Emerging Laboratory Biosecurity Issues

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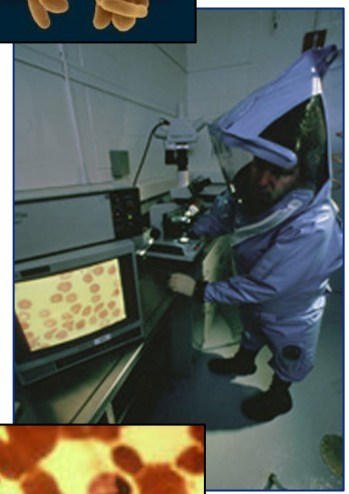
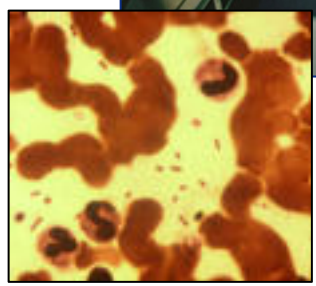
Biosafety and Biosecurity

- **Biosafety**
  - **Objective: reduce or eliminate accidental exposure to or release of potentially hazardous agents**
- **Biosecurity**
  - **Objective: protect biological agents against theft and sabotage by those who intend to cause harm**
- **Common strategy**
  - **Implement graded levels of protection based on a risk management methodology**
- **Control of certain biological materials is necessary, but *how* that is achieved must be carefully considered**
  - **Biosecurity and biosafety should be integrated systems that avoid compromising necessary infectious disease research and diagnostics**

Francisella tularensis

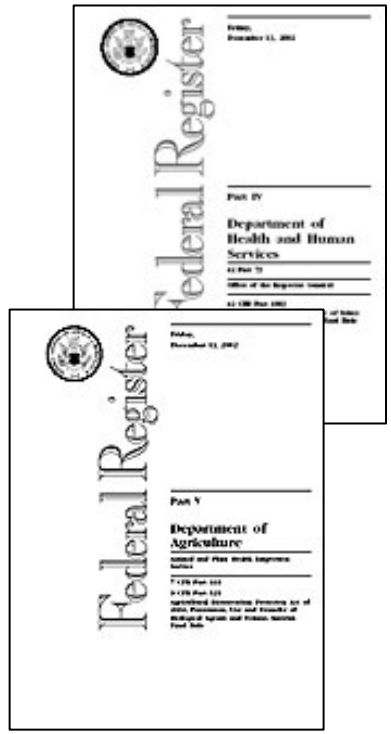




Yersinia pestis

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/or 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



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

Science, Vol. 305, 17 September 2004

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 cramped 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 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' 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 biowepons 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/osp/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,

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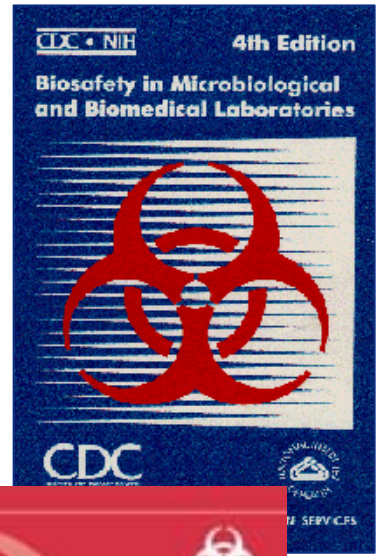
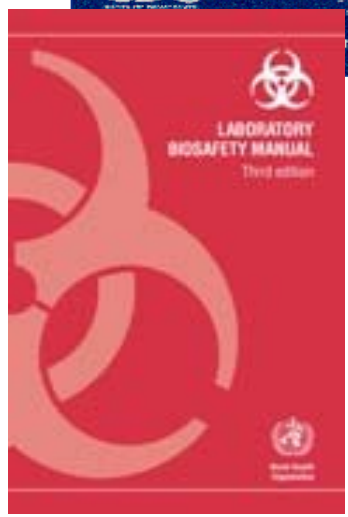
Anticipated Biosecurity Developments

