Biosafety, Biosecurity and Dual-Use Research of Concern

National Academies of Science, Engineering and Medicine

4 January 2017

Washington, D.C.

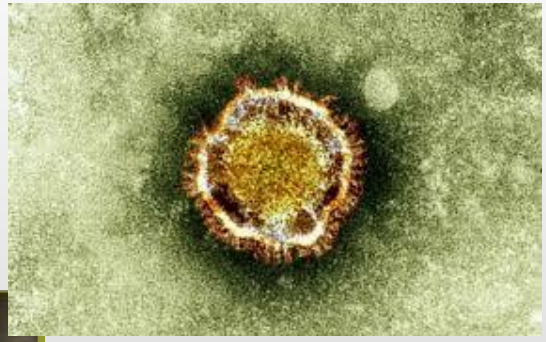
THE UNIVERSITY OF CHICAGO

Office of Research Safety

Emerging Diseases

Associated Compliance Agencies:
DHHS (CDC, NIH),USDA, DOJ, DOT/FAA, OSHA, WHO

Combating Ebola epidemic in Congo

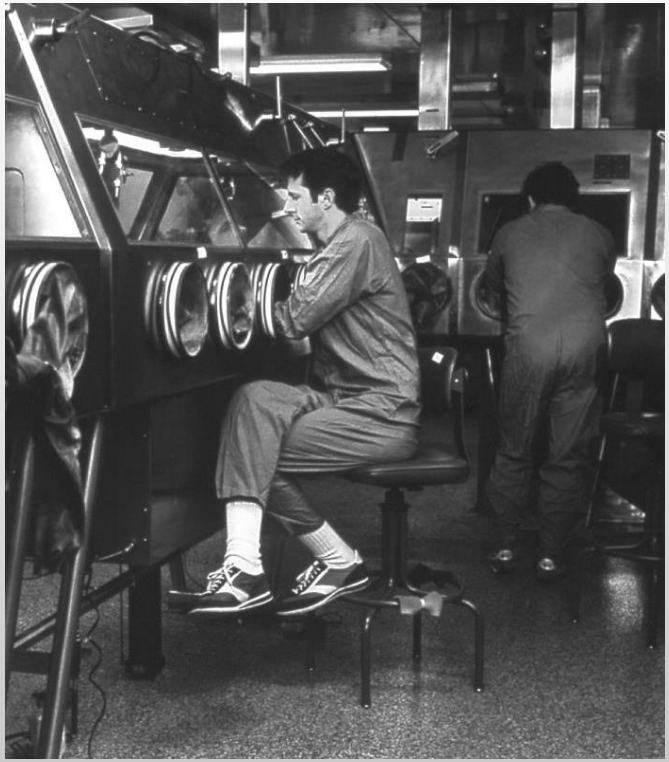


Examples of new and reemerging diseases.

Definitions

Biosafety

Laboratory biosafety describes the containment principles, technologies and practices that are implemented to prevent the unintentional exposure to pathogens and toxins, or their accidental release.



World Health Organization. *Laboratory biosafety manual*. Third edition. Geneva, World Health Organization, 2004

