
National Regulations and Legislation: US Case Study

Training Seminar on Laboratory Biosecurity and Biosafety

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And

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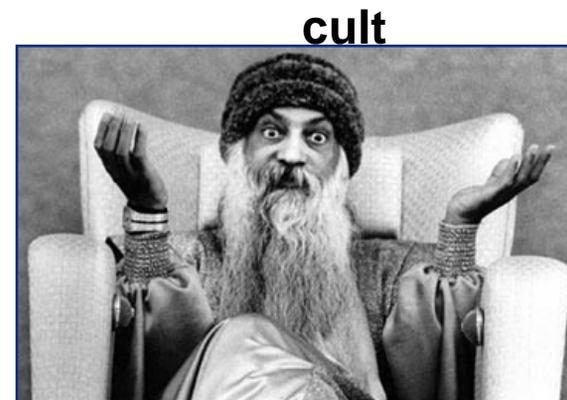


Laboratory Biosafety in US

- **Birth of the American Biological Safety Association (ABSA)**
 - In 1955, the three principal US biological weapons offensive laboratories met to discuss safety issues and,
 - By 1957, the biosafety conferences expand to include other federal laboratories
 - Formally established in 1984
- **Guidance not regulations:**
 - Centers for Disease Control (CDC), Office of Biosafety – “Classification of Etiologic Agents on the Basis of Hazard”
 - CDC/NIH – “Biosafety in Microbiological and Biomedical Laboratories”
 - NIH Guidelines on Recombinant DNA Molecules
- **“The knowledge, the techniques, and the equipment to prevent most laboratory infections are available” (Pike)**

Bioterrorism in the US: 1984

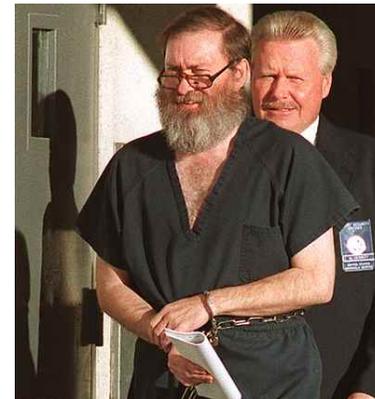
- **September 17, 1984 – First reports of gastroenteritis from recent patrons of restaurants in The Dalles, Oregon**
- **Laboratory tests confirm *Salmonella typhimurim***
- **Outbreak:**
 - 751 cases of salmonella poisoning but
 - No fatalities
- **CDC investigation concludes that outbreak resulted from food handlers' inadequate hygiene**
- **September 16, 1985 – rift between member and leader reveals incident natural outbreak**



Bhagwan Shree Rajneesh

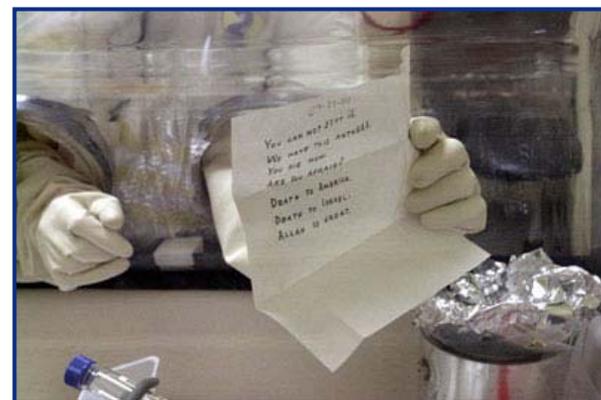
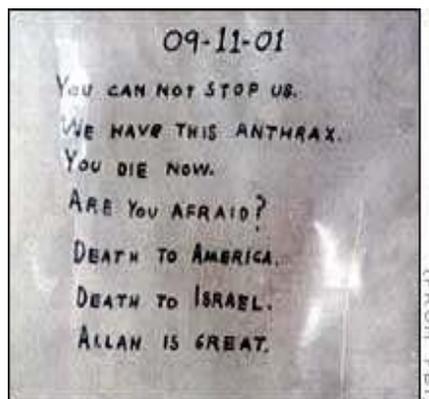
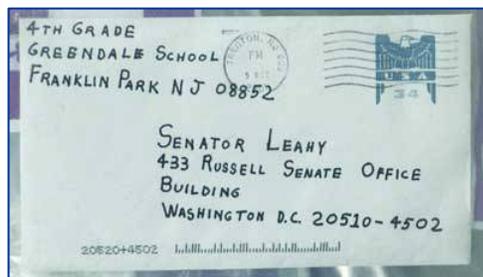
Bioterrorism in the US: 1995

