

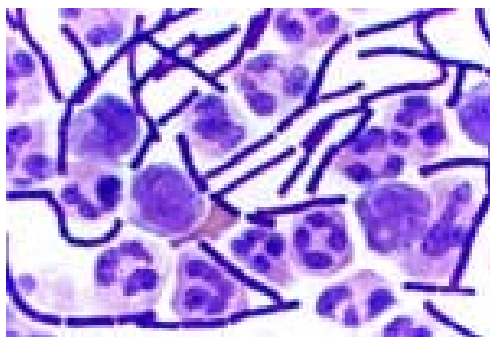
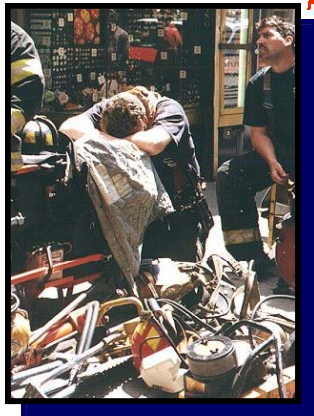
Meeting Report:
**“*Bacillus anthracis* Bioterrorism Research
Priorities for Public Health Response”**

December 10-11, 2001, CDC, Atlanta, GA

CDC/NCID

**CENTERS FOR DISEASE CONTROL
AND PREVENTION**

NATIONAL CENTER FOR INFECTIOUS DISEASES



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“*Bacillus anthracis* Bioterrorism Research Priorities for Public Health Response”

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Acknowledgements

Executive Summary

This meeting provided a forum for 132 representatives from the Department of Health and Human Services (Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), and National Institutes of Health (NIH)), Environmental Protection Agency (EPA), Department of Defense (DoD), Department of Energy (DoE), US Postal Service, State Health Departments, universities and other organizations to identify, prioritize, and coordinate near-term *Bacillus anthracis* bioterrorism research for public health response.

During the recent anthrax bioterrorism investigation CDC and its partners identified a number of areas where additional research may be useful in improving public health response. The disciplines and specific expertise required to approach many of these areas are varied and exist within multiple federal government entities and elsewhere. To address those research questions that are most critical to improving public health response to *B. anthracis*-related bioterrorism, CDC convened this meeting to obtain input on critical research priorities and coordinate with federal partners and other stakeholders in planning and conduct of applied research that needs to be initiated within the next 12 months.

The workshop format consisted of two plenary sessions in which experts provided summaries of the existing science in key topic areas. Background talks were given on the “Evaluation of *B. anthracis* containing powders or substances” by Mathew Shaw, Battelle Memorial Institute; “Epidemiologic Investigation” by Philip Brachman, Emory University, School of Public Health; “Environmental Assessment” by Edwin Kilbourne, Agency for Toxic Substances and Drug Research; “Surveillance” by Ruth Berkelman, Emory University; “Introduction to issues in Diagnosis, Treatment, and Prevention of Anthrax” by Art Friedlander, US Army Medical Research Institute for Infectious Diseases (USAMRIID), DoD; “Diagnosis” by Susan Alpert, C.R. Bard, Inc.; “Treatment” by Dennis Stevens, Veterans Affairs Medical Center, University of Washington; “Post-exposure prophylaxis” by Diane Murphy, Food and Drug Administration; and “Remediation” by Dorothy Cantor, Environmental Protection Agency.

Following the first plenary session, participants were divided into eight pre-assigned working groups. The eight working groups included: 1) Evaluation of *B. anthracis* containing powders or substances, 2) Epidemiological investigation, 3) Environmental assessment, 4) Surveillance, 5) Diagnosis, 6) Treatment, 7) Post-exposure prophylaxis, and 8) Remediation. Each of the 8 working groups had pre-assigned co-leaders, one from outside of CDC and one from CDC. Each of the CDC co-leads were senior scientists who had been heavily involved in the anthrax bioterrorism investigation and response. Lists of specific questions were given to each of the working groups to help stimulate discussion and provide direction based on observations during the anthrax bioterrorism investigation. During the second plenary session each of the groups presented interim results of discussion for input from the larger group of meeting participants. In the second working group session, groups were asked to prepare a written report of their group’s top three research priorities. The following is a summary of those research priorities by working group and title of research project:

Evaluation of *B. anthracis* containing powders or substances

- 1) Development of an *in vitro* model for the study of cutaneous anthrax using human cell culture
- 2) Rapid analysis of anthrax-containing powder: particle size distribution and matrix characteristics
- 3) Measure of particle reaerosolization using different anthrax powder preparations.

Epidemiologic Investigation

- 1) Analysis of individual host risk factors (for anthrax)
- 2) Exposure reconstruction and risk characterization
- 3) Review existing and unexamined/previously unpublished (potentially classified) animal data related to dose response.

Environmental Assessment

- 1) Validation and standardization of sampling and sample analysis techniques
- 2) Evaluation of risk of disease in contaminated environments
- 3) Determination of risk of reaerosolization

Surveillance

- 1) Veterinary surveillance, and integration with human health information
- 2) The use of other, alternative sources of data in the surveillance for bioterrorist-related events
- 3) Design and validation of surveillance systems to detect complex contamination or release scenarios

Diagnosis

- 1) Identifying the earliest detectable event in the continuum from exposure to anthrax to disease (using animal models)
- 2) Rapid diagnosis of anthrax
- 3) Developing a library of subtypes

Treatment

- 1) Investigation of the role of immune and anti-toxin therapies – a framework
- 2) Expanded investigation of antibiotic therapies in animal models
- 3) Developing other animal models

Post-exposure Prophylaxis

- 1) Long term use of antimicrobials for PEP: Monitoring of adherence, barriers to adherence, and adverse events
- 2) Pediatric safety and immunogenicity study
- 3) Animal challenge study to optimize post-exposure prophylaxis in humans

Group 8: Remediation

- 1) Evaluation of Existing and Alternative Remediation Agents

- 2) Risk-Based Decision Logic for Sampling and Remediation
- 3) Reaerosolization studies... Agent and Space-specific scenarios

Working Group 1: Evaluation of *B. anthracis* Containing Powder or Other Substance

Recommended Research Priorities

General Comments

- 1) A major goal should be to analyze the feasibility of real-time rapid powder analysis to play a role in public health decision-making
- 2) Particle sizing is valuable, but SEM alone cannot determine if it is anthrax. Also need to analyze the safety of doing rapid SEM with particles.
- 3) Relationship between level of infection and particle size, number of spores, number of particles
- 4) Aerosol characterization capabilities: SEM can be decontaminated without damaging instruments. Aerosizer can be done safely.
- 5) Irradiation and effect on particle & aerosol characteristics: irradiation destroys the electrostatic charges but the morphology remains the same
- 6) Use simulant or non-toxin forming BA and disperse into animal model
- 7) Particle size: single spore particles had $\frac{1}{4}$ LD of cluster particles, suggesting much more virulent
- 8) These groups have a lot of overlap—need combined collaboration

Research Priority 1

Title: Development of an *in vitro* model for the study of cutaneous anthrax using human cell culture

Why the research is needed: No animal models for cutaneous anthrax exist or can be developed

Research description and methods:

Identify the appropriate cell culture system through:

- a) Identification and review of published/unpublished literature, classified/unclassified studies that have been done on this topic.
- b) Identification of an appropriate cell culture model. For example, Fred Quinn's cell culture technique vs. use of transgenic mice with human ear, etc.
- c) Once model has been identified, expose or inoculate the system to various spore preparations and matrices as described in Project 2.

Location of research: CDC, DoD, Batelle, NIH, other national labs

Collaborating institutions:

Start date: ASAP

Action steps with assigned responsibility: Request for proposals (RFP)

Research Priority 2

Title: Rapid analysis of anthrax-containing powder: particle size distribution and matrix characteristics

Why the research is needed: The accuracy of rapid tests to determine particle size and composition of the powder, which determine a potential hazard, are unclear.

Research description: Assess and evaluate current technology specifically applied to rapid analysis of powder (e.g., TFMS-time flight mass spectrometry, aerosizer, FTIR, light microscopy, SEM, SEM-EDX [x-ray analysis], APS).

Methods:

1. Standardize several spore preparations using *B anthracis* and simulants (*B thurigenis*, *BG*) (which will also address the simulant issues) by several production methods (e.g., acetone drying, washing, lyophilization, weapons grade methods) coupled with matrices
2. Use a gold standard for comparison or latent class

Location of research: Appropriate facility and staff, BSL3

Collaborating institutions: Batelle, Dugway, DoE, DoD, CDC, NIOSH

Start date: ASAP

Action steps with assigned responsibility: RFP - Submission of formal proposal- to be determined

Research Priority 3

Title: Measure of particle reaerosolization using different anthrax powder preparations

Why the research is needed: To determine the risk/hazard of reaerosolization of several spore preparations that vary in particle size and matrices. Do the characteristics of particles correlate with the risk of reaerosolization?

Research description and methods:

1. Preparation as mentioned in project 2.
2. Testing would be compared in different environments: temperature, RH, applied forces as in offices and postal facilities HVAC, opening doors, walking, performing jobs
 - a. Drop preparation
 - b. Allow spores to settle
 - c. Apply force

d. Measure reaerosolization: (e.g., slit samplers, aerosizer, APS)

Location of research: Canada, Dugway

Collaborating institutions: DRES, Dugway, DoD, CDC

Start date: ASAP

Action steps with assigned responsibility: RFP

Working Group 2: Epidemiological Investigation

Recommended Research Priorities

Research Priority 1:

Title: Analysis of individual host risk factors

Why is research being done?

- To evaluate host risk factors associated with inhalational anthrax.
- To understand why exposed people did not become ill.

What is the research?

- Use exposed populations (in mail sorting facility, AMI)
- collect demographic, epidemiologic, and clinical data on cases and controls, or perform cohort study
- collect whole blood/sera to investigate role of cell mediated immunity
- consider incorporating 2 outlier cases (CT, NYC inhalational)
- interview all people (or surrogates for deceased)
- as second phase, integrate results with exposure model

Where could it be done?

AMI and/or mailsorting facilities where inhalational cases have occurred.

Who?

CDC as lead agency, with state health depts., postal unions, postal management, and AMI employers involved.

When should it be started?

Within 3 months.

Action step:

- CDC will review existing data from cohorts, and develop a brief proposal (pass through CDC IRB)
- CDC will arrange a conference call to gain input from affected parties
- review existing outbreak data, compare different locations

Research Priority 2:

Title: Exposure Reconstruction and risk characterization

Classical analysis of exposure: Source
Transport mechanism
Release mechanism
Receptor

Why is research being done?

- understand exposure associated with passage of powder-containing letters through mail
- validate the model using empirical outcome data

What is the research?

- use nonbiologic inert simulant (e.g. fluorescent) to gather empirical data on dispersion
- collect surface swab data, locations of cases and non cases from facility
- integrate results with those including host factors data
- modeling the effect of interventions
- study cross contamination in facility

Where?