Definitions

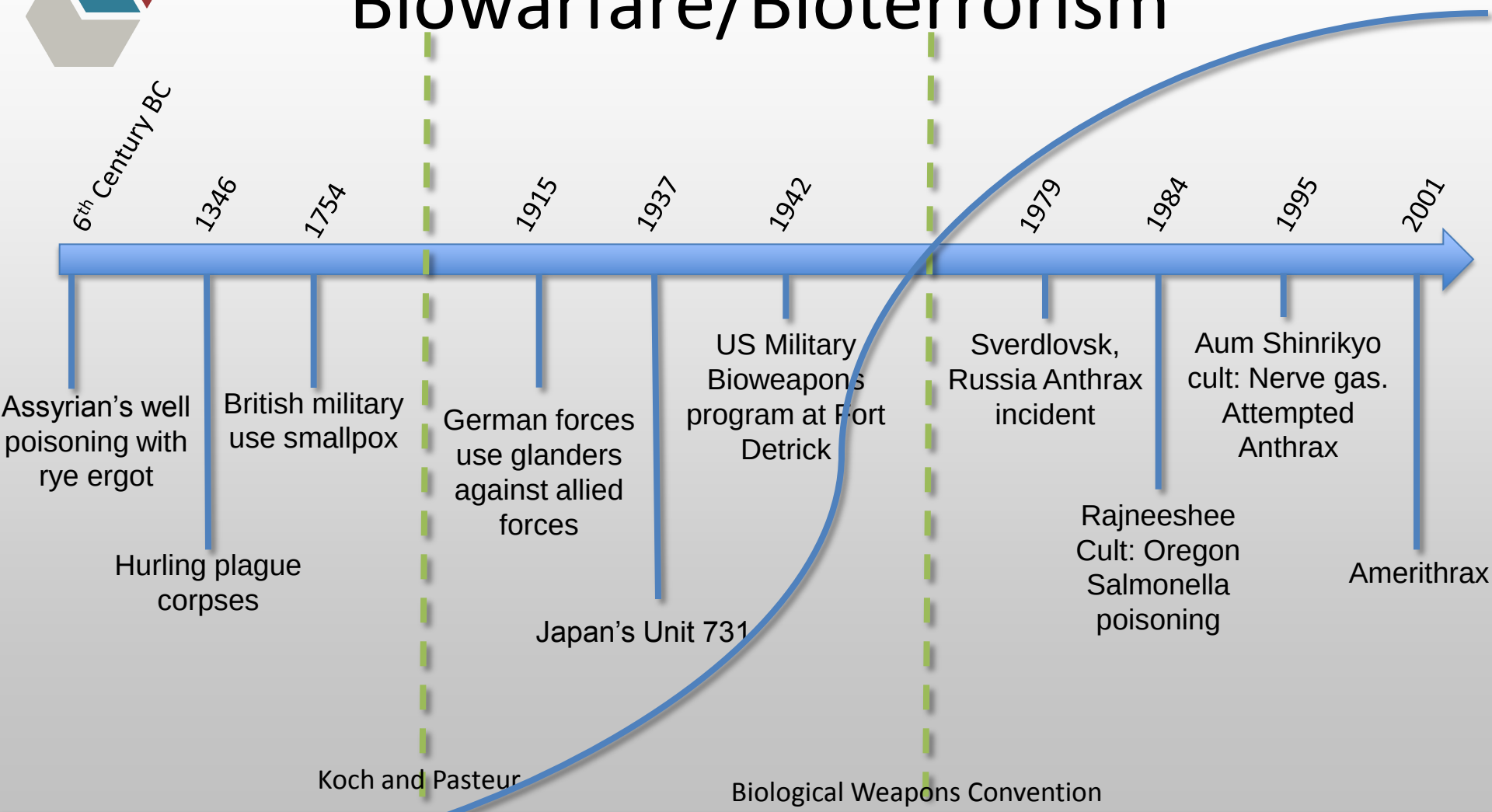
Biosecurity

Laboratory biosecurity describes the protection, control and accountability for **valuable biological materials (VBM)** within laboratories, in order to prevent their unauthorized access, loss, theft, misuse, diversion or intentional release.

- Components of a laboratory biosecurity program include:
  - Material control
  - Information security

Valuable biological materials (VBM)
Biological materials that require (according to their owners, users, custodians, caretakers or regulators) administrative oversight, control, accountability, and specific protective and monitoring measures in laboratories to protect their economic and historical (archival) value, and/or the population from their potential to cause harm. **VBM may include pathogens and toxins, as well as non-pathogenic organisms, vaccine strains, foods, genetically modified organisms (GMOs), cell components, genetic elements, and extraterrestrial samples**.