- **May 1995 – Larry Wayne Harris ordered 3 vials of *Yersinia 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**



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



Necessity of Biological Research

- **Despite risks 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
- **Biosafety and biosecurity strategies must not unduly hinder essential research**
- **New and rapid advancements in biotechnology create novel threats but allow for novel responses**



Before and after botulinum injections

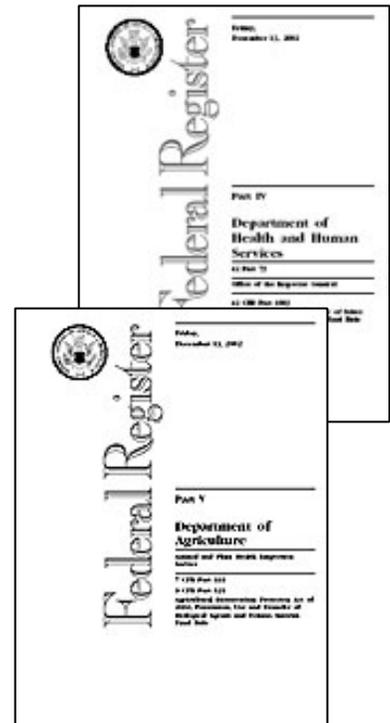
US Policy Response to the Bioterrorist Threat

- **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



Responsible Official (RO)

- **Designated by institution**
- **Has authority and responsibility for institution's compliance with CFR**
- **Develops and implements**
 - **Safety plans**
 - **Security plans**
 - **Training**
- **Authorizes access to Select Agents by authorized personnel only**
- **Responsible for transfer of Select Agents to only approved individuals and institutions**
- **Reports loss, theft, release of agents and toxins**
- **Maintains records**

RO is point-of-contact for all Select Agent regulatory activities

Security Plan

- **“Security plan must be designed according to a site-specific risk assessment and must provide graded protection in accordance with the risk of the select agent or toxin, given its intended use”**
- **Plan must be:**
 - Reviewed annually
 - Exercised annually
 - Reviewed and revised as necessary
 - After annual review, any drill, or incident



Select Agent Rule Security Plan Requirements

- Describe physical security, inventory control, and information systems control
- Describe access controls
- Describe provisions for routine cleaning, maintenance and repairs
- Establish procedures for removal of unauthorized or suspicious persons
- Describe procedures for lost or compromised keys, passwords, combinations, etc. and protocols for changing
- Describe procedures for reporting unauthorized or suspicious persons, activities, loss or theft, or alteration of records
- Ensure authorized individuals understand and comply with security
- <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5119a1.htm>

Minimum Security Plan Requirements

- SA are not stored or used in public areas
- Allow access only to DOJ-approved individuals
- Provide continuous escort by cleared individual for uncleared cleaning, maintenance and repair personnel
- SA storage areas (e.g. freezers, cabinets) have access controls
- Inspect all suspicious packages entering / leaving SA areas
- Protocol for transfer within institution
 - Including Chain of custody
- Mandates that authorized individuals do not share their access (e.g. card key, passwords)
- Report any compromises of security

Biosafety Now Part of Regulations

- **Biosafety and containment must be sufficient to contain the select agent**
- **Written biosafety plan**
 - **Commensurate with risk of the select agent**
 - **CFRs refer to:**
 - **BMBL – including all appendices**
 - **OSHA 29 CFR 1910.1200 (Hazard Communication)**
 - **OSHA 29 CFR 1910.1450 (Occupational Exposure to Hazardous Chemicals in Laboratories)**
 - **NIH Guidelines for Research Involving Recombinant DNA Molecules**
 - **Reviewed and revised annually**
 - **Exercised and evaluated annually**

Select Agents

- **Lists of agents that affect**
 - **Humans**
 - **Animals**
 - **Both humans and animals (zoonotic)**
 - **Plants**