- 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





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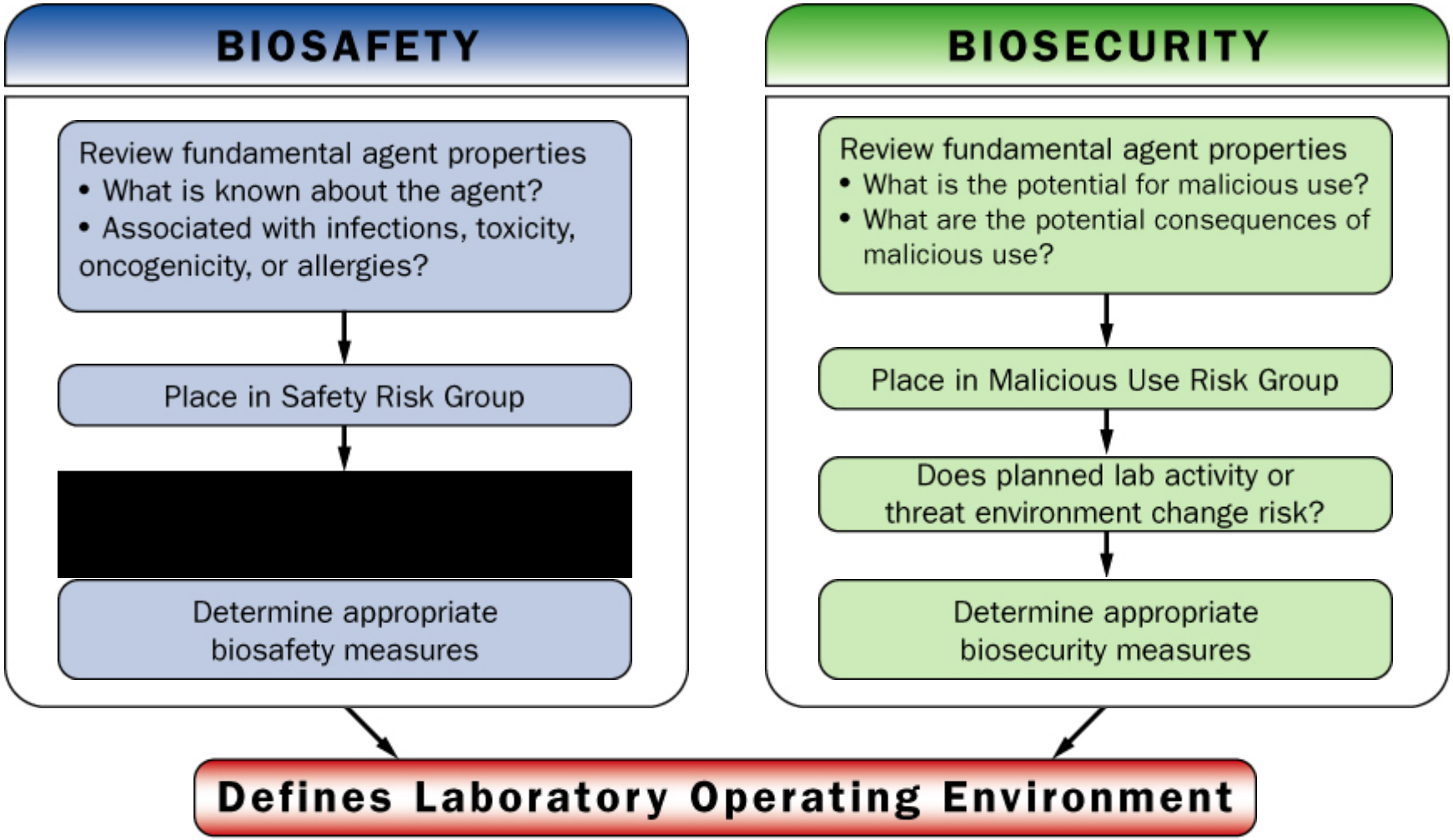
Strengthening Biological Risk Management

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"

Integrated Biosafety and Biosecurity



Malicious Use Risk Group Evaluation

- **Assess value of the agents from an adversary's perspective**
  - **Consequences**
    - Infectivity
    - Morbidity
    - Transmissibility
    - Lethality
  - **Weaponization potential**
    - Availability
    - Ease of growth
    - Ease of processing
    - Ease of distribution
    - Environmental hardiness
    - Ability to camouflage as a natural outbreak

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

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Malicious Use Risk Groups

- **Nonpathogenic**
  - **Malicious use would have insignificant or no consequences**
- **Low Malicious Use Risk (LMUR)**
  - **Difficult to deploy maliciously, and/or**
  - **Malicious use would have few consequences**
- **Moderate Malicious Use Risk (MMUR)**
  - **Relatively difficult to deploy maliciously, and**
  - **Malicious use would have localized consequences with low to moderate casualties and/or economic damage**
- **High Malicious Use Risk (HMUR)**
  - **Not particularly difficult to deploy maliciously, and**
  - **Malicious use could have national or international consequences, causing moderate to high casualties and/or economic damage**
- **Extreme Malicious Use Risk (EMUR)**
  - **Would normally be classified as HMUR, except that they are not found in nature (eradicated)**
  - **Could include genetically engineered agents, if they were suspected of being a HMUR**

