Response of the Life-Sciences Community to the Biodefense Challenge

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Anthrax Attacks 2001

- 11 cases cutaneous (skin) anthrax, 11 cases of inhalational anthrax, 5 deaths
- Ames strain, highly refined powder sent by mail
- Many unanswered questions
  - Who was the murderer? American PhD Microbiologist?
  - How many spores are required to cause disease?
  - What disinfection is necessary? How clean is safe?
What is the next threat

• Impossible to tell which leaves us trying to defend against many possible biothreat agents

• Greatest risk placed on agents of mass destruction
  – Anthrax, smallpox, tularemia, plague, botulinum toxin, hemorrhagic fevers
  – Aerosol dissemination

• What should we do to prevent bioterrorism???
Approaches for Reducing Threats of Bioterrorism

• Biodefense Research
  – Increased funding
  – Translational research leading to products

• Public Health Preparedness
  – Increased funding public health at State level

• Material Control
  – Export controls (control agents and equipment)
  – Domestic control (USA Patriot Act/Biopreparedness Act Information Control)

• Information Control
  – Classification (secret research program)
  – Constrain dissemination of “sensitive information”
Biodefense Research
Need more Research!

• National Academy Report--*Making the Nation Safer*
  – Develop Vaccines and broad spectrum antimicrobics
  – Investigate Microbial forensics
  – Study Microbial Pathogenesis
  – Revamp FDA licensing process, animal models
NIH Bioterrorism Research Funding

- TOTAL 2001 $25M
- TOTAL 2002 $275M
- TOTAL 2003 $1500M
  - Basic research and development $440.6M
  - Drug/vaccine discovery--development $591.9M
  - Clinical research $194.3M
  - Research facilities intramural $371.1M
  - Research facilities extramural $150.0M
- TOTAL 2004 $1600M
- TOTAL 2005 $1694M
NIH-NIAID Research Plan

• Basic Research into microbes with bioterrorism potential, and the specific and non-specific host defense mechanisms against these agents

• Applied/Translational Research with predetermined milestones and the ultimate production of new/improved diagnostics, vaccines, and therapies
Planned NIH research initiatives for FY 2004

• Establish animal models and standardized reagents, microarray panels, and other materials for the study of priority pathogens;

• Expand research to discover how B and T lymphocytes, help regulate immune responses to dangerous microbes;

• Accelerate testing of new biodefense therapeutics, vaccines, and diagnostics.
PUBLIC HEALTH
CDC Approach

- Increase funding to States for Public Health
  - Increase education and response capability
- Enhance surveillance
  - Build Health Alert Network
  - Build Laboratory response network
Laboratory Response Network (LRN)

- Sentinel Labs (recognize, rule-out, refer)
- Reference Labs (confirmatory testing)
- National Labs (definitive characterization)

Formerly Level A

Formerly Level B/C

CDC and USAMRIID
Levels of Microbial Identification

• **Medical Diagnosis**
  – Clinical Diagnostic Laboratory
    • What is the disease
    • Genus/Species Level, e.g. *Legionella* = legionellosis

• **Epidemiology**
  – Public Health Laboratory
    • Where did the etiologic agent come from/how is it transmitted/who else is at risk
    • Strain level, e.g. *Legionella pneumophila* serotype 3/plasmid profile

• **Forensics**
  – Specialized Laboratory
    • Where did the strain come from/how was it transmitted/who did it
    • Specific strain information, e.g. genome sequence
CDC National Biopreparedness

- **National Pharmaceutical Stockpile**
  - Ensuring rapid transport of NPS assets in response to a terrorism incident;
  - Coordination with state, local and Federal emergency responders;
  - Provision of CDC technical consultants to accompany pharmaceuticals, vaccines or other medical materiel to the area of need;
  - Operational research and program evaluation; and
  - Education and training for state, local and Federal partners.
Smallpox Issues

• Catastrophic public health consequences
  – Mass casualties which overwhelm medical systems
  – High morbidity and mortality
  – Contagious

