several others. It should be noted that PFGE testing of *F. tularensis* is in early stages of use, mandating that results be interpreted with caution.

Results

On November 22, 2004, CDC informed BPHC and MDPH their testing had revealed that the original vial from Iowa contained the pure LVS (Type B strain), but that the sub-cultured vial from Nebraska contained both Type A (virulent) and a small amount of Type B (LVS) tularemia. On December 3, 2004 CDC reported that the original vial BU received from Nebraska also contained both strains, though the amount of Type A present was less than in the sub-cultured vial that was initially tested by CDC.

By January 6, 2005, CDC testing had shown that all materials submitted by BU received from the University of Nebraska – including the original vial and the sub-cultured vials – contained a Type A strain of unknown origin. All specimens that BU had obtained from the University of Iowa contained pure Type B LVS.

The Type A strain contaminating the LVS sent from Nebraska was further characterized by PFGE. On December 8, 2004 CDC reported results of PFGE against other known Type A isolates, including the SCHU-4 strain, a clinical isolate from an outbreak in Martha's Vineyard in 2000 (MV2000), and several known Midwestern and East Coast strains (around 20 Type A strains total). Tests showed that the unknown strain from BU was distinct from the MV2000 isolate, as well as from all other East Coast isolates tested. The unknown strain was indistinguishable from the SCHU-4 isolate and some Midwestern strains. Testing by CDC also revealed that a Type A strain present at BU prior to receipt of the LVS from the University of Nebraska (ATCC 6223), was distinct from the unknown Type A strain (See below). To date, additional testing at CDC has been unable to further characterize the contaminating Type A strain found in the LVS stock BU received from Nebraska. However, results of additional CDC testing are still pending.

VIII. Review of Laboratory Isolates at Boston University

Methods

To identify possible sources of virulent *F. tularensis,* BPHC requested that BU provide dates of receipt for all shipments of *F. tularensis*. In addition to the two LVS strains, health authorities requested a description of all other tularemia strains at BU.

Results

The Type A strains identified at BU were:

- SCHU-4, a Midwestern strain, was received by BU from CDC in late August 2004
- Two Type A strains were sent from the University of Iowa in September 2004 and received by BU in October 2004.

  All three of the above Type A strains (SCHU-4 and two strains from Iowa) were handled in accordance with select agent guidelines, including dual-signatory receipt and shipment, secured storage, and video surveillance. BU reported that there was no evidence from logbooks or other sources that anyone had access to any of these strains since their receipt.

- Seven vials containing an avirulent Type A strain (ATCC 6223) from research conducted in 1990 were discovered during an inventory of the BU laboratory in 2003. Once identified these vials were reported to the CDC Select Agent program and moved into a separate secured freezer.

No isolates from cases of tularemia cared for at Boston Medical Center were stored or worked on in the research laboratory, including isolates from a Martha's Vineyard case that had received care at Boston Medical Center. BU reported that the isolate from Martha's Vineyard was destroyed in 2000 and never entered a research laboratory.

CDC investigated possible sources of contamination outside of the BU laboratory, including materials at the University of Nebraska laboratory that shipped the LVS tularemia to BU. No source has been identified in the investigation to date, and a report of CDC findings in Nebraska has not been released.

A timeline of receipt of all tularemia strains at BU follows.

Date	**Type/Strain**	**From**	**To**	**Notes**
2000	Type A, clinical isolate	Martha's Vineyard	Clinical laboratory	Isolated and destroyed in 2000
March 12, 2003	Type A, ATCC 6223	6th floor ID laboratory, BU	Select Agent freezer at BU	Discovered during inventory; declared to CDC Select Agent and moved to secured area
April 15, 2004	LVS, Type B (contaminated)	University of Nebraska	BU	Used in research, 6th floor ID laboratory
June 4, 2004	LVS, Type B	University of	BU	Used in research, 6th floor

		Iowa		ID laboratory
August 31, 2004	SCHU-4, Type A	CDC	BU	Logged in according to select agent protocols, transferred to secure area, unopened
October 14, 2004	2 Type A strains	University of Iowa	BU	Logged in according to Select Agent protocols, transferred to secure area, unopened

IX. Review of Research Related Documents

Methods

BPHC obtained documents detailing the research with *F. tularensis*, including the NIH grant under which all work was conducted, the BU research protocols for work with *F. tularensis*, laboratory notebooks, a chronologic accounting of research, shipping and receiving documents for *F. tularensis*, and other supporting documentation. Documents were reviewed for completeness as well as insights as to how infection of laboratory workers and contamination of the *F. tularensis* may have occurred. Due to the implications of work with select agents, documents were also reviewed for any indications of protocol and procedural errors.

The following documents related to research with *F. tularensis* were submitted by BU and reviewed by the BPHC:

- NIH grant
- Correspondence between NIH and BU Re: tularemia grant application
- Institutional Biosafety Committee (IBC) records and approvals
- IRB consent forms for research related phlebotomy and antibody testing
- Laboratory notebooks of the three researchers who were tularemia cases
- Research protocols and methodologies as described by the tularemia cases for the periods surrounding their illness
- Shipping and receiving documents
- Invoice for clinical agglutination kit purchased 4/2004
- Research abstracts presented by the tularemia researchers
- Chronological account of all research performed with *F. tularensis*

Results

There was no evidence to suggest intentional infection or contamination based on these records. Grant-related materials provided investigators with an overview of the research performed and the plans for future experiments. Research protocols describing manipulations performed by the tularemia cases in the time period surrounding illness

were prepared subsequent to illness based on laboratory notebooks and interviews of researchers, the principle investigator, and the internal BU investigative committee. These protocols revealed laboratory activities during which exposure may have occurred, however, no laboratory accidents were identified.