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Elements That May Modify Risk

- Consider lab experiment
  - Does planned experiment produce an agent with higher weaponization potential or higher potential consequences?
- Evaluate local threat environment
  - Insiders
    - Authorized access to the facility, dangerous pathogens, and/or restricted information
  - Outsiders
    - No authorized access
  - Evaluate threat potential of possible insiders and outsiders:
    - Capabilities
    - Tools
    - Motivation
    - Possibility of being caught

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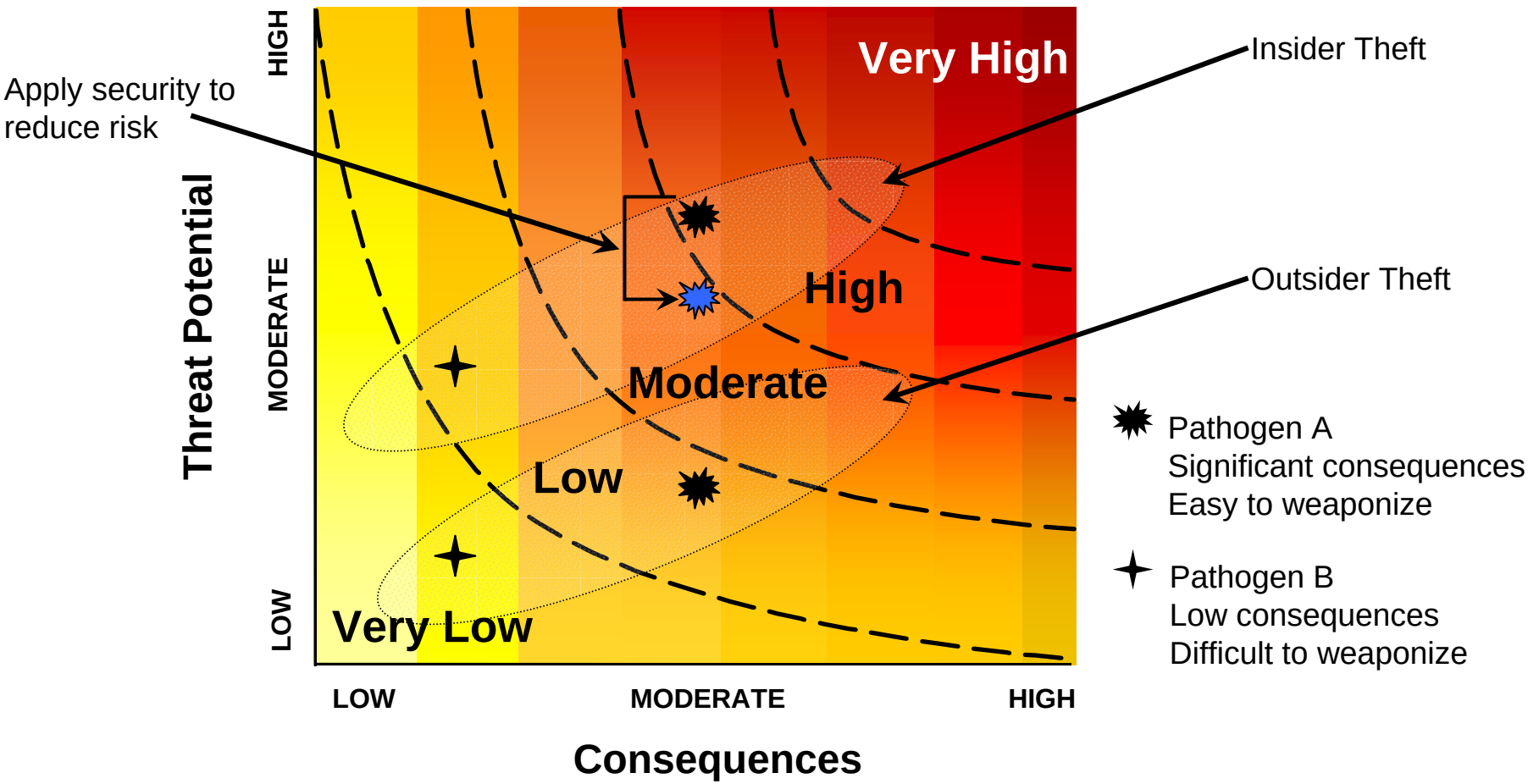
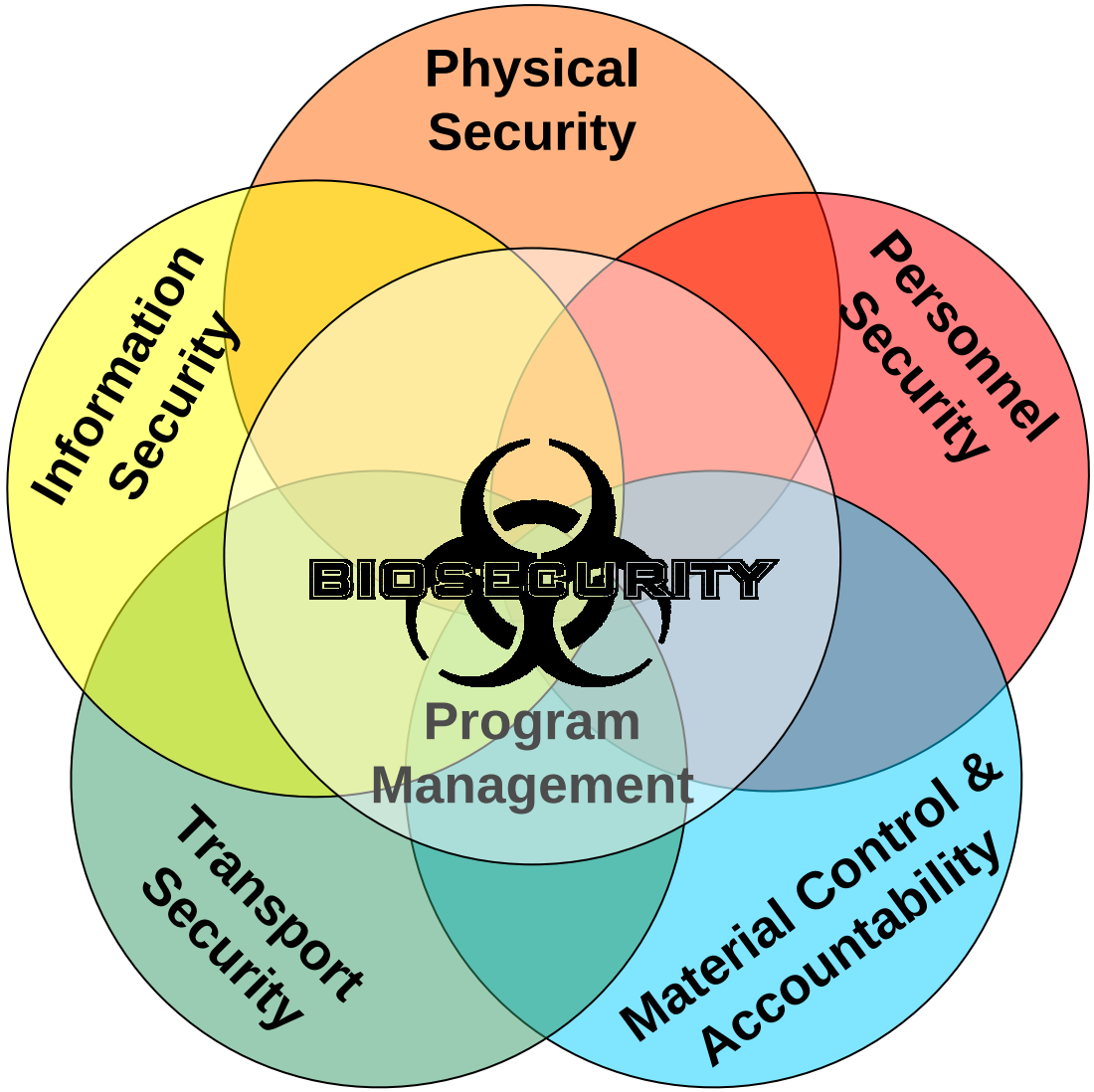
Biosecurity Risk: Insider vs. Outsider Threat