History of Biowarfare/Bioterrorism



Arnold G. Wedum

Fort Detrick (1943 - 1969)

- Considered the father of modern biosafety
- Created the Biological Safety Conference in 1956
- Provided guidance to federal agencies in support of the development of biosafety programs and guidelines
- Published papers on biosafety practices, risk assessments, and applied research projects
- Dr. Wedum was a mentor to whomever asked for his guidance

Arnold G. Wedum, M.D., Ph.D. (1903-1976)

Fort Detrick
Contributions to Biosafety
1943 – 1969

- **Occupational health program**
  - **Health and safety of workers highest priority**
  - **Treat every infection as a LAI until proven otherwise**
  - **Reporting exposures was encouraged**

- **Risk assessment**
  - **Number and severity of LAI**
  - **Infectious dose for humans**
  - **Availability of specific therapy or effective vaccine**

- **Applied research**
  - **Pioneered risk assessment studies**
  - **Developed and validated decontamination protocols**
  - **Evaluated microbial hazards and protocols**
  - **Evaluated efficiency of HEPA filters for capturing viral particles**

Estimated Rate of Laboratory-acquired Infections Among Fort Detrick Personnel
1943 - 1969

Period	Personnel at Risk	Approximate Containment Level	LAI / Million Person-hours Worked
1943-1945	Primarily military	P1	35
1954-1958	Primarily civilian	P2	9
1960-1962	Primarily civilian	P3	2
1960-1969	Primarily civilian	P4	1

Select Agent Form 3 Reports (2004-2010)

- Total population of SA investigators: ~10,000
- Total Number of Form 3 Filings: 727
- No theft reports
- One specimen lost in transit among 3412 transfers
- Eleven confirmed lab-acquired infections
  - No fatalities
  - No cases of secondary transmission

Henkel et al, *Applied Biosafety* Vol.17, No.4, 2012

Henkel et al (2012)

Year	Agent	#cases	Entity type	Lab Type
2004	*Brucella melitensis*	1	Registered	BSL2
2004	*Coccidiodes* sp.	1	Registered	BSL3
2004	*Francisella tularensis**	3	Registered	BSL2
2007	*Brucella melitensis*	1	Registered	BSL3
2007	*Brucella melitensis*	1	Exempt	BSL2
2008	*Brucella melitensis*	1	Registered	BSL3
2009	*Francisella tularensis**	1	Registered	BSL3
2010	*Brucella suis*	1	Exempt	BSL2
2010	*Brucella suis*	1	Exempt	BSL2

Biosafety Guidelines

Classification of Etiologic Agents on the Basis of Hazard

- Published by the CDC (DHHS) in 1969
- Four classes of hazard (1,2,3,4)
- A fifth class (5) of animal agents with USDA restrictions
- Scientific judgment of the PI (risk assessment)
- Competence of investigators
- Physical containment

Biosafety Guidelines:

Asilomar Conferences, Pacific Grove, CA:

1. Jan. 22-24, 1973: Led to publication of: *NCI Safety Standards for Research Involving Oncogenic Viruses*
   - Three classes of potential hazard (Low, Moderate, High)
   - PI and individual responsibility
   - Practices, safety cabinets, facilities
   - Medical surveillance
2. February 24-27, 1975: Led to publication of: *NCI Recombinant DNA Research Guidelines*

Containment
- Physical: P1, P2, P3, P4
- Biological: EK1, EK2, EK3

Experimental Guidelines
- Risk assessment
- Selecting containment

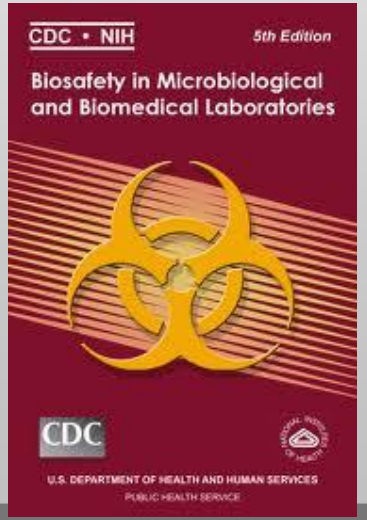
Roles and Responsibilities
- Principal investigators
- Institutions
- Institutional Biohazard Committees

Biosafety Guidelines

CDC/NIH *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*

- First edition published in 1984

- Current (5th) edition published in 2009
- Advisory recommendations
- Voluntary code of practice
- Goal of upgrading operations
- Guide for laboratory construction or renovation
- Application to laboratories is based upon risk assessment.