• Vaccination
  – Cost-benefit analysis uncertain
  – 400-1000 deaths likely in US from vaccination

• Quarantine
MATERIAL CONTROL
Material Control

- **CDC Laboratory Registration/ Select Agent Transfer Program**
  - These regulations place shipping and handling requirements on laboratory facilities that transfer or receive select agents capable of causing substantial harm to human health. They are designed to ensure that select agents are not shipped to parties who are not equipped to handle them appropriately or who lack proper authorization for their requests.
  - Regulated shipment of 36 select agents and their disease related genes
  - Requires adherence to CDC biosafety manual (BMBL)
  - Took effect April 1997

- **Export Control**
  - Australia Group
USA Patriot Act

• Restrictions on possession of select agents
  – Restricts aliens from countries designated as supporting terrorism from possessing select agents within the United States
  – Restricts individuals who are not permitted to purchase handguns, e.g. some individuals with a history of mental illness or a criminal record, from possessing select agents
  – Makes it an offense for a person to knowingly possess any biological agent, toxin or delivery system of a type or in a quantity that, under the circumstances, is not reasonably justified by prophylactic, protective, bona fide research or other peaceful purpose.
  – In effect since October 26, 2001
Biopreparedness Act

• Requires registration for possession of select agents
• Requires HHS and USDA regulations (Federal Register notice on December 9, 2002; regulations took effect February 7, 2003)
  – requires clearance by Department of Justice
  – tracks the acquisition, transfer and possession of certain biological agents and toxins
  – requires safeguards and security regulations to be followed
  – collects information for law enforcement;
  – establishes a process for alerting authorities about unauthorized attempts to acquire select agents
Select Agents

HHS NON-OVERLAP SELECT AGENTS AND TOXINS AGENTS AND TOXINS

- Crimean-Congo haemorrhagic fever virus
- Coccidioides posadasii
- Ebolavirus
- Cercopithecine herpesvirus 1 (Herpes B virus)
- Lassa fever virus
- Marburg virus
- Monkeypox virus
- Rickettsia prowazekii
- Rickettsia rickettsii
- South American haemorrhagic fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito)
- Tick-borne encephalitis complex (flavi) viruses (Central European tick-borne encephalitis, Far Eastern tick-borne encephalitis, Russian spring and summer encephalitis, Kyasanur forest disease, Omsk hemorrhagic fever)
- Variola major virus (Smallpox virus)
- Variola minor virus (Alastrim)
- Yersinia pestis
- Abrin
- Conotoxins
- Diacetoxyxirpenol
- Ricin
- Saxitoxin
- Shiga-like ribosome inactivating proteins
- Tetrodotoxin

HIGH CONSEQUENCE LIVESTOCK PATHOGENS AND TOXINS/ SELECT AGENTS (OVERLAP AGENTS)

- Bacillus anthracis
- Brucella abortus
- Brucella melitensis
- Brucella suis
- Burkholderia mallei (formerly Pseudomonas mallei)
- Burkholderia pseudomallei (formerly Pseudomonas pseudomallei)
- Botulinum neurotoxin producing species of Clostridium
- Coccidioides immitis
- Coxella burneti
- Eastern equine encephalitis virus
- Hendra virus
- Francisella tularensis
- Nipah Virus
- Rift Valley fever virus
- Venezuelan equine encephalitis virus
- Botulinum neurotoxin
- Clostridium perfringens epsilon toxin
- Shigatoxin
- Staphylococcal enterotoxin
- T-2 toxin

USDA HIGH CONSEQUENCE LIVESTOCK PATHOGENS AND TOXINS (NON-OVERLAP AGENTS AND TOXINS)

