Bioterrorism and Biosecurity in the United States

Jennifer Gaudioso, Ph.D.
Sandia National Laboratories

Seminar on Prevention and Crisis Management of Bioterrorism
Southeast Asia Regional Centre for Counter-Terrorism, Malaysia
July 18, 2005

SAND No. 2005-4329C
Sandia is a multiprogram laboratory operated by Sandia Corporation, a Lockheed Martin Company, for the United States Department of Energy's National Nuclear Security Administration under contract DE-AC04-94AL85000.

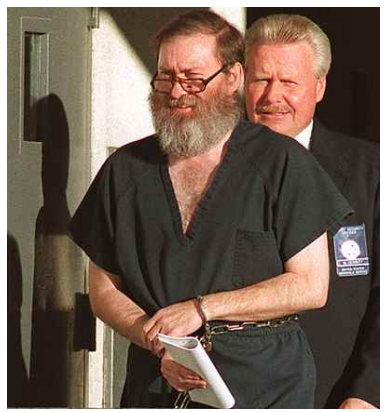
Bioterrorism in the US: 1984

- September 17, 1984 – First reports of gastroenteritis from recent patrons of restaurants in The Dalles, Oregon
- Laboratory tests confirm *Salmonella typhimurim*
- Outbreak:
  - 751 cases of salmonella poisoning but
  - No fatalities
- CDC investigation concludes that outbreak resulted from food handlers' inadequate hygiene
- September 16, 1985 – rift between cult member and leader reveals incident was not a natural outbreak

Bhagwan Shree Rajneesh

Bioterrorism in the US: 1995

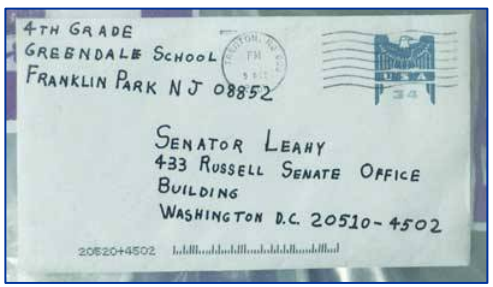
- May 1995 – Larry Wayne Harris ordered 3 vials of *Yersina pestis* from the American Type Culture Collection
- Arrested for obtaining the bacteria through falsified documents
  - Possession not a crime in 1995
- Led to the original Select Agent List – only regulated transfers
  - Anti-terrorism and Effective Death Penalty Act of 1996

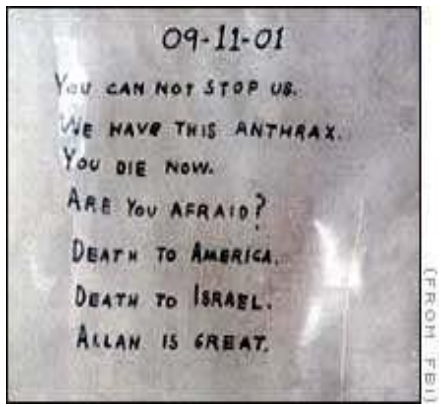


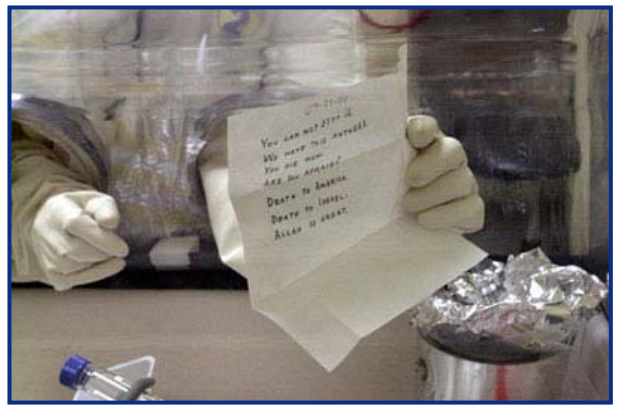
Sandia National Laboratories

Bioterrorism in the US: 2001

- **Fall 2001 anthrax attacks**
  - **Highly refined: 4-7 letters contaminated over 60 different sites**
    - **Sent to news outlets and US Congress**
  - **Highly virulent: Kills 5, wounds 21**
  - **Perpetrator(s) still unknown**