- Hamilton or Brentwood postal facility

When?

- within the next 3-6 months, but facility should be operational

Who?

- NIOSH*(lead) – Mark Hoover expressed interest
- Defense Canada
- Aberdeen
- ATSDR
- CHPPM potential lead
- NIST potential lead
- EPA
- involve postal union/management at early step

Action step:

- NIOSH will identify contacts at relevant agencies, and develop interagency funding proposal for project

Research Priority 3

Title: Review existing and unexamined/previously unpublished (potentially classified) animal data related to dose response

Why:

- this is the largest body of data addressing the various aspects of dose response
- this data is only available in summary form, reviewing the original raw data will provide new insights

What:

- meta-analysis or pooling of original data
- re-analysis of original data
- additional new analyses of original data

How:

- identifying previous studies
- finding original data
 - obtain approval to access data
 - find data
 - analyze
 - convene scientific review panel
 - publish

Where:

- wherever the original data are located

Who:

CDC and EPA should initiate contact with military, formally and informally

Action steps:

- 1) CDC and EPA should approach contacts at Ft. Detrick for insight into process of recovering military technical documents. Can this material be declassified?
- 2) EPA, HHS/CDC/ATSDR should draft a joint letter to military (e.g. letter from Christine Whitman, Tommy Thompson, Jeff Koplan) requesting access to data

Other priority areas that were considered

- reaerosolization of settled spores and risk for disease among secondarily exposed individuals
- adverse outcomes related to anthrax events (PEP, remediation)
- postal worker surveillance
 - future illnesses/adverse health effects due to stress

- other scenarios/agents
- long term, low level exposure
- particle characteristics
 - cutaneous vs inhalational disease
 - relationship to infection
- expected background level of B. anthracis in urban and rural environments
- occurrence of sporadic inhalational anthrax cases
- Sverdlovsk denominator data

Working Group 3: Environmental Assessment

Recommended Research Priorities

Research Priority 1

Title: Validation and Standardization of Sampling and Sample Analysis Techniques

Introduction

Though environmental sampling for the presence of *Bacillus anthracis* has been used extensively in the current anthrax investigation, there is very little data available to validate the accuracy of different methods or to support the use of one method over another. Currently these methods are being used to determine that a contamination event has occurred, to identify individuals potentially at risk of infection given exposure to this environmental contamination event, to determine the requirements for disinfection, to determine that disinfection has occurred, to ensure that the waste stream arising from contamination is not infective, and to ensure that after re-occupancy, no previously hidden contamination will pose a continuing health threat. Questions remain as to the validity of each type of surface sampling (swab, wipe, vacuum sample) in reflecting the true degree of spore contamination and the role of air sampling in a past exposure. Anecdotal experience from this outbreak suggest not all techniques are equally effective at measuring environmental spore contamination. As well, little data exists as to which laboratory technique (culture, PCR or immunoassay) is most accurate in detecting the presence of spores. The methods used to date during the current contamination events have been modified in real time in the field, in response to the lack of a standardized method that was suitable for the conditions encountered in the field. The effort to determine risk of disease based on environmental contamination data is predicated on the reliability of this data to reflect the true presence of *B. anthracis* spores. Perhaps the most pressing research need in this effort is to ensure that the sampling techniques and laboratory analysis methods are sufficiently standardized and validated to meet this standard.

Objectives

To perform direct comparisons of sampling techniques (including wet and dry swabs, large-area vacuum sampling and different methods of air sampling) linked to laboratory analysis methods (including PCR, culture and direct immunofluorescence)

To evaluate the accuracy of air sampling techniques in detecting environmental contamination with spores under quiescent air conditions as well as with activity

To determine whether sampling/laboratory analysis techniques can be standardized to the point where a quantitative result is meaningful and can give useful information about degree of risk of infection

A) Sampling Techniques in Known Contaminated Field Sites

A number of the of the buildings involved in the current outbreak are felt to still be contaminated with *B. anthracis* spores. Though not homogenous, this contamination represents an opportunity to perform a direct comparison of all of the techniques that are currently being used to detect surface contamination. This category of experiments would utilize buildings known to be contaminated with *B. anthracis* to perform direct side-by-side analyses of different techniques used to both collect and analyze surface and air samples. Currently, representatives of the U.S. Postal Service, U.S. Army, EPA, and a USPS contractor (IT Corporation) are working at the Brentwood mail handling facility to conduct clean-up operations. However, much of the facility remains contaminated, specifically a long shelf (1 ft X 100 ft) very near the machine that processed the Daschle and Leahy letters, the tops of inspection window ports above the work area, and suspended supply-air ventilation ports. Even though the DBCS machine which processed the letters has been cleaned by HEPA vacuum and washing with a 10% sodium hypochlorite solution, this machine is still reportedly contaminated (report obtained from Dr. David Ashford; Canadian Reaerosolization Survey). For these reasons, we believe the Brentwood facility would be one suitable location for comparing sampling and analytical methods, but similar studies could be undertaken at the AMI building, Wallingford or Hamilton postal facilities, even in light of past decontamination efforts. Specific methods of this study are attached at the end of this proposal.

The Partners conducting this survey include NIOSH, NCID, ATSDR, CHPPM, EPA, Postal Service and IT Corporation. The urgency of this study is high, as clean-up efforts and time lessen the degree of observable contamination.

B) Sampling Techniques in an Experimentally Controlled Environment

More definitive answers as to the relative accuracy of environmental sampling techniques can only be generated with a standard challenge of intentional spore contamination in a controlled environment. The first step is to establish a working group within a matter of weeks to develop a standardized set of conditions for testing methods. The tasks of this group include determination of a standardized set of simulants, including experimental matrices that simulate “weaponization” and a standardized method of spiking these matrices with organisms. The bacteria used may be an avirulent strain of *B. anthracis* or another non-pathogenic *Bacillus* spp. An experimental aerosolization facility will be determined which includes many of the surfaces of interest (e.g., carpet, flooring, metal, paper).

Once the testing conditions are established, sampling methods will need to be proposed, including not only sampling design strategy but also precise descriptions of sampling techniques, processing and specimen analysis. The initial methods used will be those used in common practice and those that have proven useful in the current anthrax investigations. If methods are to be tested that are beyond this scope, it will be imperative that the methods developer transfer the technology to this methods evaluation project, within the working parameters of the current project (time, cost and personnel).

Once a battery of sampling methods has been assembled, each method will be tested using the standardized experimental contamination system. Testing will include all phases of

methods including decontamination procedures, and cross contamination control protocols. It is conceivable that this round of methods testing will need to be repeated both for optimization of techniques and for statistical validity.

Potential research partners are the CDC/ATSDR, NIOSH-Cincinnati, USArmy (Edgewood), USArmy CHPPM, Dugway Proving Grounds, University Cincinnati, University of Colorado-Boulder, UNLV (DoD contractor), EPA, OSHA, and private labs (Battelle, Sandia).

(The following are the specific methods for the contaminated sites study)

1. Conduct a comparison of the wipe swab, and vacuum sampling techniques. The locations to be sampled include the 1 ft X 100 ft shelf, the ventilation ducts directly above processing machine #17, the inspection window ports, and the DBCS machines which have been decontaminated including those nearby DBCS machine #17. We propose to divide the locations to be sampled into equal surface areas to be sampled. For example, if a ventilation diffuser above one of the mail sorting machines was to be sampled, then the surface of the diffuser would be divided into three equal parts and each part of the surface would be sampled using one of the three sampling techniques following the CDC Interim Procedures for Collecting Environmental Samples for Culturing *B. anthracis* (Arduino, M).

The swab samples would be collected by removing a sterile, non-cotton swab from the package and moistening it with 100-200 μ L (1-2 drops) of sterile water. The selected surface will be swabbed by moving the swab back and forth across the surface with a series of horizontal strokes followed by a series of vertical strokes. Care will be taken to ensure that the entire circumference of the swab is used. The swab will be placed into a sterile conical vial, capped, prepared for shipment.

The wipe samples will be collected by donning sterile, non-powdered gloves over the two pairs of nitrile gloves that are part of standard personal protective equipment. The selected surface will be wiped with a 3" X 3" sterile cotton gauze pad moistened with about 5 mL of Baxter Sterile Water for Irrigation, USP®. The surface will be thoroughly wiped by making 3 to 4 vertical strokes, folding the exposed side of the pad and making 3 to 4 horizontal strokes over the same area. The pad will be placed into a labeled, sterile conical tube and sealed with a cap.

Surface vacuum samples will be collected by inserting a cone-shaped filtering "sock" (dust collection trap manufactured by Health Home Air) into the nozzle of a HEPA vacuum cleaner. The plastic sleeve of the dust collection trap was folded over the outside of the nozzle and hand-held in place while the vacuum nozzle was moved slowly back and forth across the sampled surface. The dust collection trap will be removed from the vacuum nozzle and placed into a labeled, sterile conical tube and sealed with a cap. Before inserting a clean sock into the vacuum nozzle and collecting a subsequent sample, the sample collector put on new pair of sterile gloves and wipe the inside of the vacuum

nozzle thoroughly with an alcohol wipe. The use of alcohol wipes is intended to physically remove contamination from the nozzle surface, not to sterilize that surface.

The samples would be sent to the appropriate laboratories for analysis—the CDC/NCID laboratory in Atlanta, Georgia will analyze the swab and wipe samples. The sock samples will be analyzed by a contract laboratory. The sock contents will be weighed on a precision balance. To a cup containing the sock and its contents, 20 to 30 mL of 0.3% tween 20 in phosphate buffer solution (PBS) will be added and placed on a shaker for 30 minutes. The contents of the cup will be allowed to settle for 5 minutes and then the supernatant was poured into a 50 mL Blue Falcon screw-top tube. The tube will be centrifuged at 3000 to 4500 rpm, for 15 to 30 minutes respectively at 10° C, then poured down to one tenth of the starting volume. The pellet in the bottom of the tube will be resuspended and 0.1 mL (two drops from a Pasteur pipette) and 0.01 mL (using a calibrated loop) of the suspension will be plated to a trypticase soy agar (TSA) with 5% sheep blood plates and streaked for quantification. The plates will be incubated at 35-37° C in ambient air and examined after 12 to 18 hours. Suspicious colonies will be screened using Level A procedures for identification of *B. anthracis*. The identification of suspicious colonies will be confirmed by direct fluorescent antibody staining (DFA) and gamma phage lysis. The results of these samples will be reported as number of colony forming units per gram of material collected (CFU/gm).

2. Comparison of culture analysis and PCR analysis. The wipe samples will be analyzed by both culture method and PCR analysis. Extractions will be collected from the each wipe sample. The extractions will be analyzed on-site by analytical chemists employed by the IT Corporation using the Ruggedized Advanced Pathogen Identification Device (RAPID) *B. Anthracis Lethal Factor* Detection Kit for specific detection of *B. anthracis Lethal Factor*. The analysts will remove the wipe sample from the bag while wearing protective clothing and sterile gloves. They will place a sterile swab into the extract. This swab will then insert into a tube containing the anthrax reagent and small glass beads. The tube will be vortexed to break the spores and DNA will be extracted from the supernatant using a column that binds DNA. The DNA is added to PCR reaction tubes and analyzed for *B. anthracis lethal factor*.