- Akabane virus
- African swine fever virus
- African horse sickness virus
- Avian influenza virus (highly pathogenic)
- Blue tongue virus (Exotic)
- Bovine spongiform encephalopathy agent
- Camel pox virus
- Classical swine fever virus
- Cowdria ruminantium (Heartwater)
- Foot and mouth disease virus
- Goat pox virus
- Lumpy skin disease virus
- Japanese encephalitis virus
- Malignant catarrhal fever virus (Exotic)
- Menangle virus
- Mycoplasma capricolum
- M.F38/M. mycoides capri
- Mycoplasma mycoides mycoides
- Newcastle disease virus (VVND)
- Peste Des Petits Ruminants virus
- Rinderpest virus
- Sheep pox virus
- Swine vesicular disease virus
- Vesicular stomatitis virus (Exotic)

LISTED PLANT PATHOGENS

- Liberobacter africanus
- Liberobacter asiaticus
- Peronosclerospora philippinensis
- Phakopsora pachyrhizi
- Plum Pox Potyvirus
- Ralstonsia solanacearum race 3, biovar 2
- Schlerophthora rayssiae var zeae
- Synchytrium endobioticum
- Xanthomonas oryzae

- Xylella fastidiosa (citrus variegated chlorosis strain)
Security Clearances and Restrictions on Access

• Each facility, responsible official, and employee with access to select agents must obtain a security clearance from the Department of Justice.

• In order to fulfill the Department of Justice responsibilities under the Act, the Federal Bureau of Investigation (FBI) is responsible for conducting security risk assessments of individuals seeking access to listed agents and toxins and individuals or entities seeking to register under the Act. The process requires fingerprint submission and additional information required by the FBI.
INFORMATION CONSTRAINT
Concern Over Scientific Information

• The anthrax attacks that followed the horror of September 11 have made scientists and physicians suspects as well as saviors.

• The fear that information from life science research may fall into the wrong hands is causing great anxiety within the scientific community and uncertainties among the public and policy makers as to how to balance national security with traditional openness of science.
Controversial Paper
IL4-Mousepox


In trying to develop a mouse contraceptive to control pest populations, the researchers inserted a gene for an immune-system molecule called interleukin-4 into the mousepox virus. Instead of rendering mice infertile, the engineered virus was far more deadly than the natural strain, killing even mice that had been vaccinated against mousepox.
Controversial Paper
Synthetic Polio Virus

- Eckard Wimmer and researchers at the State University of New York at Stony Brook Science, August 9, 2002 (online edition, July 11)
- Used the genetic sequence of poliovirus to order pieces of DNA from a company. By patching the pieces together and putting the complete DNA chain into a soup of cellular molecules, the team created poliovirus particles capable of paralyzing and killing mice.
Information Control

• How can one define what is dangerous and how can we design a system that contains that danger while allowing legitimate biomedical research to proceed in a manner acceptable to society?
  – Should more research be declared classified?
  – Should there be review boards to consider the national security implications of publications and presentations?
  – Should we restrict access and dissemination of scientific information?
  – Should scientists be constrained regarding which questions they can ask?
  – Should journals reject papers containing potentially sensitive information?
Review at the Publication Stage

• Rely on self-governance by scientists and scientific journals to review publications for their potential national security risks.
Journal Editors and Authors Group

• The process of scientific publication, through which new findings are reviewed for quality and then presented to the rest of the scientific community and the public, is a vital element in our national life.

• Questions have been asked by scientists themselves and by some political leaders about the possibility that new information published in research journals might give aid to those with malevolent ends.

• Fundamental is a view, shared by nearly all, that there is information that, although we cannot now capture it with lists or definitions, presents enough risk of use by terrorists that it should not be published. How and by what processes it might be identified will continue to challenge us, because – as all present acknowledged -- it is also true that open publication brings benefits not only to public health but also in efforts to combat terrorism.
Scientific Publication and Security

• **FIRST:** The scientific information published in peer-reviewed research journals carries special status, and confers unique responsibilities on editors and authors. We must protect the integrity of the scientific process by publishing manuscripts of high quality, in sufficient detail to permit reproducibility. Without independent verification – a requirement for scientific progress – we can neither advance biomedical research nor provide the knowledge base for building strong biodefense systems.