Sandia National Laboratories

Necessity of Biological Research

- **Despite threats associated with pathogenic microorganisms, research with these dual-use agents must continue**
  - **Most vaccines use an attenuated or dead pathogen**
  - **Therapeutic treatments may utilize dangerous pathogens or toxins**
  - **Comprehension of pathogenicity aids in disease diagnosis, treatment, mitigation, and prevention**
- **Nonproliferation and counter-terrorism strategies must not hinder essential research**
- **New and rapid advancements in biotechnology create novel threats but allow for novel responses**

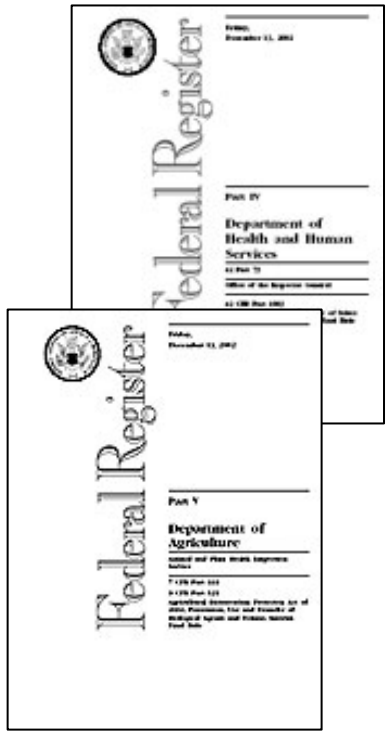
Before and after botulinum injections

US Policy Response to the Bioterrorist Threat

- Emerging US security regime has two sets of objectives
  - Enhance ability to respond to public and agricultural health emergencies
  - Reduce the risk that bioscience and biotechnology could be used maliciously
- Realization that bioscience facilities are potential sources of biological weapons material (viable and virulent pathogens)
- USA PATRIOT Act of 2001 – US Public Law 107-55
  - Restricted Persons
- Bioterrorism Preparedness Act of 2002 – US Public Law 107-188
  - 42 CFR 73 (Human and Overlap)
  - 9 CFR 121 (Animal and Overlap)
  - 7 CFR 331 (Plant)

US Select Agent Rule (2005)

- Facility registration if it possesses one of 80 Select Agents
- Facility must designate a Responsible Official
- Background checks for individuals with access to Select Agents
- Access controls for areas and containers that contain Select Agents
- Detailed inventory requirements for Select Agents
- Security, safety, and emergency response plans
- Safety and security training
- Regulation of transfers of Select Agents
- Extensive documentation and recordkeeping
- Safety and security inspections



Sandia National Laboratories

Human Select Agents and Toxins

- Crimean-Congo haemorrhagic fever virus
- Ebola viruses
- Cercopithecine herpesvirus 1 (Herpes B virus)
- Lassa fever virus
- Marburg virus
- Monkeypox virus
- South American Haemorrhagic Fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito)
- Tick-borne encephalitis complex (flavi) viruses
- Variola major virus and Variola minor virus (Alastrim)

- *Rickettsia prowazekii*
- *Rickettsia rickettsii*
- *Yersinia pestis*
- *Coccidioides posadasii*

- Abrin
- Conotoxins
- Diacetoxyscirpenol
- Ricin
- Saxitoxin
- Tetrodotoxin
- Shiga-like ribosome inactivating proteins

Overlap Select Agents and Toxins

- Eastern equine encephalitis virus
- Nipah and Hendra complex viruses
- Rift Valley fever virus
- Venezuelan equine encephalitis virus

- Botulinum neurotoxins
- *Clostridium perfringens* epsilon toxin
- Shigatoxin
- Staphylococcal enterotoxins
- T-2 toxin