- **Potential to cause substantial harm to**
 - **Human health**
 - **Animal or plant health**
 - **Animal or plant products**

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

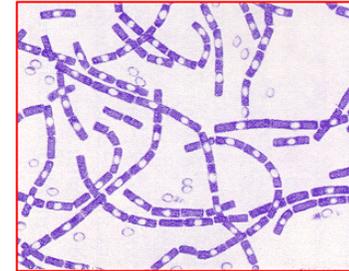
Plant Select Agents and Toxins

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

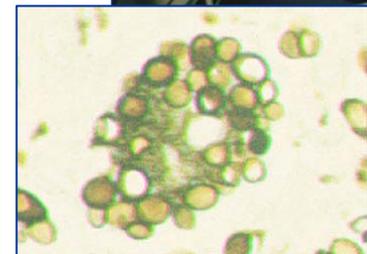
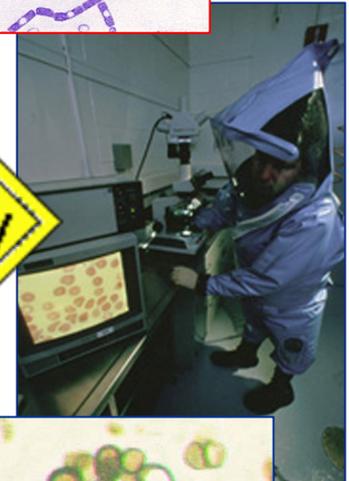
- *Peronosclerospora philippinensis*
- *Sclerophthora rayssiae*
- *Synchytrium endobioticum*

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



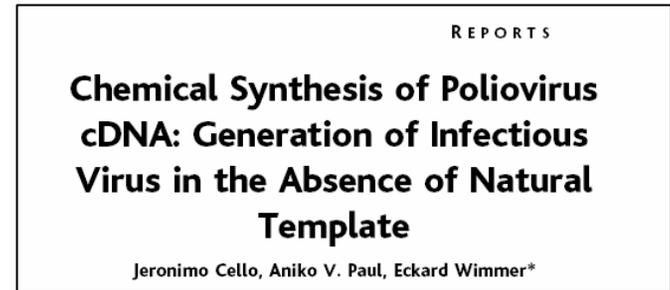
Bacillus anthracis



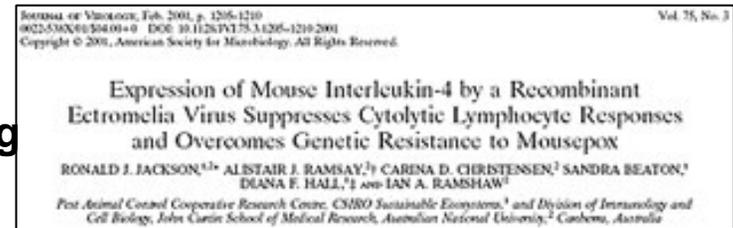
Coccidioides immitis

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**



9 AUGUST 2002 VOL 297 SCIENCE www.sciencemag.org



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 incite panic 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 Bogotà 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 sim-



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

ilar 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 Carrie Vander Linden, although the details have not been worked out.

U.S. inspectors will soon be heading out to assess lab standards overseas, scientists learned at a closed-door meeting last month. Paula Strickland, 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 Strickland 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' cher-

ished 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 Bogotà and the Central University of Venezuela and the National Institute of Hygiene in Caracas now won't have to adhere to the select-agent

A Selection of Select Agents

Smallpox virus
Crimean-Congo hemorrhagic fever virus
Lassa fever virus
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



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 Soudalchichiev, director general of the State Research Center of Virology and Biotechnology, a former bioscience 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?"

Earthquake Preparedness

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 epoch-making advance in earthquake safety," says Masato Motozaka, a Japanese earthquake engineer at Tohoku University in Sendai.

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 Oshinsky, an urban planner at the University of Illinois, Urbana-Champaign. "Investing too much of one's

agent, with colleagues in Thailand and Australia will be subject to such oversight. Month 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

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



On alert. Newcast stations are being installed across Japan.

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,

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"

Conclusions

- **Biosafety has historically been based on guidance and best practices**
- **Biosecurity is much newer and 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**