Biosafety Resources

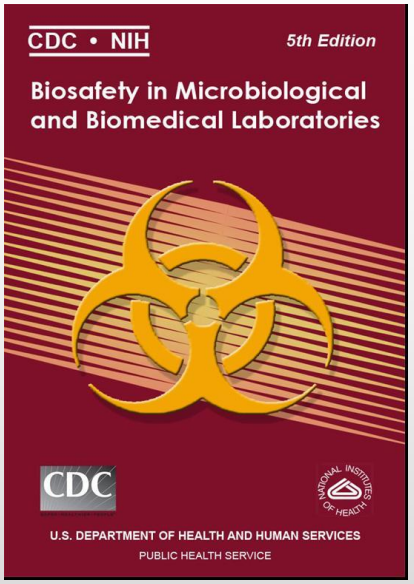
Biosafety in Microbiological and Biomedical Laboratories
[HHS Publication No.(CDC) - 5th ed., Feb 2007]

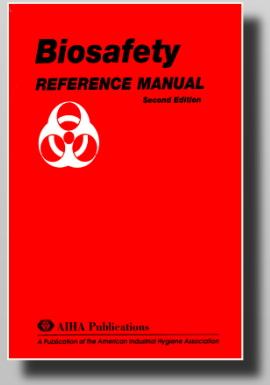
Control of Communicable Diseases Manual
[American Public Health Association - 18th ed., 2005]

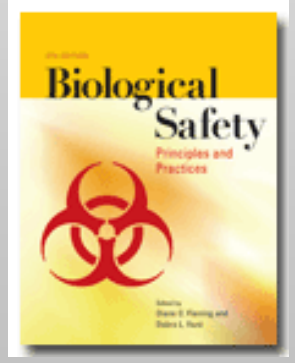
Laboratory Biosafety Manual
[World Health Organization – 3rd ed., 2004]

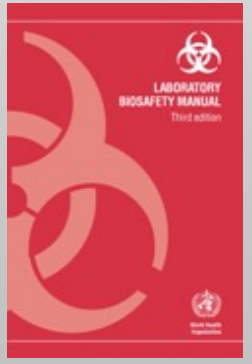
Biological Safety PRINCIPLES AND PRACTICES
[ASM Press – 4th ed., 2006]

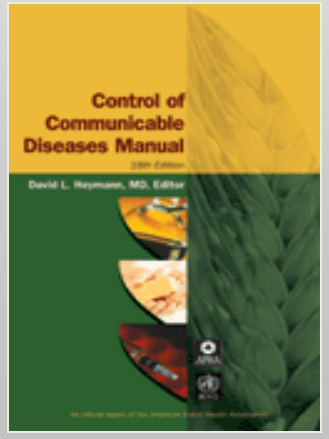
Biosafety REFERENCE MANUAL
[AIHA Publications – 2nd ed., 1995]