- *Bacillus anthracis*
- *Brucella abortus*
- *Brucella melitensis*
- *Brucella suis*
- *Burkholderia mallei*
- *Burkholderia pseudomallei*
- Botulinum neurotoxin producing species of *Clostridium*
- *Coxiella burnetii*
- *Francisella tularensis*

- *Coccidioides immitis*

Animal Select Agents and Toxins

- African horse sickness virus
- African swine fever virus
- Akabane virus
- Avian influenza virus (highly pathogenic)
- Bluetongue virus (exotic)
- Pox viruses (camel, goat, sheep)
- Classical swine fever virus
- Foot and Mouth Disease virus
- Japanese encephalitis virus
- Lumpy skin disease virus
- Malignant catarrhal fever virus
- Newcastle disease virus
- Peste des petits ruminants virus
- Rinderpest virus
- Swine vesicular disease virus
- Vesicular stomatitis virus (exotic)

- *Cowdria ruminantium*
- *Mycoplasma capricolum*
- *Mycoplasma mycoides*

- Bovine spongiform encephalopathy agent

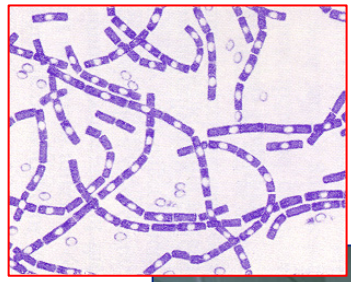
Plant Select Agents and Toxins

- ***Liberobacter africanus***
- ***Liberobacter asiaticus***
- ***Ralstonia solanacearum***
- ***Xanthomonas oryzae***
- ***Xylella fastidiosa***

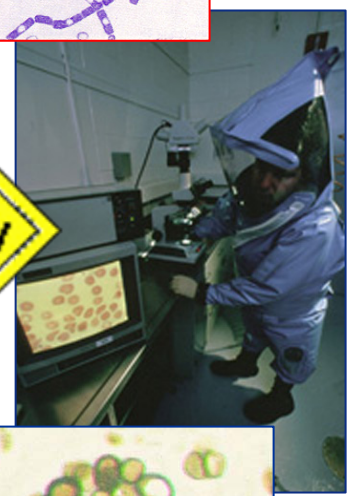
- ***Peronosclerospora philippinensis***
- ***Sclerophthora rayssiae***
- ***Synchtrium endobioticum***

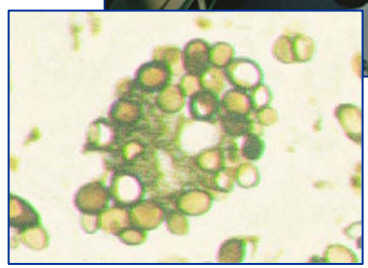
Hazardous Material Transportation Security

- Infectious substances (Class 6.2) and toxins (Class 6.1) are defined as Hazardous Material
- 49 Code of Federal Regulations (CFR) 172 (2003) – HM 232 – mandates security measures for the transport of some Hazardous Material
  - Select Agents regulated under 42 CFR 73 require Hazardous Material transport security measures
- Hazardous Material regulated security requirements include:
  - Training
    - Security awareness training
    - Specific training as appropriate
  - Written security plan
    - Based on assessment of transportation security risks
    - Address personnel security, unauthorized access, en route security



Bacillus anthracis



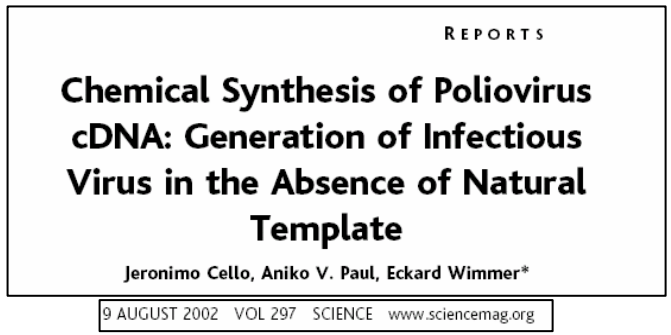


Coccidioides immitis

Sandia National Laboratories

Concerns About US Select Agent Rule

- Top-down security regime not tailored to laboratory realities
- No need to steal a Select Agent to perpetrate bioterrorism
- Fear that security will trump biosafety, increasing the risk of accidental release or exposure
- Security requirements increasing operational impediments and compromising research funding
- Identical protection measures for the 80 agents and toxins despite their various degrees of attractiveness to adversaries
- No protection if personnel do not understand and accept security