The number of samples for each of the three sampling methods will be determined after consultation with statisticians, but is likely to be approximately 100-150 samples of each type.

Research Priority 2

Title: Evaluation of Risk of Disease in Contaminated Environments

Introduction

Only very limited data exists correlating degree of exposure to *B anthracis* spores to risk of anthrax infection and disease in humans. This data is needed to assist in making decisions about need for decontamination, effectiveness of decontamination, and reoccupation of previously contaminated environments. We recognize that decontamination of a facility to a “zero-spore” level may not be a realistic objective. We propose using sero-conversion as a marker of subclinical anthrax infection as a health effect of interest in this study since the prevalence of clinical disease from contaminated environments has been low. We also propose that sero-conversion must be evaluated a period of months after exposure, since even clinical disease can take up to two months to develop after exposure and antibody responses take approximately 3 weeks to occur after significant challenge of relevant lymphoid tissues with antigen.

Hypothesis

There is a relationship between level of exposure to an anthrax-contaminated environment and risk for asymptomatic infection and clinical disease. Furthermore, that asymptomatic disease can be documented by measurement of serum antibody responses to anthrax-related antigens.

Objectives

To establish a “target level” of contamination to which sampling techniques would be oriented in order to declare a site below the level of *B. anthracis* spore contamination which represents a public health threat

Methods

- 1) All existing data documenting levels of environmental contamination with anthrax collected over the last several months will be gathered into a single data base. Data will be assessed for quality (use of final rather than preliminary results) prior to entry.
- 2) In addition to currently-available environmental assessments, follow-up assessment will be performed post-decontamination and at intervals after re-occupation corresponding to the period of assessment for sero-conversion.
- 3) A panel of experts (primarily industrial hygiene specialists with statistical experts supporting the effort) will assess data from various sites and categorize sites/areas as contaminated or not. In addition, an effort will be made to semi-quantitate degree of contamination. If the expert panel determines that insufficient environmental evaluation was performed to assess level of exposure in potential study subjects, additional environmental assessment will be performed in these subjects' work areas.
- 4) A registry of potentially exposed individuals who occupied these areas will be established. Exposed individuals will undergo evaluation by questionnaire to determine their personal and demographic characteristics, medical characteristics, occupational

characteristics, post-exposure prophylaxis, immunization status, etc). Individuals will also have blood drawn between 3 and 4 months after exposure to assess serologic responses to a panel of anthrax-related antigens.

- 5) Data evaluation will assess the prevalence of disease and sero-conversion as the health outcomes; measures of exposure (environmental assessments) will be evaluated as the primary risk factor for the health outcomes. A univariate analysis will be done to evaluate exposure and exposure related variables (such as work site or job), PEP, etc. as risk factors for the health outcomes of interest. A multivariate analysis will be performed to assess for confounding and effect modifiers.

A secondary objective of this study could be to assess of degree of background *B. anthracis* spore contamination that exists in the environment both in endemic and non-endemic epizootic areas where no human disease has occurred. This could be correlated to serological testing of banked blood in these regions. The hypothesis to be tested by this aspect of the study would be that low-grade environmental contamination of spores exists in places where anthrax is enzootic without causing human disease.

Who will do project

CDC/ATSDR, EPA, State and Local Health Departments, Postal Service, OSHA, etc.

When to start project

As soon as possible, while decontamination and post-exposure prophylaxis efforts are still active at many sites.

Action Steps

Connecticut -do air and surface sampling Thursday and Friday
low levels of contamination-pool data with other postal facilities
decide on sampling techniques-pool samples and pick method
assign statistical team to look at data

Quality Assurance to be done on existing data lab confirmed only (not rapid detector data to be used)

-Contractors increased chance of cross contamination? Some sites not lead by CDC,EPA

Research Priority 3

Title: Determination of Risk of Reaerosolization

Introduction

One of the observations that has emerged from the current anthrax outbreak is that spores of *B. anthracis* have a greater ability to reaerosolize after primary release than was thought possible. While it may be primarily a function of the processing method used to manufacture the powder used in at least two of the releases, it is clear that in DC there reaerosolization occurring both at the point of release (Hart Building) and the points of contamination (with operation of mail sorter #17 at the Brentwood facility). In light of this experience, there is a need to resolve the conflict between past data downplaying reaerosolization potential and recent data which clearly demonstrates secondary reaerosolization. This is necessary not only from the perspective of ability to declare a building safe after decontamination but also to be able to estimate the health hazard that is posed by fomites secondarily carrying spores such as cross-contaminated mail. Analysis of the reaerosolization characteristics of a spore-containing powder may also allow us to characterize the properties of the original spore release even though the vehicle may not have been recovered.

Objectives

To establish a body of knowledge about the reaerosolization potential of *B. anthracis* by comparing different agent preparations (wet, dry, w/additives, etc.) and compare energizing methods

To be able to estimate risk posed to people in facilities after decontamination from a particular powder exposure and through use of decontaminated equipment (e.g., mail sorters)

What is the research?

Controlled testing in which a number of different surfaces are exposed to a series of well-characterized simulant formulations via the aerosol route, at which point specified energies are applied via practical means and the rates of aerosolization measured. This will generate a matrix of reaerosolization properties of spores in many different situations which can be utilized in any future release of spores. These properties include particle size and charge, as well as spatial and temporal characteristics of the plume created by energizing spore preparations.

How would it be done?

In a controlled aerosol chamber, a combination of surfaces (carpet, tile, paper, mail, etc.), simulant formulations (*B. globigii*, *B. thuringiensis*, variable vs homogenous/respirable spore size mixtures) and preparations (wet and dry powders, additives such as silica or benzonite, fluids, etc.), and means of applying energy (walking on, shuffling papers, fanned, etc.) would be specified. A test matrix would be derived from the above, and the rates of aerosolization measured via air sampling and selected analytical methods (culture, PCR, immunoassay, etc.).

Materials containing fomites resulting from cross-contamination will be tested to see if there is sufficient amount of material to create a secondary aerosolization.(opening a letter that is cross contaminated via a mail sorting machine)

It is possible that similar experiments could be carried out at field sites where contamination is already evident (especially the very heavy contamination of sites like the Hart Building) but this would have to be organized in the very near term as decontamination efforts will soon make this data difficult to obtain from these sites. These experiments would be particularly useful in the context of cross-contaminated mail which could also be transported to an aerosol chamber for attempted reaerosolization of residual spores.

Possible Locations

Research Triangle Institute, University of Cincinnati, UNLV, University of Colorado Boulder, USArmy (CDBC), Battelle, USArmy (Edgewood)

When should it be started?

The fomite (cross-contamination) assessment can be immediately piggy backed to ongoing experiments at Edgewood where they are using mail containing BG and determining the aerosolization risk when the contaminated letters are sent through a mail sorter machine. The controlled room and surface experiments can be completed for using a RFP.

Working Group 4: Surveillance

Recommended Research Priorities

Background

During the months of September through November, 2001, eleven cases of inhalational anthrax and 12 cases of cutaneous anthrax were seen in the United States in the wake of a deliberate introduction of the bacterium through the U.S. Postal System. Initial cases were first reported from Florida and New York City; subsequent cases were later reported in Washington, DC, New Jersey, and Connecticut.

In order to detect potential cases as early as possible, to provide continuous case-finding capacity, and to retrospectively identify additional cases that might have been missed, each site implemented some combination of active and passive surveillance for both inhalational and cutaneous disease. Although specifics differed slightly between sites, the surveillance generally took the form of active emergency room and intensive care unit surveillance, and a passive reporting system of suspicious cases by local providers. In addition, active surveillance was conducted among several groups who seemed to be at particularly high risk (postal workers, transit authority workers, media employees).

In a retrospective assessment of the implemented surveillance systems, it was clear that several aspects of these systems had significant gaps, and there were several areas in which improvement could be made. The purpose of the surveillance working group was to identify such gaps or problems with the current systems; to identify the key areas of surveillance in which further consideration and research is most needed; and to prioritize these research needs for the next 12 months.

During discussions, the working group identified several key issues and topics that were displayed by the current surveillance systems; such issues included the importance of physician and provider education in the success of an anthrax surveillance system, and the need for a strong partnership with physicians and providers; the potential importance of animal and veterinary surveillance with regard to anthrax, and the problems associated with the merging of animal and human surveillance; the need for reliable, accurate and rapid diagnostic testing for anthrax; the potential utility of the media as a partner in bioterrorism-related surveillance; and the need for continued active surveillance among those groups seemingly at highest risk (postal workers).

From these issues, the five key items for the near-term research agenda were identified. These included the need for continued surveillance of illness and absenteeism in U.S. Postal Workers; the need for veterinary surveillance and the need to integrate it with human surveillance; the use of other, alternative sources for surveillance; the development of potential scenarios with respect to GI anthrax and complex release situations; and a comprehensive evaluation of the systems used with this outbreak, and with the World Trade Center incident.

Research Priority 1

Title: Veterinary surveillance, and integration with human health information

Why is the research being done?

Previous outbreaks have indicated that many animals may serve as sensitive sentinels for public health events, and may portend upcoming outbreaks of illness among human populations (ex. Crows in West Nile virus outbreaks; prairie dog die-offs in plague)

What is the research?

1. Development and evaluation of scenarios in which animals might serve as sentinels for the early detection of public health events
2. The evaluation of the ability of the current animal health surveillance system to detect bioterrorism-related diseases, and the capacity of these systems to communicate these events to the human public health system
3. To evaluate which particular species of animals may best serve as sentinels for bioterrorism-related disease, and to determine disease-specific animals in question.

How would it be done?

A veterinary working group would develop and analyze various scenarios. Barriers to communication, and exact communication needs between veterinary groups and the human public health system would be assessed.

Who should do it?

Members/representatives of the national public health system and various local and state public health systems would collaborate with members/representatives of various veterinary groups (AAVLD, USAHA, AVMA, F&WL)

When should it be done?

Immediately. CDC should work to identify other potential stakeholders in this issue.