The integrity of science must be maintained—Science is too important to jeopardize it
Scientific Publication and Security

• SECOND: We recognize that the prospect of bioterrorism has raised legitimate concerns about the potential abuse of published information, but also recognize that research in the very same fields will be critical to society in meeting the challenges of defense. We are committed to dealing responsibly and effectively with safety and security issues that may be raised by papers submitted for publication, and to increasing our capacity to identify such issues as they arise.

Editors and scientists will act responsibly without government intervention
Scientific Publication and Security

• **THIRD:** Scientists and their journals should consider the appropriate level and design of processes to accomplish effective review of papers that raise such security issues. Journals in disciplines that have attracted numbers of such papers have already devised procedures that might be employed as models in considering process design. Some of us represent some of those journals; others among us are committed to the timely implementation of such processes, about which we will notify our readers and authors.

• **Each field is different and needs specific ethical practices to protect against its misuse**
Scientific Publication and Security

• **FOURTH:** We recognize that on occasions an editor may conclude that the potential harm of publication outweighs the potential societal benefits. Under such circumstances, the paper should be modified, or not be published. Scientific information is also communicated by other means: seminars, meetings, electronic posting, etc. Journals and scientific societies can play an important role in encouraging investigators to communicate results of research in ways that maximize public benefits and minimize risks of misuse.

We will constrain information we consider could do harm
ASM Publication Position

- “The ASM recognizes that there are valid concerns regarding the publication of information in scientific journals that could be put to inappropriate use.."

- The editors of the ASM journals are trying to be responsible stewards of scientific information and communication by carefully balancing national security with the value of advancing science for the benefit of humanity.

- This is a policy of responsible citizenship—not one of censorship
Statistics for ASM’s 11 journals –2001-2002

• 14,000 Total submitted manuscripts
  – 4-5 authors each
  – about 60% of non-US origin
  – from at least 100 foreign countries.

• 224 “Select Agents” manuscripts submitted
  – 90 rejected--57 with non-US authors;
  – 134 accepted --58 with non-US authors
  – 2 (<0.015%) elicited elevated concern--each was considered by the entire Publications Board and were published with some modification.
SCIENTIFIC ETHICS AND ETHOS
ASM Resolution on Bioethics

• Microbiologists will work for the proper and beneficent application of science and will call to the attention of the public or the appropriate authorities misuses of microbiology or of information derived from microbiology.

• ASM members are obligated to discourage any use of microbiology contrary to the welfare of humankind, including the use of microbes as biological weapons.

• Bioterrorism violates the fundamental principles expressed in the Code of Ethics of the Society and is abhorrent to the ASM and its members.
BIOTECHNOLOGY RESEARCH IN AN AGE OF TERRORISM: CONFRONTING THE DUAL USE DILEMMA

Report of the Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology
“Fink Committee”
National Research Council
OF THE NATIONAL ACADEMIES
• Develop an architecture to help protect the life sciences scientific community against the potential misuse of biological materials and information
  – Bottom up approach aimed at helping reduce the threat of misuse of the life sciences

• Protect scientific enquiry and communication to the maximum extent possible
  – Build upon the previous (1982) NAS Corson report which dealt with the physical sciences.
• The Committee proposed a system that would establish a number of stages at which scientists would review experiments and eventually their results to provide reassurance that advances in biotechnology with potential applications for bioterrorism or biological weapons development receive responsible oversight.
Proposed Experiments for Review

• The Committee identified seven classes of “experiments of concern” that illustrate the types of endeavors or discoveries that should undergo review and discussion by informed members of the scientific and medical community before they are undertaken or, if carried out, before they are published in full detail.
Experiments of Concern

1. Would demonstrate how to render a vaccine ineffective.
   This would apply to both human and animal vaccines.
   IL-4 mousepox experiments could fall into this category of experiments of concern.
Experiments of Concern

2. Would confer resistance to therapeutically useful antibiotics or antiviral agents
   This would apply to therapeutic agents that are used to control disease agents in humans, animals, or crops.