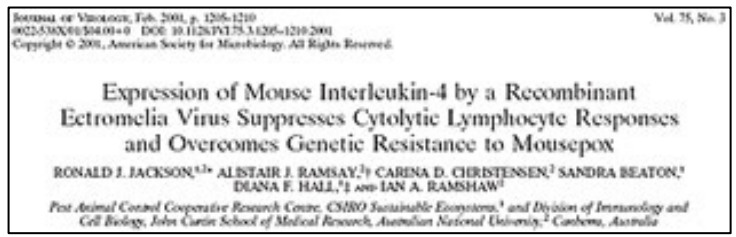


REPORTS

Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template

Jeronimo Cello, Aniko V. Paul, Eckard Wimmer*

9 AUGUST 2002 VOL 297 SCIENCE www.sciencemag.org



JOURNAL OF VIROLOGY, Feb. 2001, p. 1205–1210 Vol. 75, No. 3

0022-538X/01/$04.00+0 DOI: 10.1128/JVI.75.3.1205–1210.2001

Copyright © 2001, American Society for Microbiology. All Rights Reserved.

Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox

RONALD J. JACKSON,[1,2]* ALISTAIR J. RAMSAY,[2]† CARINA D. CHRISTENSEN,[2] SANDRA BEATON,[1] DIANA F. HALL,[1]‡ AND IAN A. RAMSHAW[2]

Pest Animal Control Cooperative Research Centre, CSIRO Sustainable Ecosystems,[1] and Division of Immunology and Cell Biology, John Curtin School of Medical Research, Australian National University,[2] Canberra, Australia

Sandia National Laboratories

Heightened Security or Neocolonial Science?

New restrictions on federally funded research involving the world's most dangerous pathogens are hampering foreign collaborations

ALMATY, KAZAKHSTAN—Scott Weaver thought he had a green light for a great research partnership. After an expensive security upgrade of his labs and hours of paperwork, the director for tropical and emerging infectious disease research at the University of Texas Medical Branch (UTMB) in Galveston was ready to resume research on the Venezuelan equine encephalitis (VEE) virus in Colombia, Peru, and Venezuela. The mosquito-borne disease, endemic in all three countries, is not the worst of its kind: The alphavirus kills less than 1% of its human victims. But VEE's potential to incapacitate has landed it on a list of "select agents": several dozen of the nastiest sorts of pathogens that the U.S. government fears could be turned into biological weapons. That designation has thrown up new hurdles for Weaver and his collaborators in South America—and for many other U.S. scientists working overseas.

In August, the U.S. National Institute of Allergy and Infectious Diseases (NIAID) informed Weaver that under the terms of his two VEE grants, the laboratories of his foreign colleagues must have procedures in place for handling select agents that are equivalent to tough U.S. regulations* imposed last year. "I seriously doubt whether my collaborators in Caracas or Bogotá could ever meet U.S. standards for select-agent security," says Weaver. "These developing countries cannot afford the kinds of elaborate systems that labs in the U.S. have been required to install," such as sophisticated security and inventory systems and background checks on employees. He's since had to alter his projects to avoid isolating the VEE virus in the labs south of the border. Because the new policy may force some foreign partners to serve as mere sample exporters, it resurrects "the stereotype of the ugly American: arrogant, demanding, and insensitive," Weaver charges: "American collaborations will be unwelcome in many developing countries of the world."