X. Review of Biosafety Laboratory Procedures

Methods

BPHC reviewed all biosafety laboratory procedures, safety training, accident logs, and occupational health guidelines for laboratory exposures submitted by BU. Two areas of biosafety were reviewed:

(1) General BSL2 practice
(2) Select agent handling and practices

BPHC requested training records for all researchers in the tularemia laboratory and reviewed responses related to laboratory activities obtained through the epidemiological survey. BPHC also assessed occupational health practices and policies for evaluation of potential laboratory exposures and acquired infections, and reporting of communicable diseases to BPHC as required by state and city laws and regulations. Select agent storage and handling procedures were reviewed as well. Next steps were identified for tularemia research to resume.

Results

General BSL2 Practice

If followed, generally accepted BSL2 practices should lessen the risk of acquiring illness during the handling of virulent tularemia (Type A). However, researchers cited routine failure to comply with safety protocols. For example, researchers noted the lack use of personal protective equipment when counting colonies on an open bench.

All employees had completed BSL2 level training. Of the seven tularemia researchers, five had completed BSL3 level training. However, survey responses to questions about safety measures actually used in the laboratory varied widely.

The BU Occupational Health Center policies regarding illness in laboratory personnel were reviewed, and requirements for notification of public health agencies were emphasized. A delay in reporting illness was in part attributable to the fact that contamination of the LVS strains with wild type tularemia was unknown, and the belief that LVS did not cause disease. In addition, cases sought medical care at three different health care sites without initial involvement of the BU Occupational Health Center.

Select Agent Handling and Practices

Select agent protocols regarding the receipt and storage of Type A *F. tularensis* were reviewed for the three strains BU knowingly received. Select agents were stored in a

separate locked freezer with video monitoring. Receipt required at least two signatures, and there was no evidence of any use of these materials after they were received. The Type A *F. tularensis* was being stored in storage in anticipation of aerosol challenge experiments to be conducted at a later date. Despite stringent guidelines on receipt and storage of Select Agents, the BU laboratory did not have a system of laboratory testing in place to verify that the organisms being used in research were those that had been requested.

The Boston Public Health Commission identified the following steps to be completed before tularemia research resumes at BU:

1. Retraining
    - BSL3 training for all tularemia researchers, provided by the State Laboratory Institute
    - Refresher training on laboratory safety for all other laboratory personnel on the 6th floor
    - Retraining on Select Agent requirements for appropriate personnel regarding protocols and handling
    - Consultation with BU Occupational Health Center for all workers regarding risks, illness reporting requirements, obtaining baseline serum, and vaccination as appropriate

2. Communication
    - IBC and IRC protocols provided to all workers by Principal Investigators – to be read and signed as understood

3. Standard Operating Procedures (SOP) and Infrastructure
    - Modification and strengthening of SOPs by any Principal Investigator who conducts work using a BSL2 and/or a BSL3 laboratory, in conjunction with an outside expert
    - Updating of SOPs by Principal Investigators for any laboratory activities that may cause aerosolization
    - Review of all laboratory equipment by the BPHC Office of Environmental Health and Safety, along with Principal Investigators

XI. Conclusions

Several conclusions have resulted from this investigation.

1. **At this time, the source of Type A *F. tularensis* in the BU laboratory remains unknown.** However, this highly virulent strain of bacteria likely caused the illness in all three researchers. Laboratory practices and safety measures used in the BSL2 laboratory were inadequate to prevent exposure, and the pathogenicity of the Type A strain of *F. tularensis* increased the risk of disease.

2. **The extensive investigation to date has found no evidence to indicate that either the contamination of the LVS stock or the infections of the BU researchers were intentional.** Based on discussions with all parties involved and review of the laboratory and research records, it is unlikely that BU researchers were aware that the LVS stock was contaminated until DNA tests performed in October as part of the research showed differences between stocks of bacteria that should have been identical.

   Testing at CDC continues in the effort to determine the time and place of contamination of the original vial. CDC is currently focusing its investigation on potential sources of the Type A tularemia outside Boston. The local investigation may need to be reopened pending the outcome of further CDC investigation or the availability of additional information.

3. **The tularemia outbreak at BU was limited to three BU employees and never posed a risk to the public at large.** Since tularemia is not transmitted person-to-person, secondary cases in laboratory or non-laboratory contacts of the cases were not expected and were not found. Furthermore, epidemiological and serological survey of employees working at the lab showed that no other lab workers were infected.

4. **The failure to identify work-related illness in laboratory staff is a major concern for health officials.** BU should have had stronger procedures in place to monitor its laboratory personnel. Had such procedures been in place, the cluster of suspicious illness in the tularemia lab would likely have been detected earlier and the third case may have been prevented.

5. **The failure to immediately report suspicious work-related illness to local and state health departments is a major concern.** BU should have reported the suspect cases of tularemia as soon as they were identified. BU needs to ensure that in the future there is a vigilant approach to regular monitoring the health of lab workers and to immediately reporting suspicious illnesses among laboratory workers to the appropriate governmental authorities.

6. **Appropriate infection control practices in laboratories must be clearly documented for all workers and enforced.** The BU tularemia laboratory failed to consistently utilize adequate precautions when handling and manipulating laboratory specimens. A systematic approach to retraining laboratory personnel is essential to insure that the required knowledge and skill levels are met and maintained. Special attention needs to be paid to the training and monitoring of laboratory personnel working with Select Agents.

7. **The BU Institutional Biosafety Committee was not able to ensure compliance with appropriate laboratory protocols and procedures.** BU should review staffing, resources and designated authority of this critically important body to insure it has the means to guarantee maximal safety in the future.