Biosecurity Based on Risk Management

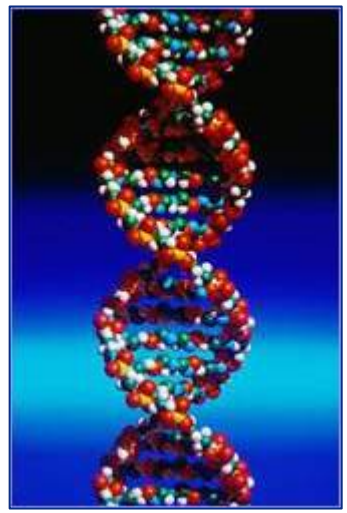
- **Biosecurity fundamentals**
  - **Security in a biological environment will never be perfect**
  - **Most biological materials can be isolated from nature**
  - **Critical not to compromise legitimate bioscience operations**
- **Management must identify the protection objectives of the biosecurity system**
  - **Scenarios to protect against – the "unacceptable" risks**
  - **Scenarios to be prepared to respond to – the "acceptable" risks**
  - **Ensure that protection for an agent, and the cost, is proportional to the risk of theft or sabotage of that agent**
- **Design the system**
  - **Physical security**
  - **Security policies and procedures**
- **Write security and emergency response plans**
- **Conduct regular training and internal reviews**
- **Allocate resources**