Although his case may be one of the first, Weaver is not the only researcher feeling the chill. According to a prominent U.S. specialist on select agents, researchers with the U.S. Centers for Disease Control and Prevention (CDC) have seen a curtailment of foreign collaborations on avian flu and viral hemorrhagic fevers. (CDC officials declined to comment.) Scientists at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Frederick, Maryland, are experiencing similar constraints on projects involving Congo-Crimean hemorrhagic fever and related diseases. "The important work we need to do will get done," says USAMRIID public affairs officer Caree Vander Linden, although the details have not been worked out.

No picnic. Venezuelan scientists draw blood from rodents to isolate VEE virus. New NIH rules have clamped projects on this and other select agents.

U.S. inspectors will soon be heading out to assess lab standards overseas, scientists learned at a closed-door meeting last month. Paula Stricklland, acting director of NIAID's Office of International Extramural Activities, told a group at the annual meeting of the American Society of Tropical Medicine and Hygiene (ASTMH) in Miami, Florida, that security teams will include senior microbiologists from CDC's select-agents program. An interagency committee chaired by Stricklland with representatives from the U.S. State and Justice departments will determine whether foreign labs "meet minimum biosafety and biosecurity requirements."

The stepped-up regulations are the latest example of the clash between scientists' cherished ways of doing business and the urgent need to reduce the potential for bioterrorism, and some researchers say the rules make sense. "It would be very embarrassing for a U.S. collaborator and a U.S. agency to be funding a facility that had a major accident, or one that was involved in a bioterrorism event," says Paul Keim, an anthrax specialist at Northern Arizona University in Flagstaff.

But others fear that the tightened security could stifle cooperation. "One doesn't develop productive collaborative relationships with foreign counterparts by announcing upon arrival that 'from now on we must do things the American way,'" says UTMB arbovirus specialist Robert Tesh. "Each country has its security priorities. The U.S. cannot demand that they conform to ours."

Adds Weaver: "By inhibiting research on the ecology and epidemiology of potential biological weapons in their natural settings overseas, we will be less prepared to respond optimally to the introduction of these agents by a terrorist."

Clampdown

After letters containing powdered anthrax were mailed to members of Congress and others in the fall of 2001, the U.S. government crafted tough requirements for scientists it funds to study dangerous pathogens. In addition to tightening security at facilities in which the microbes are kept and studied, U.S. regulations now demand rigorous protocols covering security assessments, emergency response plans, training, transfers of materials, and inspections.

Under the new NIAID rules, which the institute began developing in 2003, U.S. grantees must submit a dossier on a foreign collaborating institution detailing its "policies and procedures for the possession, use, and transport of select agents." For what NIAID calls "security risk assessments," grantees "must be willing to provide the names of all individuals who will have access to the select agents."

Weaver says the new rules prompted him to drop his original plan to process field samples potentially infected with VEE virus in South America. Now, he says, he will have all the samples shipped to Galveston. "This seems to have gotten me off the hook for the time being," he says, in that his colleagues at the National Institute of Health in Bogotá and the Central University of Venezuela and the National Institute of Hygiene in Caracas now won't have to adhere to the select-agent terms. But the change will reduce efficiency and timeliness, he says.

"Basically, the NIH [U.S. National Institutes of Health] left me with little choice," because it would have taken "months or years" to bring overseas labs into compliance, Weaver says. Already, the labs in Colombia and Venezuela store many VEE virus isolates in their freezers: Preventing the isolation of a few more strains, he says, will not deny the virus to a potential terrorist.

Although security at foreign facilities working with select agents generally has been strengthened since the 9-11 attacks, most labs would still run afoul of the new U.S. rules. Many outside the United States appear to be unaware of the regulations. "I haven't heard much," says Lev Sandakhchiev, director general of the State Research Center of Virology and Biotechnology, a former bioweapons lab near Novosibirsk, Russia, that collaborates with the United States on smallpox research.

Foreign researchers say they hope to find a way to continue working with U.S. counterparts because it would bolster security in their home countries. "If collaborations will continue, that will inevitably bring the standards up," says Bakyt Atshabar, director of the Kazakh Science Center for Quarantine and Zoonotic Diseases in Almaty, Kazakhstan, which specializes in studying endemic plague with Pentagon funding (*Science*, 17 December, p. 2021).