Research Priority 2

Title: The use of other, alternative sources of data in the surveillance for bioterrorist-related events

A. Why should the research be done?

It is possible that systems already in place could augment or aid traditional surveillance systems for bioterrorism-related disease. In addition, it is necessary to identify ways in which current data sets used for surveillance can be improved

B. What is the research?

1. Descriptive: to address the timeliness, utility, sensitivity/specificity, usefulness, and portability of information available from alternative data sources, and to assess the ability for this information to be rapidly used.
2. Demonstration: To apply a scenario to each data source and demonstrate its ability to detect cases
3. Development: To develop standard queries that can be applied to data sets

Essentially, three categories of data sources were envisioned:

1. Hospital information systems, including:
 - a. Hospital utilization data
 - b. Infection control personnel
 - c. Laboratory data
 - d. HEDIS/Quality measures
 - e. Intensive care unit (ICU) surveillance
 - f. Emergency department (ED) surveillance
2. Emergency services
 - a. 911 data
 - b. Emergency medical technician (EMT) data
 - c. Poison control data
 - d. Nurse call lines
 - e. Urgent care outpatient centers
3. Other non-reportable data
 - a. Pharmacies/pharmaceutical services
 - b. Veterinarian laboratory data
 - c. Medical examiners/coroners
 - d. Commercial laboratories
 - e. Employee absenteeism from occupational data sets

C. How would the research be done?

1. Data sources for study would be identified, using a working group of subject matter experts
2. External grants and cooperative agreements with bodies/agencies with interest in the matter would be used to help facilitate working groups

D. Who would do the research?

Data sources would be obtained from a variety of sources of interest, including but not limited to:

- a. Hospitals
- b. Academic medical centers
- c. Peer-review organizations
- d. Healthcare providers
- e. HMO's
- f. Association of Schools of Public Health
- g. CDC
- h. State and local health departments

- i. Foundations (Robert Wood Johnson, Carter Center, etc.)
- E. When should the research be done?
Now. Coordination could be arranged through NCID channels or DHQP prevention epicenters.

Research Priority 3

Title: Design and validation of surveillance systems to detect complex contamination or release scenarios

- A. Why is the research being done?

The present outbreak presented a multitude of challenges in terms of surveillance, diagnosis, treatment, and public health action in general. There are several potential scenarios in which these problems could potentially be multiplied; such scenarios include contamination of a widely dispersed food source, leading to a large and disperse outbreak of gastrointestinal anthrax; exposure in a mobile population; and attack or contamination with multiple bioterrorism agents. Thinking out these possible scenarios, and designing effective surveillance approaches beforehand, may lead to much greater preparedness in these events.

- B. What is the research?

Exposure scenarios, including those mentioned above and others, would be created by the involved groups. Systems for effective surveillance would be proposed to these outlined scenarios. The systems would be validated by methodologies to be determined.

- C. How would it be done?

Methodologies would be determined by the working groups

- D. Who should do the research?

Federal, state, and local public health departments; academic institutions; and other professional organizations with particular bodies of expertise should be included.

- F. When should it start?

Immediately.

Research Priority 4

Title: Evaluation of event-specific surveillance activities in the wake of the current outbreak

A. Why should the research be done?

Since September 11, 2001, a number of surveillance activities have been conducted, but the exact utility of these systems has not been clear, and the potential role for future situations has not been assessed. Similarly, event-specific surveillance activities have been conducted around the recent events and others (World Trade Center incident; conventions; sporting events); evaluation of these surveillance activities remains to be conducted.

B. What is the research?

Application of the basic methodologies of surveillance system analysis (eg. Sensitivity, specificity, positive and negative predictive value, timeliness, acceptability, cost) to recent surveillance activities.

C. How should the research be conducted?

1. Surveillance for human anthrax in DC, NJ/PA/DE, NYC, CT, FL, Postal facilities
 - a. The surveillance system analysis described above should be conducted
 - b. How were cases/suspect cases identified? How did this change over time during the investigations? What are strategies for making the systems more specific and more manageable?
 - c. What is the role of various other parties, including state and local health departments, health care providers, and others?
 - d. How do we optimize the role of other important players including infection control personnel, provider networks, etc.
 - e. Are the current systems sustainable, in terms of cost, manpower, and efficiency, and if not, how can they be made sustainable?
 - f. What was the efficacy of the various efforts to relay information and communicate, including mass faxes, internet postings to solicit reports, mailings, etc.
2. Other event-specific surveillance activities, including “drop-in” surveillance
 - a. Formal surveillance system analysis should be conducted

D. How should the research be conducted?

It should be coordinated internally or through contacts or cooperative agreements

When should it be conducted?

Should be commenced immediately, through coordination of the multiple involved stakeholders, including NCID, EPO, and state and local health agencies.

Research Priority 5

Title: Surveillance of Illness and Absenteeism in U.S. Postal Workers

A. Why is the research being done: Recent mailings of envelopes with *Bacillus anthracis* have resulted in environmental contamination of several USPS facilities and cases of inhalation and cutaneous anthrax among exposed workers. To help protect workers from further exposure and disease a number of interventions have been put into place including administration of PEP, when indicated, coupled with monitoring of adherence and development of any associated adverse events; recommendations for engineering, administrative, and housekeeping controls, and personal protective equipment; and environmental cleaning and remediation of facilities. Nonetheless, postal workers may be at increased risk for exposure to *B. anthracis* as a result of the initial contamination of the mail system that occurred in September and October or from new contamination events.

B. What is the research: Development, evaluation, and comparison of different systems of surveillance to detect unexplained absenteeism and illness among postal workers that may represent cases of inhalational and cutaneous anthrax.

C. How would it be done:

1) Obtain relevant background information from USPS

USPS has an ongoing system of absenteeism tracking among workers; in addition, USPS in response to the cases of anthrax in its work force developed a plan to augmented this routine system to be more pro-active (i.e., initiate calls to workers for unexplained absenteeism). More information is needed about the mechanics of these systems and how they have performed to date (e.g., their sensitivity and completeness in capturing information about workers with “suspect anthrax” who were reported to other entities, such as CDC’s State and Field Teams).

Additional information is needed regarding provision of health care to postal workers (e.g., are there certain HMOs or other networks that postal workers preferentially enroll in; does this differ by geographic area, etc.) and existing occupational health services within USPS.

2) Identify cohorts of workers for surveillance

Workers theoretically at highest risk of exposure would be those who worked at the “index” processing and distribution centers (e.g., Hamilton, Brentwood, Morgan, Wallingford, West Palm Beach Main). Lower risk cohorts would include those who worked at postal facilities (both with and without high speed sorting machines) “downstream” from the index facilities. Workers at facilities that did not receive mail from index processing and distribution centers facilities (if such facilities can be identified) or workers at facilities that have not been part of the outbreak investigations and have tested “negative” by environmental sampling by USPS theoretically would be at lowest risk.

Workers in the highest exposure risk group should be included. Resources and other factors will determine ability to expand beyond this group.

3) Design, implement, and evaluate different systems of surveillance

a) Absenteeism evaluation

Methods: Building on efforts that USPS has already developed, employees would be contacted after a pre-determined period (e.g., 48 hours) of unexplained absence from work to establish if the worker is ill. If so, a systematic, brief query of worker (or proxy, if too ill) would be performed to establish if 1) respiratory or cutaneous illness present; 2) worker hospitalized, or 3) further follow-up required.

b) Hospital-based surveillance

Methods: Hospitals in the catchment areas where postal workers under surveillance might seek care would report on a pre-determined basis (e.g., daily vs 2-3x/week) any hospitalizations or Emergency Department visits by postal workers to health departments. Further follow-up would be initiated for “high-risk” respiratory or cutaneous illness.

c) Provider surveillance

Methods: If a sizeable fraction of postal workers in catchment areas under surveillance receive care from a circumscribed network of providers or HMOs, such providers or organizations would report on a pre-determined basis (daily vs 2-3x/week) any visits by postal workers to health departments. Further follow-up would be initiated for “high-risk” respiratory or cutaneous illness.

d) Death certificate review

Methods: Death certificates in states where postal workers are under surveillance would be reviewed for any death in a person identified to be a postal worker.

Analyses: The various surveillance approaches could be individually evaluated as well as compared regarding detection of “high-risk” illnesses (not necessarily limited to anthrax) in high risk cohorts of workers. Other research questions of potential interest could include estimation of the frequency of “high-risk” illnesses (would require denominator data) and if that varied by level of exposure in the cohorts (provided more than the highest risk cohort of workers was evaluated) and comparison of temporal trends in worker absenteeism for the 6-month/12 month (?) period following October 4, 2001 with the previous year.

D. Where/who should do: Multiple partners including CDC (including NIOSH), USPS (both management and labor), health departments, hospitals, health departments.

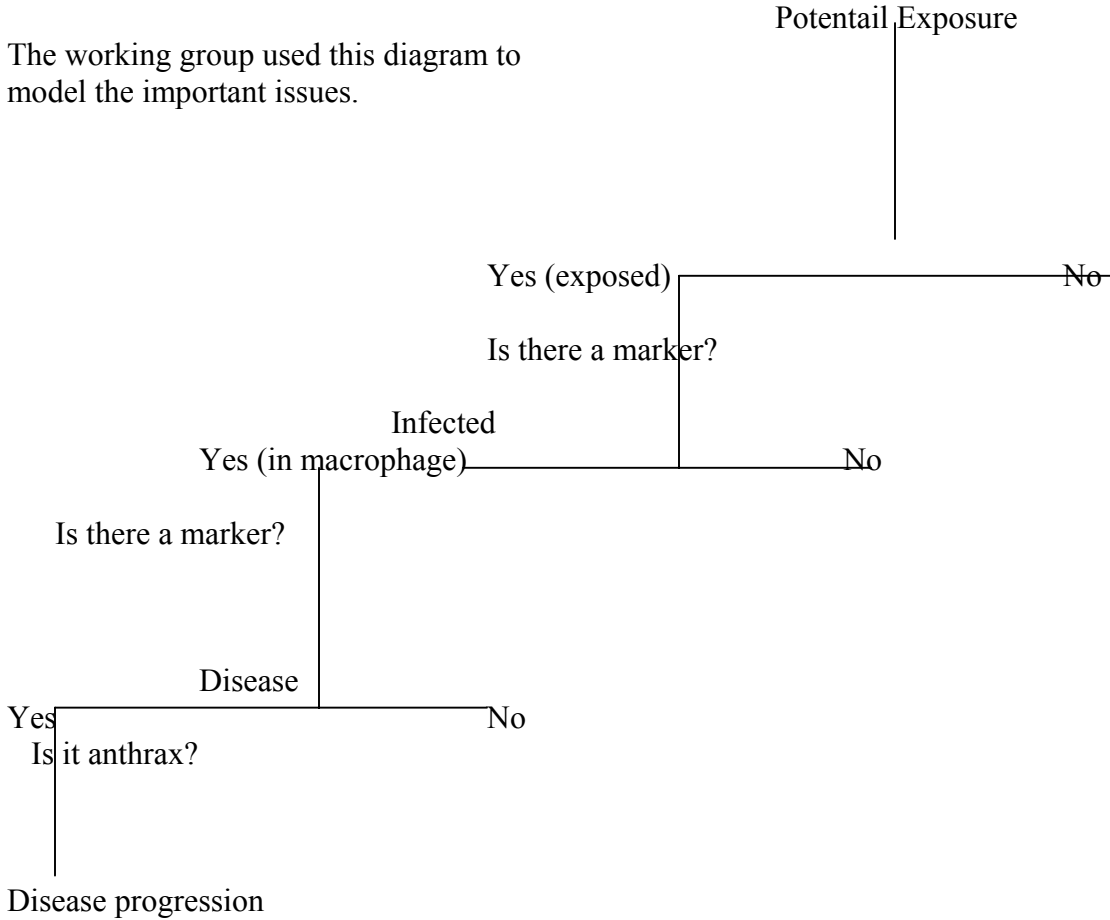
E. When should it start: Very high priority that should be initiated immediately.