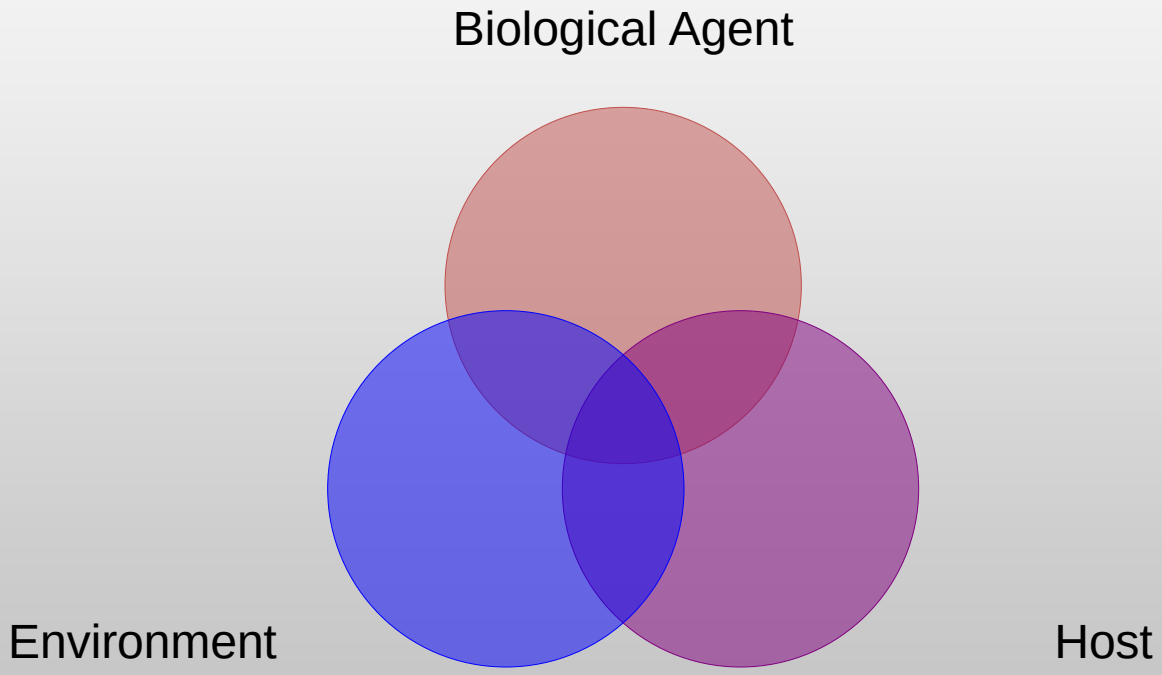




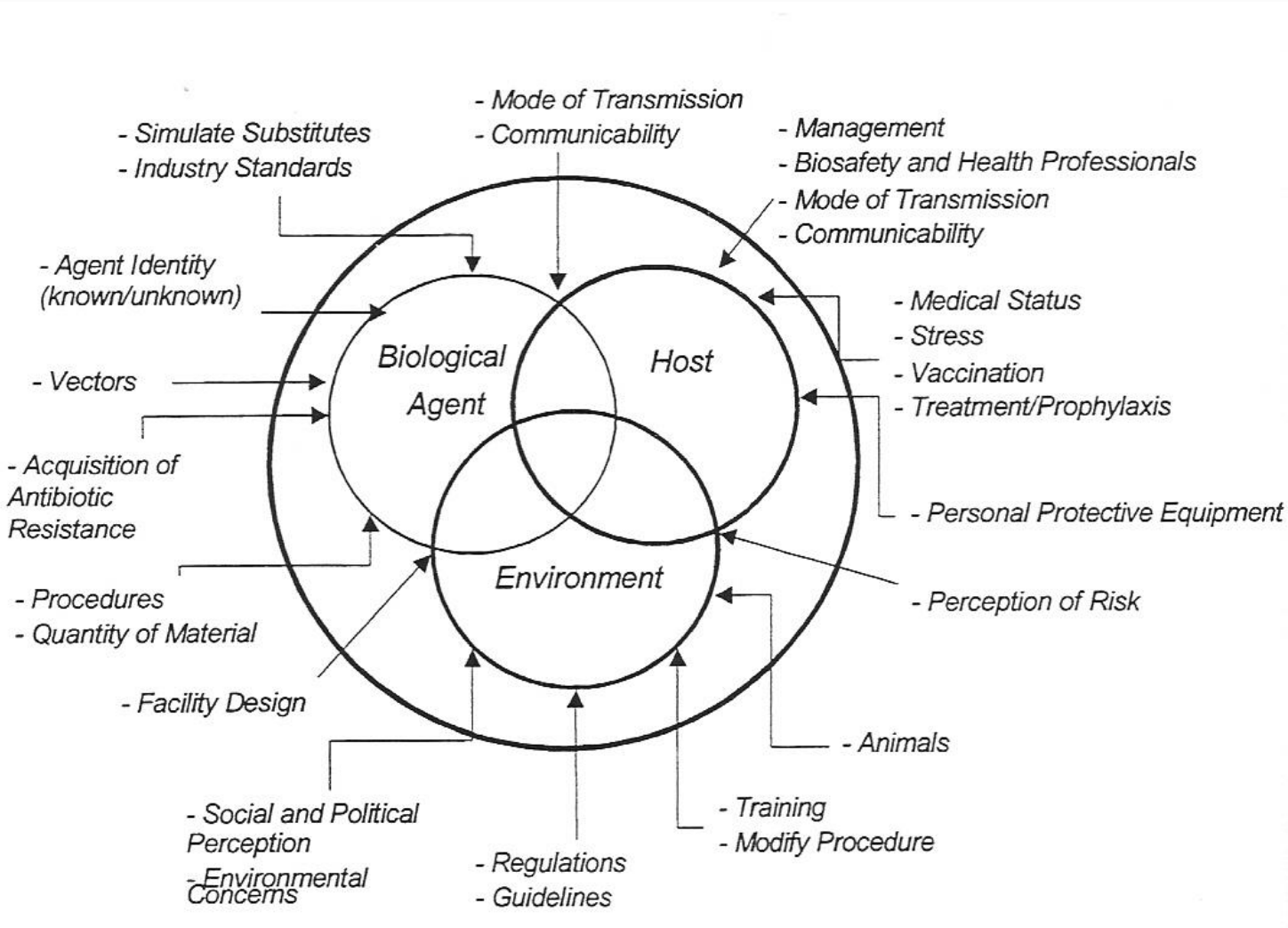
Regulatory Oversight of Biosafety Laboratories