Components of Biosecurity



Summary

- **Biosecurity regulations, guidelines, and implementation methodologies are evolving**
- **The "internationalization" of laboratory biosecurity practices is an important development**
- **Elements of laboratory biosecurity are emerging that should help define the future practice of laboratory biosecurity**
  - **Concept of integrated biosafety and biosecurity**
  - **Tiered system of protection based on risk assessment and management methodologies**



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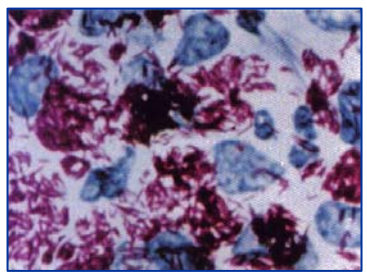
LMUR Agent Example: *Mycobacterium leprae*

- **Consequences**
  - **Leprosy**
    - **Not highly virulent, most exposed people do not develop leprosy**
    - **Not highly contagious**
    - **Completely curable – majority recover without treatment**
- **Weaponization potential**
  - **Production is a significant challenge**
  - **Not environmentally hardy**
- **Assessment: low consequences and low weaponization potential**



Mycobacterium leprae

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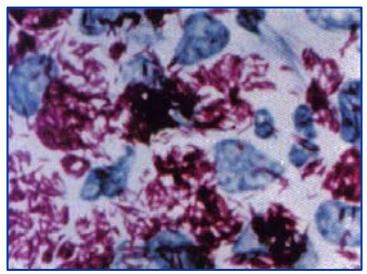
Low Risk Security Level

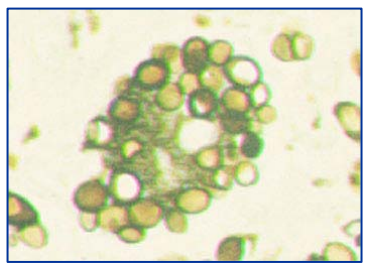
- Doors on unattended laboratories should be locked
- Principal Investigator should be aware of work and individuals in his/her lab
- Laboratory notebooks should document the stocks and use of agents



Mycobacterium leprae

MMUR Agent Example: *Coccidioides immitis*

- **Consequences**
  - **Coccidioidomycosis (Valley fever)**
    - **Usually asymptomatic, 30-40% of infected become ill**
    - **Not contagious**
    - **5-10 out of every 1000 infected develop life-threatening infection**
- **Weaponization potential**
  - **Requires technical skills to handle**
  - **Easy to procure virulent strain (wide endemic area)**
  - **Easy to grow colonies and produce spores**
- **Assessment: low to moderate consequences and moderate weaponization potential**



Coccidioides immitis

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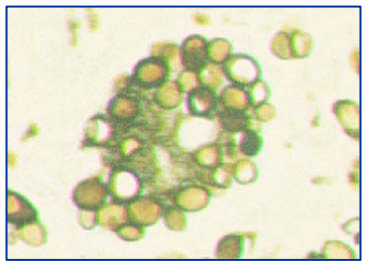
Moderate Risk Security Level

- **Basic access controls (e.g. controlled keys) for areas where agents are used and stored**
- **Basic personnel suitability check should be completed for all those who enter the controlled area**
- **Materials should be accounted for and inventoried in databases**



Coccidioides immitis

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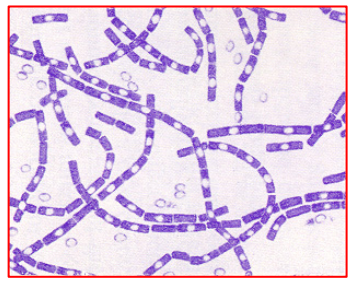
HMUR Agent Example: *Bacillus anthracis*

- **Consequences**
  - **Pulmonary anthrax (via aerosolized anthrax)**
    - **High fatality rate**
    - **Not contagious, relatively high infectious dose required**
    - **Early diagnosis is difficult**
- **Weaponization potential**
  - **History of weaponization and terrorist use**
  - **Wide endemic area but many less virulent strains**
  - **Easy to grow colonies and produce spores**
  - **Very stable in environment and storage**
- **Assessment: moderate to high consequences and relatively high weaponization potential**