Working Group 5: Diagnosis

Recommended Research Priorities

Background

The working group used this diagram to model the important issues.



Research Priority 1

Title: Identifying the earliest detectable event in the continuum from exposure to anthrax → disease

Goal: To identify a test which will assist the clinician in answering the following two questions:

1. Does an asymptomatic potentially exposed individual require PEP?
2. When can the asymptomatic individual on PEP discontinue their antibiotics?

Objective: Use animal models to identify and prioritize potential early markers within the continuum of exposure to disease.

- A. Technologies to investigate and prioritize [not exhaustive, currently existing or under development]:
 1. Pathogen-related technologies

- a. Culture
- b. DNA [technology=diagnostic PCR by microarray]
- c. Toxins [technology= Time Released Fluorescence (TRF)]
- d. Spores [technology=TRF]
- 2. Host-related technologies
 - a. Gene transcription [technology=microarray; PCR]
 - b. Host Cell Response [technology=Proteomics; C-fiber stimulation]
 - c. Immune Response
 - i. Cytokine upregulation and downregulation
 - ii. IgM, IgG [targets=PA, LF, EF, spore, capsule]
- B. Aspects of animal model to consider:
 - 1. Timing of specimen collection
 - 2. Manner of collection and preservation
 - 3. Specimen types
 - 4. Species
 - 5. Other groups' ongoing research and possibility of serial sacrifices

Who:

- CDC
- Battelle
- University of GA
- Emory University
- NIH
- USAMRIID
- Harvard Medical School
- Stanford
- Pasteur Institute
- Israel – Weisman Institute
- England – Porton Down

Where: Consider Plum Island (60,000 sq ft available)

When: Start now / as soon as protocols approved by all groups

Research Priority 2

Title: Rapid Diagnosis of Anthrax

Goal: To make available a rapid test at the facility-level to assist the clinician who suspects anthrax (To address question 4 of introduction)

Objectives:

1. Perform inventory of diagnostic tests currently available in commercial institutes, academic institutions, government agencies.
 - a. Complete a survey of rapid tests for all infectious agents to develop platform technologies. This will involve coordinating a meeting to promote collaboration and pooling of resources.
 - b. Develop validation process for tests
 - c. Evaluate tests
2. Determine how better to use and distribute diagnostic technologies currently available.
3. Reevaluate currently available tests in setting of new technologies.
4. Identify gaps in current diagnostic methods.

Where: NIH/CDC to facilitate collaboration between multiple agencies

When: First quarter 2002 [Planning of meeting to begin immediately involving identification of all appropriate companies, agencies, and departments for inclusion]

Research Priority 3

Title: Developing a library of subtypes

Goal: To enhance resolution of current subtyping techniques to prepare for future outbreaks of *B. anthracis* and other BT agents

Objectives:

1. To develop a representative and diverse sample collection with a curator (at CDC).
Collection should include:
 - a. Geographic diversity
 - b. Temporal diversity
 - c. Species diversity
 - d. Source diversity
2. To characterize these samples by all known subtyping methods
3. To obtain collection of control organisms [organisms closely related to *B. anthracis*]
4. To develop similar libraries of other BT agents

Who:

- * CDC
- * ATCC
- Louisiana State University
- Los Alamos
- AFIP
- Northern Arizona Univ
- Caspary

When: Now

Working Group 6: Treatment

Recommended Research Priorities

Research Priority 1

Title: Investigation of the role of immune and anti-toxin therapies – a framework.

- I. Passive Immunotherapies
 - A. Antitoxin Therapies
 - i. Immunoglobulin – Human – immune modulating effect?
 1. 10 U available for compassionate use
 2. human consent, double-blind study on serum from 450 vaccinated individuals, dosage?
 3. Potential cost: \$2 million for processing of sera from 1200 donors
 4. Small scale treatment vs. stockpile
 - ii. Immunoglobulin – Animal: decreased adverse effects with equine sera stripped of F_c
 1. different effectiveness of animal vs. human immunoglobulin ?
 2. difference in mortalities with use of equine antisera- data from Europe?
 3. protection in animals if given prophylactically
 - iii. Polyclonal immune therapy – other components of product-LEF, opsonic
 1. test in parallel with Anti-PA
 2. how well do adjuncts work?
 3. measure antibody levels and compare with antigen levels in immunized
 - iv. Monoclonal immune therapy – specifically directed against PA (trials ongoing), target single epitope, toxin in human does not differ substantially, developing monoclonal antibodies with increasing affinities- predicted product in 18 mos?
 - v. Dominant Negative Mutants
 1. assess levels, pharmacokinetics, t_{1/2} of product in human system
 2. phase 1: assess efficacy in animal model
 3. phase 2: assess pharmacokinetics in human system
 4. can GNP be developed quickly?
 - vi. Metalloprotease inhibitors (ACE I)
 - vii. Activated Protein C
 - viii. Amines

B. Antibody response from survivors: Late response, earliest response seen at 10 days, cutaneous with greater delayed anti PA response

Research Priority 2

Title: Expanded investigation of antibiotic therapies in animal models.

- II. Antibiotic Therapies – 2 beta lactamases produced; “penicillinase” and “cephalosporinase”; when is each activated?
 - A. Monotherapy: advantage of single agent for treatment is decreased toxicity
 1. Develop animal models to obtain additional data: clindamycin, tetracyclines, rifampin, amoxicillin (increased risk of mutational event)
 2. Obtain additional data: linezolid, carbapenems, ketolides (low MIC, unknown safety), lincomycin, macrolides, (azithromycin, clarithromycin MIC < 0.25 in 15 strains tested)
 3. clindamycin: more potent suppression based on antibiotic concentrations, actively transported
 - 1) excellent results with *Clostridium perfringens* and group A strep
 - B. Synergistic Therapy: difficult to show additive effects
 1. *in vitro* vs. *in vivo*
 2. animal model to evaluate toxin production with synergistic therapy
 3. aminoglycosides in combination with other antibiotics
 4. carbapenems; appear active with good penetrance
 5. ciprofloxacin and rifampin: increased tissue penetrance?
 6. rifampin exerts effect during stationary growth phase
 - C. Combine antitoxins and antibiotics for treatment: early intervention proposed; study to evaluate with variable arms to compare treatments; antitoxin alone, antitox + abx, abx alone
 - D. in previous 10 cases, no DIC, clinical course differed from acute bacterial sepsis
 - E. disease caused by *B. anthracis* appears to be more toxin mediated
 - F. develop cytokine profiles

Research Priority 3

Title: Developing Alternative Animal Models

Other nonhuman primates (other than *rhesus* monkeys)

Rabbits: rapid progression of disease, ?more susceptible to *B. anthracis*, not ideal for immunological studies, different cytokines and complements

Guinea pigs: do not reflect primate response for vaccine evaluations

Evaluate pharmacokinetics, toxin levels, viable organisms in animal models

Bridging studies between species and from animals to human

Other Discussion

Empiric Therapy: oral mass casualty versus individual treatment

naturally occurring quinolone resistance?, low organism burden, gyrase related

extracellular vs. intracellular manifestations; do spores vegetate in macrophages?

1. toxin assay (biological activity) measure suppression, macrophage assay
2. protein inhibitors appear effective

Steroids: used in some of current inhalational and 1 cutaneous case

3. anecdotal reports in literature, studies ongoing with steroids in septic shock
4. studies planned with lethal toxin and edema toxin, *in vitro* studies examining cAMP
5. in 10 clinical cases: hemorrhagic events with organisms obstructing blood vessels
6. lymphatic obstruction in mediastinum with dilated lymphatic channels

Long Term Therapy (2^o Prophylaxis); likely intracellular activities

antibiotic regimen does not affect spores, concern based on inoculum cutaneous disease – no recurrence known with zoonotic cutaneous ds.

Reports of meningitis developing from cutaneous disease
inhalational disease – induction of immune response due to bacteremia, spectrum of immune response varies

pathways: 1) stop tx, monitor clinically and serologically OR 2) administer antibiotic therapy for number of weeks, follow with vaccine

outcome with cutaneous disease in setting of inhalational exposure:

- what is the immune response?
- who should be vaccinated?
- is there subclinical infection?
- is there degradation of spores?

Limitation of Studies:

Ability of animal models, availability of animals

Facilities for creating inhalational exposures, but for therapy investigations, may not have to aerosolize as action may be primarily extracellular

Working Group 7: Post-exposure Prophylaxis

Research Priority 1

Title: Long Term Use of Antimicrobials for PEP: Monitoring of Adherence, Barriers to Adherence, and Adverse Events

Why is the research being done?:

Prepare a series of materials so adherence is monitored and promoted more effectively during potential future anthrax post exposure prophylaxis campaigns.

Optimize compliance with recommendations for PEP

What is the research?:

Monitor level and process of adherence to PEP

Identify individuals at risk for non-adherence

Identify barriers to adherence, including side effects that may affect adherence

Clarify and specify the interventions that will improve adherence

- Clarify/educate/communicate regarding rationale for antibiotics
- Explore the use of a hotline for persons on PEP with questions about their antibiotic use
- Communicate for the buy-in of affected cohort – address potential cynicism/mistrust; develop method for delivering message to achieve buy-in (e.g. explanation of environmental data relevant to the individual and what it means as far as risk)
- Proactive management of side effects
- Identification of environmental cues (e.g. calendars, beepers, pill bottle next to toothbrush) to decrease forgetting pills

Evaluate the systems through which these assessments/interventions will be implemented

Develop blueprint for identifying critical organizations/players/systems (e.g. occupational health clinics; local/county/state health departments; management; unions; professional organizations)

Monitor impact of adverse events on adherence

Evaluate messages obtained from media during current campaign and their effect on knowledge/attitudes/beliefs

How would it be done?

Immediate projects:

1. Post-60 day quantitative evaluations of adherence, barriers to adherence (e.g. could not get to refill, misperception of risk, etc.) at least 3 sites
 - representative sample from each area
 - appropriate method (telephone survey, interview) to be determined
2. Real time evaluation of adherence and barriers to adherence in Connecticut using MEMS caps and brief survey/questionnaire in a representative sample
3. Employ MEMS caps and/or diaries for a subset of those getting vaccine in addition to antibiotics following the initial 60 day PEP campaign.

Projects in the event of subsequent anthrax release:

1. Development of introductory screening survey that collects demographic information (e.g. employment info, work schedule, contact information, living situation, gender, race/ethnicity). This survey would be administered on day 1 to anyone receiving antibiotics for PEP from the National Pharmaceutical Stockpile.