ASTMH and other societies intend to lobby for a relaxation of the rules. "The approach to this will not be easy," says Peter Weller, an immunologist at Harvard Medical School in Boston and ASTMH's most recent past president. For one, many agencies will want to weigh in on any change of policy. Second, Weller says, "the facile reply is that you scientists gave the Pakistanis nuclear secrets; how do we trust you on these issues?" In an e-mail response to questions from *Science*, NIAID officials say they expect no change to the select-agent terms "in the immediate future."

But some experts such as Keim say raising global security levels to U.S. standards makes sense. "We should not allow U.S. researchers to avoid regulatory oversight by going abroad. This would certainly apply to human subjects in clinical trials and animal-care standards in animal protocols. Why not security of dangerous pathogens?"

Critics of the policy say they are not opposed to strengthened security overseas. Rather, they decry how the U.S. government is going about it. NIH "seems to be hell-bent on enforcing the regulations," says Thomas Monath, chief scientific officer at Acambis in Cambridge, Massachusetts, and president of ASTMH. He wonders whether his company's research on Japanese encephalitis, a select agent, with colleagues in Thailand and Australia will be subject to such oversight. Monath fears that U.S. researchers might be held criminally responsible for violations by collaborators. When he raised this issue with Strickland at the ASTMH meeting, he says, it was apparent that "NIH had neither thought about this nor had any clear response."

NIAID officials say they are simply in step with the times; later they plan to adopt standards being developed by the World Health Organization. "We will do what we can to ensure that every possible avenue has been pursued that will allow our NIH-funded researchers to be able to conduct their research safely and securely," the officials say. Much of that work, it appears, may well have to be done inside U.S. borders.

–RICHARD STONE

* www.cdc.gov/od/sap/docs/42cfr73.pdf

A Selection of Select Agents

- Smallpox virus
- Crimean-Congo hemorrhagic fever virus
- Lassa fever viruses
- Central European tick-borne encephalitis
- *Yersinia pestis* (plague)
- Foot-and-mouth disease virus
- Ebola viruses
- Ricin
- Tetrodotoxin
- *Bacillus anthracis* (anthrax)
- Venezuelan equine encephalitis virus
- Botulinum neurotoxin

Some Countries Are Betting That A Few Seconds Can Save Lives

Japan, Mexico, and Taiwan are investing in early warning systems that can offer precious seconds of warning before a major tremor

TOKYO—What would you do with 5 to 50 seconds' warning of a major earthquake?

It's not an academic question. Systems that can detect earthquakes near their source and issue warnings before the shaking starts are in place or being deployed in Mexico, Taiwan, and Japan and are being studied for locales from southern California to Istanbul. Enthusiasts are convinced that short-term warnings can save lives by stopping trains before they pass over damaged track, emptying out elevators, and alerting rescue units. "It is an epochmaking" advance in earthquake safety, says Masato Motosaka, a Japanese earthquake engineer at Tohoku University in Sendai.

On alert. Nowcast stations are being installed across Japan.

Not everyone agrees, however. Skeptics note that warning systems don't provide enough time to reduce casualties close to the epicenter of an earthquake. They also worry that such systems could divert spending from earthquake preparedness, which they say has the potential to do much greater good. "Warnings only help in some cases," says Robert Olshansky, an urban planner at the University of Illinois, Urbana-Champaign. "Investing too much of one's money and hopes in a short-term warning system is a distraction from the hard and less sexy work, such as upgrading older structures, that is really needed to improve seismic safety."