Bacillus anthracis

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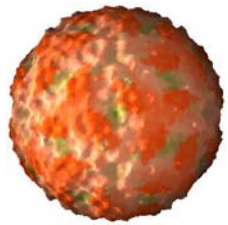
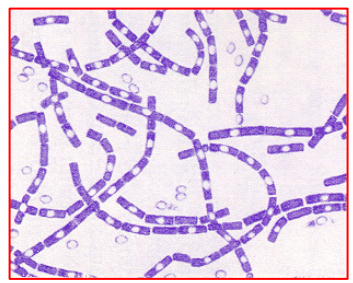
High Risk Security Levels

- Electronic access controls
- Personnel screening should include more comprehensive background investigations
- Accountability records should be maintained
- Material transfers should be pre-approved and require a continuous chain of custody
- Information about the security of these agents should be protected
- Biosecurity Officer should oversee the implementation of appropriate biosecurity measures



FMD virus

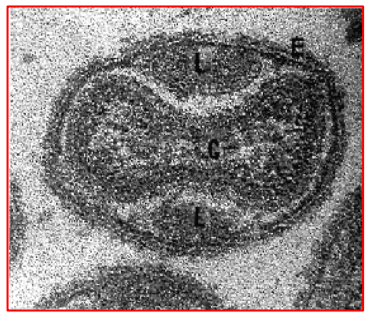
Yersinia pestis



Bacillus anthracis

EMUR Agent Example: Variola major virus

- **Consequences**
  - **Smallpox**
    - **High fatality rate**
    - **Contagious**
    - **Very few people vaccinated**
- **Weaponization potential**
  - **History of weaponization**
  - **Very stable in aerosol**
  - **Extremely difficult to obtain**
- **Assessment: high consequences and moderate weaponization potential**

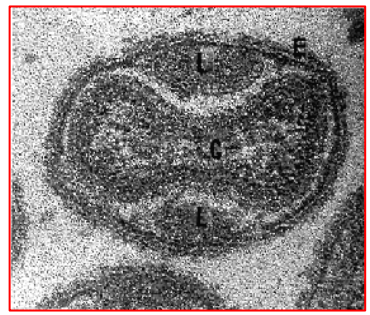


Variola major

Patient's leg covered in smallpox

Extreme Risk Security Level

- Two- or three-level electronic access controls
- In-depth personnel suitability background checks
- Accountability records should be maintained
- Two authorized individuals should be required for access to repository stocks
- Material transfers should be pre-approved and require a continuous chain of custody
- Information about the security of these agents should be protected
- Local guard force should be able to respond to intrusions
- Biosecurity Officer should oversee the implementation of appropriate biosecurity measures



Variola major

Patient's leg covered in smallpox

Result of Biosecurity Risk Management

- Most pathogens and toxins would likely be LMUR
- Most current Select Agents would likely be MMUR
- Security associated with LMUR and MMUR would be achievable at reasonable cost for the broad biological research community
  - Rely largely on existing biosafety measures

- Very few Select Agents would be HMUR or EMUR
- Security for facilities that work with HMUR or EMUR would be relatively significant, but should still
  - Rely largely on policies and procedures
  - Be transparent to the users
  - Use resources efficiently
  - Not unnecessarily hinder normal operations (e.g. research, diagnostics, biosafety)