Data would be used for the following purposes:

- lay groundwork for later identification of predictors of non-adherence (inconsistent work schedule, living alone, gender/race)
 - identify individuals at risk for non-adherence and direct interventions based on what is already known about risk factors for non-adherence
 - determine whether follow-up information draws from a representative sample of the cohort in question
2. Develop a system such that a random sample of individuals getting antimicrobials for PEP from the National Pharmaceutical Stockpile receive bottles with MEMS caps. Study the adherence to PEP in this subset from the day one.

Where could it be done?:

Post 60 day follow-up: Washington DC, New York, New Jersey, Florida

Real time adherence data using MEMS caps: Connecticut

Development of adherence/adverse event monitoring materials for future event: Atlanta - CDC/contractor

Who could do it? (which institutions should collaborate?)

CDC/NCID (contractor)

collaborators: FDA, NIH, academic experts, CDC/NIP

When should it be started (including action step with assigned responsibility)?

60 day follow-up plans that are already underway should continue to be developed under the lead of an additional staff member assigned to the CDC's adverse events and adherence working group.

30 day follow-up plans in Connecticut (and consideration of the addition of MEMS caps to monitor adherence) should fall to an additional staff member assigned to the CDC's adverse events and adherence working group.

Research Priority 2

Title: Pediatric safety and immunogenicity study

Why is the research being done? No pediatric data. Need FDA indication for pediatrics. Children compose 20% of the US population, and maybe specifically targeted by terrorists particularly in locations such as schools and Day Care Centers. Young infants may be at higher risk for infection related to immature immune response, anatomic, physiologic, and behavioral differences. Prolonged antibiotic exposure may have more adverse consequences than observed in adults. A 60-day course of antibiotics alone may not be protective in this population sub-group.

What is the research? Phase I, Open-label, dose-escalation, immunogenicity, and safety in three age cohorts.

Age Cohorts
11-17
2-11

<2 years

Ten males and 10 females in each group to identify possible gender differences.

Route: IM

Schedule: 0, 2 weeks, 4 weeks

Formulation: 1:10 dose, 1:5 dose; full dose

Bleed Schedule: 4 weeks, 8 weeks for essential end-points with six-week bleed to capture peak antibody level.

How would it be done? The CDC Human Anthrax Vaccine Research Network and additional pediatric centers. Research results can be compared with adult studies currently underway.

Where could it be done? See above.

Who could do it? See above.

When should it be started? This can begin as soon as IND and IRB approval are obtained. Sufficient vaccine stocks will be available.

Research Priority 3

Title: Animal challenge study to optimize post-exposure prophylaxis in humans

Why is this research being done:

Recent bioterrorist dissemination of B. anthracis through the mail together with aerosolization models suggest that the level of exposure to B. anthracis in future events may be much greater than that for which PEP effectiveness information is available. Concerns that 1% retention of spores at 60 days may represent a dangerous level if initial exposures are very high lead to the need to evaluate alternative PEP regimens against a higher dose exposure.

What is the research:

This proposal involves a large animal challenge study which incorporates survival, estimate of spore retention/clearance (either via autopsy or if feasible, bronchoscopic biopsy evaluation), and in certain arms, serologic evaluation. The principal objectives are to:

- a. Determine whether a high dose (400 LD 50's? something comparable to Canadian aerosolization model and to Daschle letter content) challenge requires PEP to be continued for >60 days
- b. Determine whether vaccine administration early in PEP can shorten the duration of PEP needed for protection following a high dose exposure
- c. Evaluate the utility of alternate antibiotic agents which are preferred for populations with unmet needs (eg, pregnant women, children) or which may lead to greater adherence (eg, fewer side effects or less frequent dosing) or which would expand armamentarium in the event of engineered resistance to current drugs

- d. Determine whether intermittent dosing of the standard agent can enhance effectiveness through initiating immune response to transient exposure to germinated organisms

How would the research be done: (see table)

Using acceptable animal model, deliver 200-400 LD₅₀ anthrax aerosol challenge on Day 0, institute the following post-exposure regimens on Day 1:

Group	N	Day 1	Day 14	Day 30	Day 42	Day 60	Day 90	Day 120	Day 150
Doxy for 30 days + 3 doses AVA	?	V	V,B	V,B	B	B	B	B	B, N
Doxy for 30 days	?								N
Doxy for 30 days	?	N							
Doxy for 60 days	?					N			
Doxy for 60 days	?								N
Doxy for 10 days, then Mon, Wed, Fri for total of 60 days	?			B		B	B		N
Doxy for 90 days	?								N
Doxy for 120 days	?	B	B	B	B	B	B	B	B,N
Doxy for 120 days	?							N	
Amoxi BID for 60 days	?			B		B	B		N
Long-acting macrolide SID for 60 days	?			B		B	B		N
Controls (no PEP)	?	(Necropsy to count spores and to confirm death as anthrax)							

Legend: V = anthrax vaccine B= bleed for serology (ELISA and TNA) N=necropsy & spore count

Who could do it: This will be a multiagency collaboration with an integrated project team involved in planning and a scientific steering committee providing oversight. Partners with the ability to undertake this type of large-scale animal study with BSL3 requirements include Battelle & USAMRID. The public health questions at the centerpiece suggest a need for CDC involvement in the collaboration.

When should it be started/action step w/ assigned responsibility:

The lack of available macaques in addition to their price make the most urgent action step that of identifying a suitable alternate animal model. Immediate steps to identify such a model will involve the convening of an “Integrated Project Team’ with subject matter experts and others to review available data regarding alternate animals (USAMRID proposed to organize this meeting by February 1 if possible). The next step following the identification of a potentially suitable alternate model would be to conduct a small pilot study of infectious challenge, autopsy review, and serology assessment in the proposed animal. In the meantime, protocol development for the full-scale study could go forward including biostatistical assessments of the sample size needed for each study arm for the highest priority research questions

Working Group 8: Remediation

Recommended Research Priorities

INTRODUCTION

Remediation strategies would depend on a number of factors including the level of contamination, the type of space being treated, and whether contamination was localized or disperse. These strategies range from physical cleaning methods to physically remove contaminants from surfaces to the use of more potent chemical biocides. The World Health Organization in their Guidelines for the Surveillance and Control of Anthrax in Human and Animals (3rd Edition; http://www.who.int/emc-documents/zoonoses/docs/whoemczdi986_nofigs.html) recommends the use of formaldehyde for disinfecting areas contaminated with *Bacillus anthracis* spores. Other agents recommend by WHO include: glutaraldehyde, peracetic acid, and hydrogen peroxide.

Formaldehyde has been used in the for decontamination of biological safety cabinets (BSCs), procedure rooms, and laboratories by CDC, USDA, DOD, in addition to textile mills (Young LS, Feeley JC, Brachman PS. Vaporized formaldehyde treatment of a textile mill contaminated with *Bacillus anthracis*. *Arch Environ Health*. 1970;20[3]:400-403). However, based on environmental protection and human/animal health hazards, alternatives to formaldehyde as the recommended general-purpose disinfectant have been sought. We have no experience with the use of large-area decontamination of more complex spaces, i.e. postal sorting facilities and large office complexes, or outdoor spaces such as stadiums.

Currently available sterilization methods for miscellaneous articles, critical items, and large spaces include the following:

Artifacts, office articles and critical items: depending on the nature of the items that need to be recovered, treatments may vary and may include the following options: ethylene oxide sterilization, vapor phase hydrogen peroxide, chambered formaldehyde; and autoclaved of heat stable items.

Areas: Clean up will depend on the level of contamination and whether it is diffuse or point source. The dispersion of spores from an aerosolization event would be characterized by sampling and indicated by wide spread contamination within a facility. Remediation options may range from surface cleaning to fumigation.

- a. Disperse contamination may be indicative of an aerosolization event.
- b. Point source contamination along the pathway of mail or foot traffic supports localized cross-contamination. Point source contamination may lead to wide spread dispersal by means of reaerosolization following the laws of particle physics.

The simplest method to use is soap and water cleaning to physically remove spores from contaminated surfaces. However, if germicidal activity is needed then sodium hypochlorite or chlorine dioxide solution can be used. If sterilization is attempted formaldehyde, glutaraldehyde, hydrogen peroxide, peracetic (peroxyacetic) acid, peracetic acid and hydrogen peroxide mixture, amyphenol, amyphenol+phenylphenol can be used. Each of these substances has advantages and limitations, including potential carcinogenicity and other associated health risks.

Other potential surface decontamination agents include Enviro-foam, nanoemulsion, EDT, GD-5, etc which require further evaluation.

Sporicidal fumigants include: Ethylene oxide, Formaldehyde, Ozone and Chlorine dioxide gas. The weaknesses are that there have been no standardized studies relevant to the large-area decontamination of federal facilities, airports, subways, office buildings, sports arenas, etc.

Many of these chemicals are toxic to humans. Ethylene oxide and formaldehyde are probable human carcinogens. Exposure to ethylene oxide (ETO) concentrations above 2,000 ppm has resulted in headache, nausea, vomiting, dyspnea, hematological abnormalities, and respiratory irritation. Exposure to formaldehyde (HCHO) concentrations of 10 to 20 ppm produces immediate eye irritation and a sharp burning sensation of the nose and throat which may be associated with sneezing, difficulty in taking a deep breath, and coughing; recovery is prompt from these transient effects. Prolonged formaldehyde exposure can also result in chronic allergenicity.

The IDLHs for these chemical substance are as follows: chlorine dioxide 5 ppm, formaldehyde 20 ppm, and 800ppm for Ethylene oxide. All fumigants require off gassing (aeration) and/or inactivation prior to allowing personnel to reenter

Irradiation by UV, X-rays, gamma rays and high-energy electrons may also be used for surface and penetrating decontamination.

Research Needs

The group identified 12 high-need research areas and down selected these into three priority knowledge gaps: (1) evaluation of existing and innovative sporicidal remediation methods, (2) risk based decision logic for bioagent sampling and remediation, and (3) re-aerosolization and transport studies. The additional research needs that are would be of interest include: collection, treatment, QA of decontamination waste; sampling standardization; efficacy of control strategies for airborne infectious agents; building protection; re-occupancy and article release criteria; development of evacuation and isolation criteria; and effective communication of risk.

Research Priority 1

Title: Evaluation of Existing and Alternative Remediation Agents

Rationale: As a result of the recent events involving anthrax-laced letters sent through the mail, many buildings have been contaminated in the Eastern United States. Contaminated buildings include US Postal facilities, News media buildings/offices, and many government buildings in the District of Columbia. Contamination in those buildings includes areas that were contaminated by cross-contaminated mail, foot traffic, or and aerosol dispersion from contaminated mail sorting equipment that processed that anthrax containing letters and in offices where anthrax containing letters were opened.