   Introduction of ciprofloxacin resistance in *Bacillus anthracis* would fall in this class.
Experiments of Concern

3. Would enhance the virulence of a pathogen or render a nonpathogen virulent
   This would apply to plant, animal, and human pathogens.
   Introduction of cereolysin toxin gene into *Bacillus anthracis* would fall into this class.
Experiments of Concern

4. Would increase transmissibility of a pathogen.
   This would include enhancing transmission within or between species.
   Altering vector competence to enhance disease transmission would fall into this class.
Experiments of Concern

5. Would alter the host range of a pathogen.
   This would include making nonzoonotics into zoonotic agents.
   Altering the tropism of viruses would fit into this class.
Experiments of Concern

6. Would enable the evasion of diagnostic/detection modalities.
   This could include microencapsulation to avoid antibody based detection and/or the alteration of gene sequences to avoid detection by established molecular methods.
Experiments of Concern

7. Would enable the weaponization of a biological agent or toxin. This would include environmental stabilization of pathogens. Synthesis of viruses could also fall into this class of experiments.
Review of Proposed Research

- All of the experiments that fall within the seven areas of concern should currently require review by an Institutional Biosafety Committee (IBC).

- The Committee recommended initial review by the IBC because this provides an assessment of research at its earliest stages.
Creation of a National Science Advisory Board for Biodefense

- Recommend that the Department of Health and Human Services create a National Science Advisory Board for Biodefense (NSABB) to provide advice, guidance, and leadership for the system of review and oversight we are proposing.
At the most general (strategic) level, it would serve as a point of continuing dialogue between the scientific community and the national security community and as a forum for addressing issues of interest or concern.

At the operational (tactical) level, it would provide case-specific advice on the oversight of research and the communication and dissemination of life sciences research information that is relevant for national security and biodefense purposes.
US Government Biosecurity Initiative

• Establish the National Science Advisory Board for Biosecurity (NSABB) to advise and guide the government.

  – NSABB will provide advice and guidance regarding biological research that has the potential for misuse and could pose a biologic threat to public health or national security.

  – NSABB will advise HHS Secretary, NIH Director, heads of all Federal entities that conduct/support life sciences research.
National Biosecurity Initiative

• Develop and promulgate national guidelines for local (e.g. IBCs) and federal oversight of dual use research

• Develop a code of conduct for scientists and laboratory workers in life sciences research.

• Develop and implement programs for education and training in biosecurity issues for all scientists and laboratory workers at federal as well as federally funded institutions.

• Develop and promulgate guidelines for the appropriate communication of dual use research methodology and research results.

• Foster the extension of these biosecurity policies to the international arena.
INTERNATIONAL EFFORTS
Rejecting Biological Weapons

• 1969 US unilaterally abandons its biological weapons program. President Richard Nixon issues declaration:
  – “Mankind already carries in its own hands too many of the seeds of its own destruction. By the examples we set today, we hope to contribute to an atmosphere of peace and understanding between nations and among men”

• 1972 A number of countries followed the US lead to disavow biological weapons and signed the BWC
BWC Agreement

• Never under any circumstances to develop, produce, stockpile or otherwise acquire or retain
  – microbial or other biological agents, or toxins in quantities that have no justification for peaceful purposes
  – weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes.
• Not to transfer agents, toxins, weapons, equipment or means of delivery of biological weapons to others
• Take necessary measures to prohibit and prevent the development, or acquisition of biological weapons by its military or citizens.
Harmonized International Oversight

– Any serious attempt to reduce the risks associated with biotechnology must ultimately be international in scope, because the technologies that could be misused are available and being developed throughout the globe.

– Build upon the model for oversight of recombinant DNA technologies
Concluding Remarks

• It is up to us in the scientific community to define the standards and to establish the framework to ensure that biothreat agents and critical information is withheld from terrorists while permitting the continued advancement of biomedical research and the protection of public health.

• We cannot do this alone. The scientific and national security communities must establish a dialog and the outcome must be acceptable to the public.

• We need to make sure that this is an international effort--if we are to achieve national security we must achieve global security.