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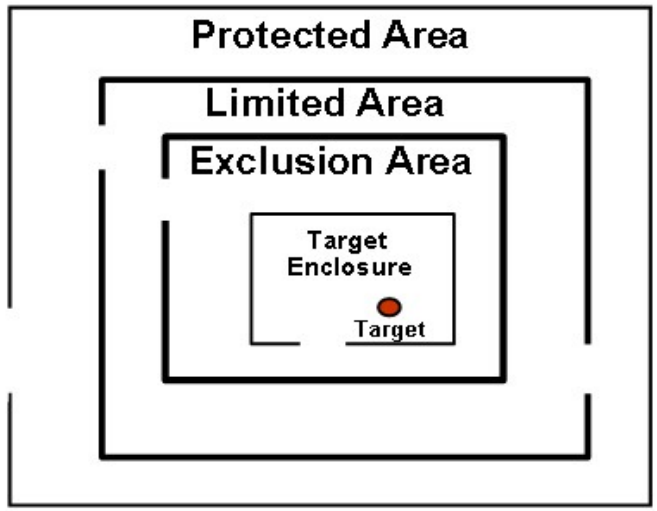
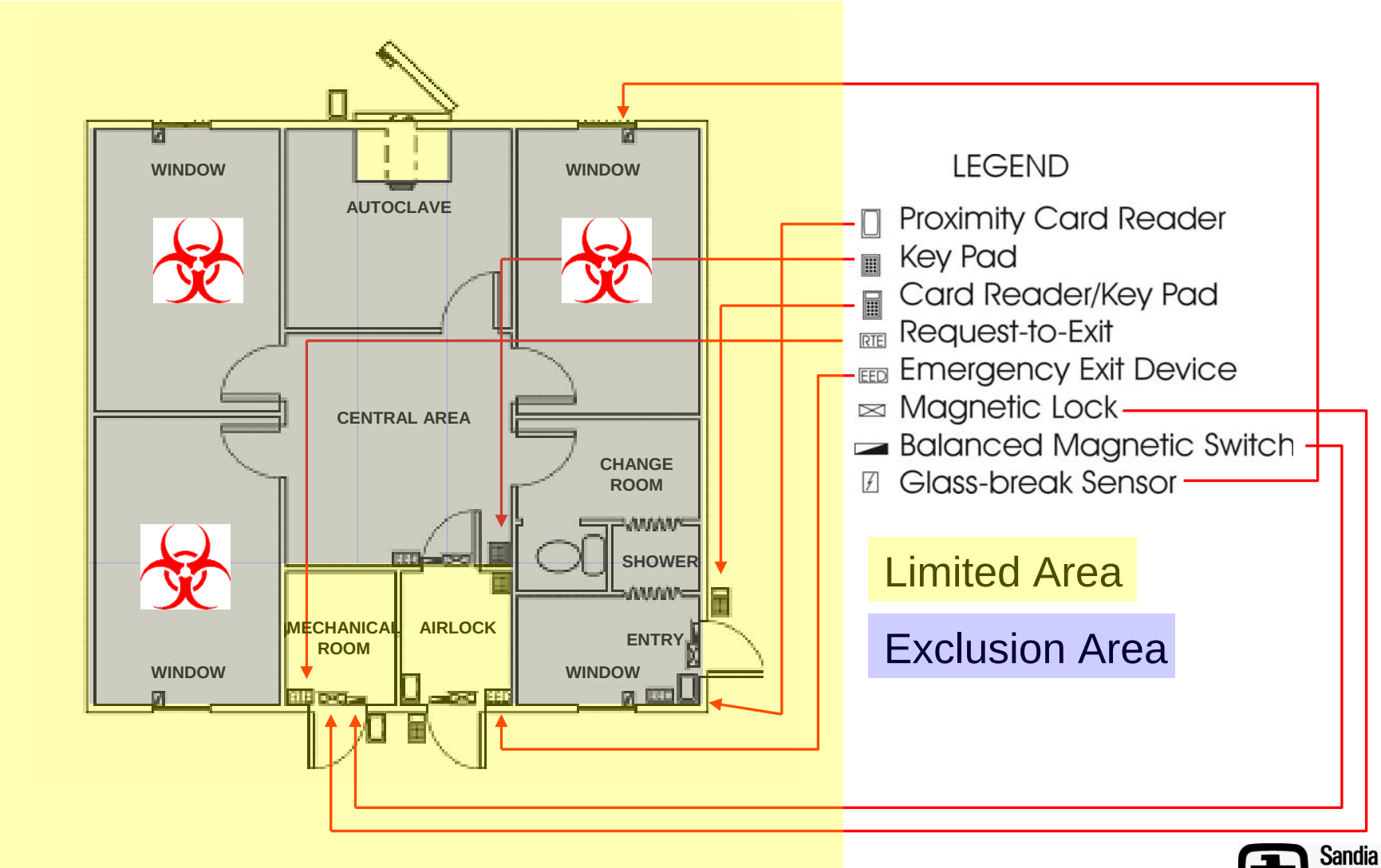
Physical Security

- **Graded protection**
  - **Increasingly strict controls from one protection area to another**
- **Access control**
  - **Ensures only authorized individuals are allowed entry**
- **Intrusion detection**
  - **Detects unauthorized access**