Bacillus anthracis spores are the most difficult of the bioweapons to address in remediation processes. Little is known about how to in actual fact remediate the most contaminated source sites and there are few choices that can be made based on existing products or technologies. In order to make the best choices for selecting the appropriate agents to clean contaminated buildings well validated methods to assess currently available products or technologies and to assess new and innovative methods are needed.

Nature of Research: The research should address areas which have an impact on site remediation and may include physical, mechanical, or chemical approaches. In addition, there is also a need for real-time tools that can be used to assess the remediation process. Research focal areas should include

- Analysis of physical and mechanical methods for reducing bioburden or load.
- Controlled, comparative studies on the efficacy of existing liquid agents.
- Model studies on gaseous and vapor space treatments.
- Studies of emerging methods or approaches to decontamination and disinfection.
- Tools for assessing remediation efficiency in real time real-time.

Site of research: The working group proposes that studies be initiated under well-controlled laboratory conditions. Once laboratory studies have been completed then pilot-scale studies could begin followed by field-testing. Portions of this research could be performed at EPA, CDC, DOD, Academia, National labs, and private industry partners. The project would require a certain number of workgroup meetings, as well as teleconferences on an as-needed basis.

Project leader(s): A joint CDC/EPA/DOD lead would be appropriate for the anthrax-specific part of the project given the nature of the research to be accomplished. Scientists from other agencies and organizations should be included. An appropriate core group for the research could be a subset of the members of the remediation workgroup from the CDC December 10-11 research priorities meeting. This work could be done through interagency agreements, grants, and cooperative agreements.

Projected start date: As soon as possible

Research Priority 2

Title: Risk-Based Decision Logic for Sampling and Remediation

Rationale for project: As a result of the recent bioattacks with *Bacillus anthracis*, a number of sites need to be remediated. Each of these sites may pose unique problems. Current guidelines for sampling are incomplete and have not been validated. In addition, it is not clear that existing guidelines and protocols are being applied consistently. Further, comprehensive guidelines do not exist for the remediation of office, commercial, industrial and residential buildings or areas within such buildings. In fact, previous cleanups of anthrax contamination have occurred only at military and laboratory sites.

Nature of the research: The research will consist of two tasks related to sampling and remediation of anthrax-contaminated sites. Task 1 will be the development of sampling strategies. This effort will include identification and refinement of the appropriate techniques, when and where to apply them, characterization of the identified contamination, and determination of the efficacy of the remediation that will be performed. Emphasis will be placed upon the development and implementation of statistically valid sampling methods.

In Task 2 remediation strategies will be developed based upon the nature and extent of the identified contamination. It will provide a strategy for matching the remediation techniques with the characteristics of the contamination on a site- and space-specific basis. The decision logic for remediation will take into account the following considerations: type of contamination, availability and efficacy of remediation methods, available resources, duration of remediation, post-remediation use of site, and stakeholder input.

Performance of project: The first step will be the establishment of a multi-disciplinary, multi-organization group of experts who will assemble and review existing guidelines on sampling and remediation. After considering all the data, the workgroup will prepare decision logic appropriate for the range of contamination scenarios. The workgroup will also identify research needs to improve the decision logic over time. Finally, the workgroup will examine methods to generalize/adapt the decision logic to other biological and chemical agents of terrorism for which remediation will be needed.

Site of research: Any centrally located site. The project would require a certain number of workgroup meetings, as well as teleconferences on an as-needed basis. This work could be done through interagency agreements, grants, and cooperative agreements.

Project leader(s): A joint CDC/EPA/USPS lead would be appropriate for the anthrax-specific part of the project given the nature of the current bioattack. Scientists from other agencies and organizations should be included. An appropriate core group for the research could be a subset of the members of the remediation workgroup from the CDC December 10-11 research priorities meeting.

Projected start date: As soon as possible

Research Priority 3

Title: Reaerosolization studies . . . Agent- and Space-specific scenarios

Studies that define the parameters affecting the extent of reaerosolization of *Bacillus anthracis* endospores are needed as input to potential risk assessment studies for potentially exposed groups before before, during, and after remediation.

Methods are needed to quantitatively assess the potential for *B. anthracis* endospores to be reaerosolized during human activity (normal work/usage as well as during remediation). Relevant parameters that may affect reaerosolization during static and dynamic situations will be evaluated. Parameters may include (but are not limited to) size distribution of weaponized *B. anthracis*, particle charge, spore surface characteristics, spore powder additive characteristics, contaminated surface characteristics (smooth, porous, fibrous, et al.), level of surface contamination, RH, air flow, and other parameters. An appropriate simulant needs to be identified that meets the parameters identified above for use in applied studies. Using this simulant, pilot- and field-scale studies will be performed to validate the laboratory findings as well as to validate (or at least provide input to programmers) various exposure and dispersion models. Currently contaminated locations (AMI, selected POs, offices, mail investigation sites, etc.) may be ideal opportunities to initiate these studies; however, expansion to other scenarios/locations (train, metro, schools, shopping malls, existing federal test beds, etc).

This work could be done through interagency agreements, grants, and cooperative agreements. Investigators at Dugway Proving Grounds, Battelle Labs, Lovelace Respiratory Research Institute, Argonne National Lab, University of Cincinnati, University of Iowa, University of Minnesota, University of California Berkeley, University of Michigan, NIOSH, NCID, SWRI, Sandia National Laboratories, DOE, DOD, USPS, AFL-CIO, LSU, and others could conduct the studies.

Start as soon as possible.

Agenda

***Bacillus anthracis* Bioterrorism Research Priorities for Public Health Response**

Objective: To work with federal partners and other stakeholders to identify, prioritize, and coordinate near-term B. anthracis bioterrorism research for public health response.

Monday, December 10, 2001

Plenary Session I

- 08:00-08:30 Registration
- 08:30-08:35 Welcome *Jim Hughes*, Director, NCID, CDC
- 08:35-08:45 Overview of Anthrax Bioterrorism Investigation
Julie Gerberding, Acting Deputy Director, NCID, CDC
- 08:45-08:50 Administrative Issues
Richard Skibicki, DBMD/NCID/CDC
- 08:50-09:00 Meeting Objective and Organization
Bradley A. Perkins, Chief, Meningitis & Special Pathogens
Branch, DBMD/NCID/CDC

Hazard Assessment

- 09:00-09:20 Evaluation of *B. anthracis* containing powders or substances
Mathew Shaw, Battelle Memorial Institute
- 09:20-09:40 Epidemiologic Investigation
Philip Brachman, Emory University
- 09:40-10:00 Environmental Assessment
Edwin Kilbourne, ATSDR
- 10:00-10:20 Surveillance
Ruth Berkelman, Emory University
- 10:20-10:40 Break

Diagnosis, Treatment, & Prevention of Anthrax

- 10:40-11:00 Introduction
Art Friedlander, USAMRIID, DoD
- 11:00-11:20 Diagnosis
Susan Alpert, C.R. Bard Inc.
- 11:20-11:40 Treatment
Dennis Stevens, Veterans Affairs Medical Center and University of Washington
- 11:40-12:00 Post-exposure prophylaxis
Diane Murphy, FDA
- 12:00-12:20 Remediation
Dorothy Canter, EPA
- 12:20-12:40 Break (pick up lunches)

Working Group Session I (& working lunch)

- 12:40-17:30 **Working Group 1 (Red) □ Room, Mary Gay D**
Evaluation of *B. anthracis* containing powders or substances
Co-leaders:
Mike Miller, NCID/CDC (for David Wilson, FBI, who was not able to attend)
Richard Meyer, NCID/CDC
- Working Group 2 (Dark Green) □ Room, Mary Gay C**
Epidemiologic Investigation
Co-leaders:
Martin Hugh Jones, Emory University
Beth Bell, NCID/CDC
- Working Group 3 (Yellow) □ Room, Oakhurst**
Environmental Assessment
Co-leaders:
?, EPA
Ken Martinez, NISOH/CDC
- Working Group 4 (Blue) □ Room, Swanton**
Surveillance
Co-leaders:
Ruth Berkelman, Emory University
Tracee Treadwell, NCID/CDC
- Working Group 5 (Black) □ Room, Rutland**
Diagnosis

Co-leaders:

Susan Alpert, C.R. Bard
Janet Nicholson, NCID/DBMD

**Working Group 6 (Orange) □ Room, Henry Oliver E
Treatment**

Co-leaders:

Dennis Stevens, University of Washington
David Stephens, CDC/Emory University

**Working Group 7 (Lime Green) □ Room, Suite TBA
Post-Exposure Prophylaxis**

Co-leaders:

John Grabenstein, DoD
Anne Schuchat, NCID/CDC

**Working Group 8 (Pink) □ Room, Suite TBA
Remediation**

Co-leaders:

Dorothy Canter, EPA
Matthew Arduino, NCID/CDC

Tuesday, December 11

Plenary Session II

- | | |
|-------------|--|
| 08:30-08:55 | Working Group 1 Presentation
Evaluation of <i>B. anthracis</i> containing powders or substances
<i>Arnold Kaufman, NCEH, CDC</i> |
| 08:55-09:20 | Working Group 2 Presentation
Epidemiologic Investigation
<i>Don Milton, Harvard University</i> |
| 09:20-09:45 | Working Group 3 Presentation
Environmental Assessment
<i>Ken Martinez, NISOH, CDC</i> |
| 09:45-10:10 | Working Group 4 Presentation
Surveillance
<i>Ruth Berkelman, Emory University</i> |
| 10:10-10:30 | Break |
| 10:30-10:55 | Working Group 5 Presentation
Diagnosis
<i>Susan Alpert, C.R. Bard</i> |
| 10:55-11:20 | Working Group 6 Presentation
Treatment
<i>David Stephens, NCID, CDC</i> |
| 11:20-11:45 | Working Group 7 Presentation |

Post-Exposure Prophylaxis

John Grabenstein, DoD

11:45-12:10

Working Group 8 Presentation

Remediation

Matthew Arduino, NCID/CDC

Working Group Session II

12:30-15:00

Working Group 1 (Red) □ Room, Mary Gay D

Evaluation of *B. anthracis* containing powders or substances

**Working Group 2 (Dark Green) □ Room, Mary Gay C
Epidemiologic Investigation**

**Working Group 3 (Yellow) □ Room, Oakhurst
Environmental Assessment**

**Working Group 4 (Blue) □ Room, Swanton
Surveillance**

**Working Group 5 (Black) □ Room, Rutland
Diagnosis**

**Working Group 6 (Orange) □ Room, Henry Oliver E
Treatment**

**Working Group 7 (Lime Green) □ Room, Suite TBA
Post-Exposure Prophylaxis**

**Working Group 8 (Pink) □ Room, Suite TBA
Remediation**

Meeting Guidance and Suggestions for Working Group Sessions I and II

Objective:

To work with federal partners and other stakeholders to identify, prioritize, and coordinate near-term *Bacillus anthracis* bioterrorism research for public health response.