Faster than a speeding S wave

Early warning systems are not forecasts. Instead, they detect actual quakes near their source and issue warnings to automated systems and humans up to several hundred kilometers away. They work because electronic signals transmitted through wires or air travel faster than seismic waves moving through the earth. Warning schemes also take advantage of the two types of seismic waves that are generated when a fault ruptures. The first—and faster moving—primary (P) waves radiate directly outward from the epicenter. The secondary (S) waves, which cause the oscillating motions responsible for the most damage, lag by tens of seconds over a distance of a few hundred kilometers. "The P waves carry information; the S waves carry energy," explains Hiroo Kanamori, a seismologist at the California Institute of Technology (Caltech) in Pasadena. Unfortunately,

Biosecurity Goes Global

The 2001 anthrax letters triggered a strong U.S. response. Now the rest of the world is starting to take biosecurity more seriously—but not necessarily by adopting the U.S. approach

Three years ago, the small number of life scientists using the term "biosecurity" were talking about ways to keep diseased crops and livestock from crossing national borders. Then came the fatal October 2001 anthrax letter attacks against several U.S. targets. In short order, thousands of U.S. scientists were confronted with an avalanche of new and often unpopular rules designed to keep potentially dangerous pathogens and toxins away from bioterrorists. Researchers who break those rules could face significant criminal penalties.

Despite these aggressive steps on the home front, U.S. officials readily acknowledged that unilateral action was insufficient and that the world needed to form a united front against increasingly sophisticated biotechnologies. But many nations were skeptical of the threat. They also doubted the value of what critics call "the guns, guards, and gates" approach to biosecurity. The result, says Reynolds Salerno, a biosecurity expert at Sandia National Laboratories in Albuquerque, New Mexico, has been "tremendous confusion and concern in the international life sciences community about biosecurity."

That confusion may be giving way to cooperation, however, as an increasingly global effort to define and implement biosecurity is gaining speed. Nations are moving to pass new biosecurity laws, while public health and security experts are hammering out voluntary biosecurity guidelines and debating "codes of conduct" for life scientists. Many countries are thinking about looser rules for less risky agents than in the United States, which critics say has imposed a one-size-fits-all approach, and few are likely to require the extensive criminal background checks carried out by U.S. agencies.

The new world order may not resemble the U.S. model. But like it or not, life scientists worldwide are about to become much more familiar with the term biosecurity.

–David Malakoff

Strengthening Biological Risk Management

Vision for Integrated BioRisk Management:

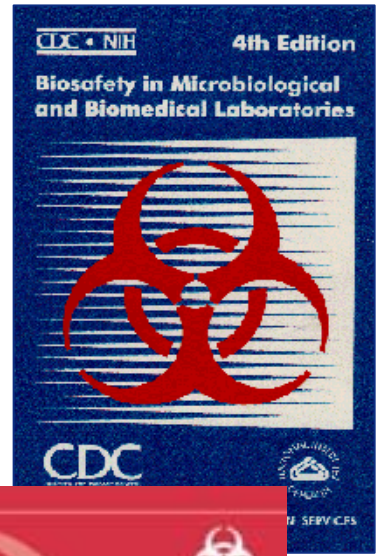
- ✓ Increased focus on "awareness" to change current culture
- ✓ Clarify terminology
- ✓ Development of targeted "training strategies"
- ✓ Securing "commitment" from key stakeholders, including government officials, who must be on board
- ✓ Continue increasing "capacity" based on Regional/Country needs and establish accountability through development of Country "report cards"

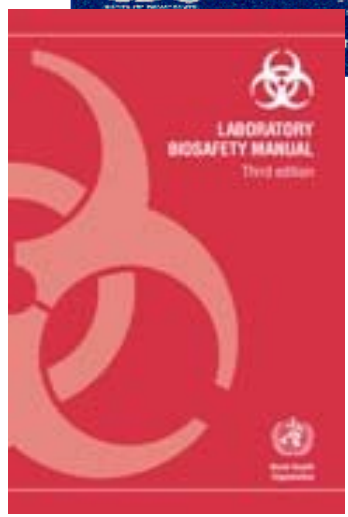
International Perspectives

- Bioterrorism not perceived as a serious threat in much of the world
- Apprehension that US biosecurity methods, or international regulatory regime, would hinder advances in basic biomedical research
- Acknowledgement that dangerous pathogens need to be protected globally
  - Biosecurity will support and strengthen the biosafety agenda
  - Biosecurity will maintain citizens' confidence in the activities of the bioscience research community
  - Biosecurity will provide confidence to investors in the biotechnology industries
  - Biosecurity will protect valuable assets research and commercial assets
  - Biosecurity can reduce the risk of crime and bioterrorism
- Ultimately, success of biosecurity will depend on willing implementation by the international scientific community and internationally available resources