Example Laboratory Building



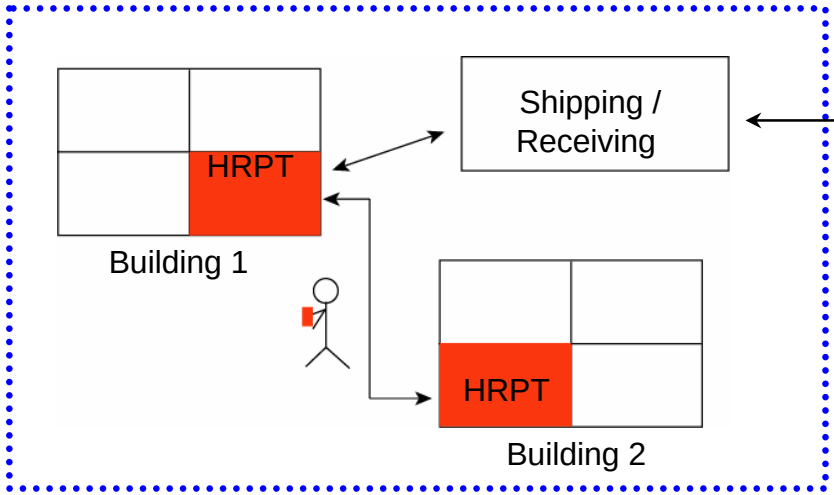
Personnel Security

- **Personnel Screening**
  - **Review and verify personal information**
  - **Conduct background investigations**
  - **Increasing level of scrutiny for higher risk positions**
- **Badges**
- **Visitor Control**
- **Training**

Material Control and Accountability

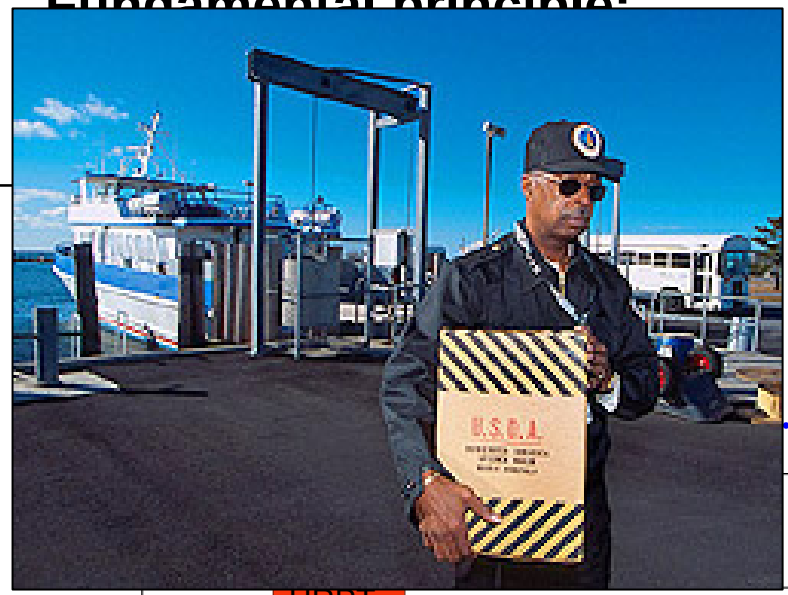
- **Responsibility**
  - **Accountable individual**
- **Documentation**
  - **Agent name and description**
  - **Quantity**
    - **Based on containers or other "units" NOT the number of microbes**
  - **Location**
- **Control**
  - **Physical, personnel, information, and transfer security**
  - **Biosafety/Biocontainment**

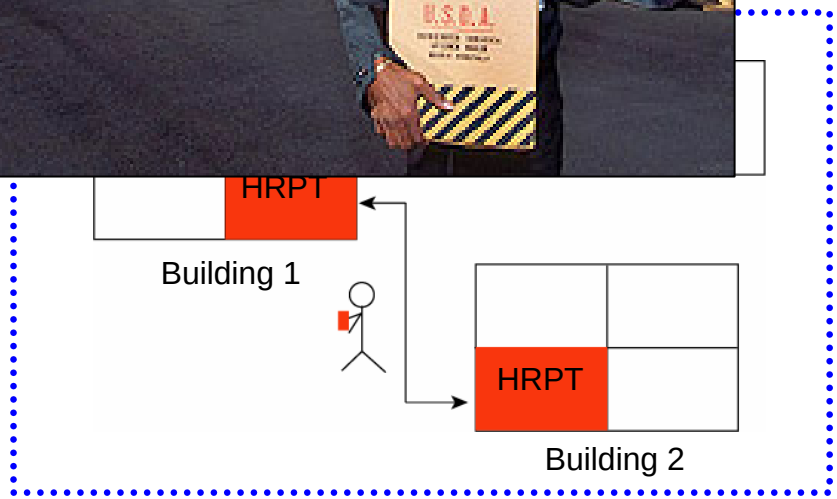
Transport Security



Facility A

Fundamental principle:





Facility B

Transport may occur:

- **Across international borders**
- **Within a country**
- **Within a facility or building**

Information Security

- Protect information that is too sensitive for public distribution
  - Label information as restricted
  - Limit distribution
  - Restrict methods of communication
  - Implement network and desktop security
- Types of sensitive information
  - Security of dangerous pathogens and toxins
    - Risk assessments
    - Security system design
    - Access authorizations
  - Personnel records
  - Financial records

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