Problem:

During the recent anthrax bioterrorism investigation CDC and its partners identified a number of areas where additional research may be useful in improving public health response. The disciplines and specific expertise required to approach many of these areas are varied and exist within multiple federal government entities and elsewhere. To address those research questions that are most critical to improving public health response to *B. anthracis*-related bioterrorism, CDC has convened this meeting to obtain input on critical research priorities and coordinate with federal partners and other stakeholders in **planning and conduct of applied research that needs to be initiated within the next 12 months.**

Meeting Design:

There will be 2 plenary sessions (AM of December 10 and 11) and 2 working group sessions (PM of December 10 and 11).

Monday, December 10, 2001

Plenary session I will serve as an orientation to each of the topics areas for all meeting participants, and provide some opportunity for discussion and comments on the general topic areas. After this, in the afternoon, participants will be divided into eight working groups for **Working Group Session I**. The eight working groups include: 1) Evaluation of *B. anthracis* containing powders or substances; 2) Epidemiologic investigation; 3) Environmental assessment; 4) Surveillance; 5) Diagnosis; 6) Treatment; 7) Post-exposure prophylaxis; 8) Remediation. Each of the working groups has pre-assigned co-leaders, one from outside of CDC and one from CDC. The co-leaders from outside of CDC are subject matter experts in the area of assignment. Each of the CDC co-leads are senior scientists who have been heavily involved in the anthrax bioterrorism investigation and response. In addition to the co-leaders, there is an assigned EISO or other epidemiologist to capture ideas on flip charts, and a recorder to capture ideas in a laptop for each of the working groups. We have provided a list of questions for each of the working groups to help stimulate discussion and provide some direction based on observations during the investigation.

Tuesday, December 11, 2001

Plenary session II will provide each of the working groups an opportunity to present the results of previous days' deliberations to all meeting participants, and obtain input from meeting participants in other working groups. After this morning session, participants will return to their working groups for **Working Group Session II** to incorporate input from the larger group of meeting participants and complete a final written report by 3PM.

Follow-up

Working group written reports will be edited, collated, and distributed to all meeting participants during the week of December 17.

For each of the identified research priorities, at least clear action step with assigned responsibility will be included in the written report.

A summary of the meeting and resulting research priorities will be prepared for publication in *Emerging Infectious Diseases*.

Working group process:

- Review the list of working group-specific questions for clarification, modification, additions or deletions
- For each of the questions, answer the following:
 - Can this question be addressed using existing published or unpublished, classified or unclassified data?**
 - Is additional research needed to address this question?**
 - Can additional research be done to address this question?**
 - If yes, what research is needed?**
- Brainstorm each question recording responses and discussion on flip charts and typing into a laptop
- Review and combine or split as needed, and then **prioritize** brainstorming ideas
- Select a working group member to present the results of the working group meeting in **Plenary Session II** the next morning
- Use the brainstorming results and **Plenary Session II** presentation feedback to prepare a final written report using the following format for each of the **three top priority research projects** identified (max of 2 pages/project):
 - Title of the research project:**
 - Why is the research being done?**
 - What is the research?**
 - How would it be done?**
 - Where could it be done?**
 - Who could do it (i.e., which institutions should collaborate)?**
 - When should it be started (including action step with assigned responsibility)?**

Desired outcomes:

- Presentation of working group discussions in Plenary Session II
- Typed brainstorming list
- Typed report to including input from Plenary Session II
- Minimum of one action step with assigned responsibility for each near-term research priority identified by the working groups
- Meeting summary to all participants during week of December 17, 2001
- Published summary of the meeting in *Emerging Infectious Diseases*

Ground rules:

- Start and stop on time
- Only one person speaking at a time
- No side conversations
- Encourage each other to participate
- Treat each other with respect
- Stay focused on the task

Role of subject matter expert co-leader for working groups:

- Focuses on task, not process
- Be sure everyone understands the problem/issue
- Communicate clear purpose and desired outcomes

Role of facilitator co-leader for working groups:

- Responsible for keeping the meeting focused and moving
- Focuses on process, not task
- Directs team energy toward common task
- Suggests alternative methods and procedures
- Protects individuals and their ideas from attack
- Encourages participation from all team members
- Manages the meeting time
- Manages the brainstorming session
- Be aware of and deal with non-verbal communications
- Enforce the ground rules

Role of the pre-assigned Flip Chart manager (EISO or other epidemiologist):

- Record the brainstorming session on flip charts and assist in preparation of presentation for Plenary Session II and writing final report

Role of the pre-assigned note taker:

- Type the brainstorming comments into the laptop and assist in preparation of presentation for Plenary Session II and writing final report

Questions for Working Groups

1. Evaluation of *B. anthracis*-containing powders or substances

- Which rapid analyses of *B. anthracis* containing powders or substances can be used to help characterize the anthrax disease risk?
- What samples can be utilized to describe the characteristics of suspicious powders or substances? (i.e. swabs, washes, or powder only)
- How do these characteristics relate to the risk of re-aerosolization?
- How do these characteristics relate to the expected disease risk in a given setting?
- What is the role and importance of microbiology & taxonomy studies in identifying all bacterial species in powders or substances?
- When is a powder or substance completely characterized?
- In addition to the physical and chemical characteristics of the suspicious substance or powder, what additional information is needed to define disease risk of disease in a given scenario (envelope, building, subway, outdoor event)?
- How do simulates currently used in modeling of aerosol distribution compare to known *B. anthracis* containing products?
- Do powder characteristics influence anthrax pathogenesis ?
- How do particle size or components involved in preparation of the powder influence development of cutaneous anthrax?

2. Epidemiologic Investigation

- What is the infectious dose for inhalational anthrax in humans and how does it vary in response to host factors including age, underlying disease, medications?
- What is the relationship between *B. anthracis*-containing particle size and risk for inhalational anthrax in humans?
- What risk does re-aerosolization of *B. anthracis* containing particles pose for inhalational anthrax?
- Is the incubation period for inhalational anthrax in humans influenced by dose or host factors?
- What is the infectious dose for cutaneous anthrax in humans and how does it vary in response to host factors including age, underlying disease, medications?
- What is the relationship between occurrence of cutaneous anthrax and risk for inhalational disease?
- What are the factors that would influence development of sepsis as a result of cutaneous anthrax (e.g., immunosuppression, age)
- What additional studies needed of other potential release scenarios? Which scenarios?
- What is the impact of multiple exposures to small numbers of spores over several weeks?

3. Environmental Assessment

- Can environmental testing after an exposure for *B. anthracis* be used to assess human disease risk for inhalational and cutaneous anthrax?

- What is the role of air sampling?
- What is the role of surface sampling?
- What methods of environmental testing can be used to assess the disease risk for inhalational and cutaneous anthrax?
- How reliable and important are quantitative or semi-quantitative methods for assessment of level of contamination?
- How does particle size distribution of the source impact on environmental testing?
- What, if anything, can be learned about particle size distribution of the source powder from air or surface sampling of the exposed environment?
- Is there a level of background *B. anthracis* spore contamination in occupational settings and homes that pose a negligible risk to human health?
- Should we determine background rates of naturally occurring anthrax spores?
- What is the potential utility of real-time environmental-biometers for detection of *B. anthracis*-containing particles in high risk locations?
- Are there any potential alternatives to culture-based methods for rapid assessment of environmental testing for *B. anthracis*?
- Are specific environmental characteristics of mail processing associated with a high risk for inhalational anthrax?

4. Surveillance

- What are the most effective surveillance strategies to detect inhalational anthrax?
- What are the most effective surveillance strategies to detect cutaneous anthrax?
- What is the role of emergency room surveillance?
- What is the role of laboratory surveillance?
- How should surveillance methodologies change once an initial case or event is identified?
- How long after an initial case or event should active surveillance be maintained?
- Once this “outbreak” is over, what are the priorities for surveillance?
- How should surveillance be evaluated to identify weaknesses?

5. Diagnosis

- What are the diagnostic strategies for detection of anthrax in clinically ill patients?
 - Laboratory tests?
 - Clinical algorithm?
 - Should strategies change for patients already on antibiotics?
- Which laboratory diagnostic strategies might also have application for detection of *B. anthracis* in the environment?
- What are the diagnostic strategies to identify persons who are exposed but not clinically ill?
- What are the critical questions for use of serology in diagnosis and identification of exposed individuals?
 - Role of currently available serological assays?
 - Role of other serologic tests (e.g. toxin neutralization, antibody to lethal factor, anti-spore serology)?

- What is the role of molecular subtyping of *B. anthracis*? How well are current methodologies performing? Are additional subtyping methods needed?

6. Treatment

- What is the role of IgG, antitoxin, steroids, antitoxin antimicrobials (e.g. clindamycin) in the management of inhalational or systemic anthrax?
- What is the significance of inducible beta-lactamases and the cephalosporinase in treatment regimens?
- Are there clear synergistic antimicrobial combinations for the treatment of inhalational anthrax?
- What is the role of intercellular antibiotic concentrations in the treatment of inhalational anthrax ?
- Do ACE inhibitors, calcium channel blockers or other drugs have a beneficial or detrimental role in the treatment of anthrax?
- At what point in evaluation of patients should treatment be initiated?

7. Post-exposure prophylaxis

- For antibiotic therapy, is a 60day regimen necessary?
 - What if antibiotics are initiated late (i.e., 30 days after exposure)?
- For antibiotic therapy, is a 60day regimen sufficient?
- What is the efficacy of various antibiotics for prophylaxis?
 - Is amoxicillin efficacious (drug of choice for pediatrics)?
 - Is levoquin efficacious?
 - Are there other effective prophylaxis agents, such as macrolides, ketolides, and other fluoroquinolones?
- Can synergistic combinations of agents be used to shorten prophylaxis?
- What are the most effective mechanisms/interventions to promote and monitor adherence to prophylaxis?
- How should adverse events associated with antibiotics be monitored? Should all adverse events be monitored or only severe adverse events?
- What is the efficacy prophylaxis for prevention of cutaneous anthrax?
- What is the impact of prolonged prophylaxis on the development of antimicrobial resistance?
- What is the time course of antibiotics that should be used when the person has already been vaccinated (pre-exposure vaccination)
- Are there specific indications for vaccination as a part of post-exposure prophylaxis or treatment?
- What is the time course of antibiotics when vaccine is given as part of post-exposure prophylaxis?
- What is the efficacy of anthrax vaccine against laboratory manipulated strains?

8. Remediation

- What are effective compounds for decontaminating various surfaces and environments?
- What are the parameters that influence the choice of decontamination methods?
- What is an acceptable level of *B. anthracis* spores post decontamination?
- What are the parameters and indices to for effectiveness of decontamination?
- What are the long-term health effects of various decontamination methods on the different populations potentially exposed (decontamination workers, users of decontaminated space, public)?
- What are the most effective methods for decontamination of large buildings or individual floors in large buildings?
- What is the risk of exposure to *B. anthracis* for decontamination workers and how should we moderate that risk?

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Protocols, instruments, and documents used in surveillance during the anthrax incident among the various sites will be provided and utilized.

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