Anticipated Developments

- Next edition of CDC/NIH *Biosafety in Microbiological and Biomedical Laboratories* will include extensive recommendations on biosecurity
- WHO/FAO/OIE developing joint international biosecurity guidelines
- OECD has expressed interest in establishing biosecurity guidelines
- Hopefully, these initiatives will
  - Avoid conflicting recommendations
  - Promote the concept of integrated biosafety and biosecurity
  - Introduce a tiered system of protection based on risk assessment and management methodologies

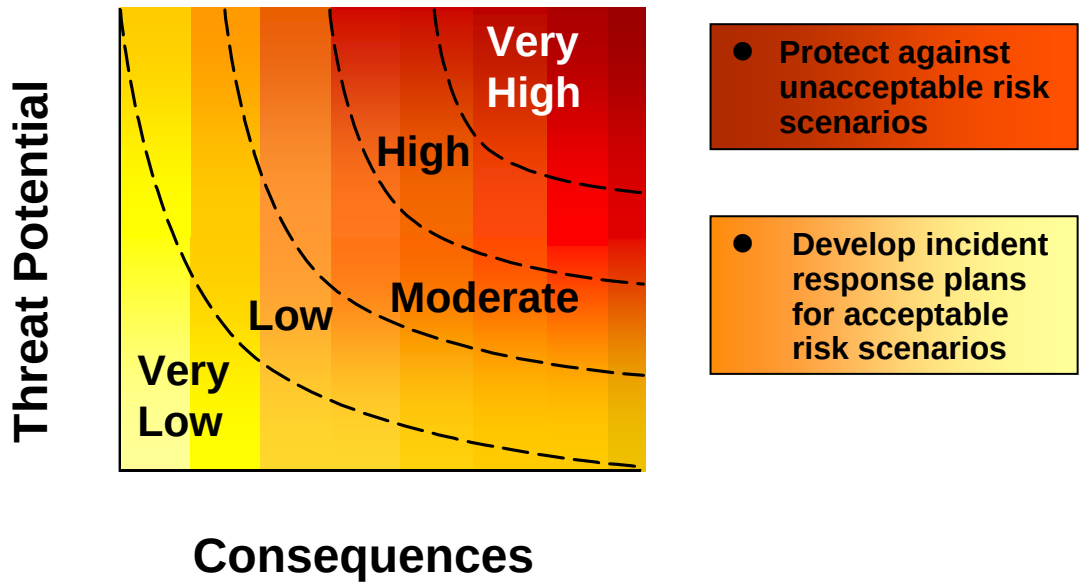




Sandia National Laboratories

Biosecurity Based on Risk Management

- Security in a biological environment will never be perfect
- Most biological materials can be isolated from nature
- Critical not to compromise legitimate bioscience operations
- Management must distinguish between “acceptable” and “unacceptable” risks
  - Ensure that protection for an asset, and the cost, is proportional to the risk of theft or sabotage of that asset



Conclusions

- **Biosecurity regulations, guidelines, and implementation methodologies are evolving**
- **The "internationalization" of laboratory biosecurity practices is an important development**
  - **Securing dangerous pathogens in one or a few countries is insufficient to mitigate the threat of bioterrorism or biological weapons proliferation**
- **However, the US Select Agent Rule is not universally applicable**
  - **Laboratory biosecurity guidelines and requirements need to reflect local and national concerns and priorities**

"Infectious diseases make no distinctions among people and recognize no borders"
President George Bush, November 2001

Contact Information

Jennifer Gaudioso, Ph.D.
Sandia National Laboratories
PO Box 5800, MS 1371
Albuquerque, NM 87185
USA
Tel. 505-284-9489
email: jmgaudi@sandia.gov

www.biosecurity.sandia.gov

Sandia National Laboratories