- **Interstate Shipment of Etiological Agents**
  - DOT 42 CFR Part 72 (1957)
- **Occupational Exposure to Bloodborne Pathogens**
  - OSHA 29 CFR Part 1910.1030 (1991)
- **Possession, Use and Transfer of Select Agents**
  - CDC 43 CFR Part 73 (2005)
  - APHIS 9 CFR Part 121, and 7 CFR 331 (2005)
- **Public Health Security & Bioterrorism Preparedness & Response Act-2002**
  - Regulations for the transfer, possession and use of select agents
  - Risk assessment (including children and vulnerable populations)
  - Ensure appropriate training and skill in handling select agents
  - Containment laboratories
  - Security measures commensurate with the risk such agent or toxin poses to public health and safety (including the risk of use in domestic or international terrorism
  - Availability of select agents for research, education & other legitimate purposes.

Risk Assessment Considerations



Risk Assessment Factors



Anthology of Biosafety IV, Issues in Public Health, Chapter 10. J.Y. Richmond, Ed. ABSA, 2001 page 152

Hierarchy of Controls

- Anticipation of hazard
- Recognition of hazard
- Evaluation of hazard
- Control of hazard (OSHA)
  - **Elimination/Substitution (surrogate organisms?)**
  - **Engineering controls**
  - **Administrative (access control , information dissemination, communication)**
  - **Work practices**
  - **Personal protective clothing/equipment**

Biological Containment

- Important containment mechanism, especially when assessing rDNA risks.
- Based upon existence of natural barriers that limit either:
  - Infectivity of an agent (pathogen, vector) for specific hosts
  - Ability of agent to disseminate or survive in the environment.

Physical and Biological Containment

"Since these…means of containment are complimentary, different levels of containment can be established that apply various combinations of the physical and biological barriers along with a constant use of standard practices." NIH *Guidelines*

Physical Containment

- Engineering Controls
  - Facility
    - HVAC configuration and controls
    - HEPA filtration
  - Equipment
    - Biological Safety Cabinets
    - Fume Hoods
    - Centrifuge rotors/buckets w/gaskets
- Work Practices
  - Standard Microbiological Practices
  - Specialized procedures, equipment and facility installations that are applied in varying degrees according to the risk assessment
- Personal Protective Equipment

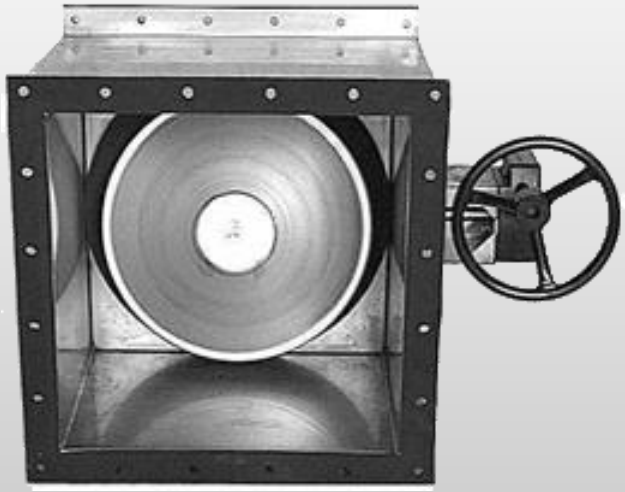
Biosafety Level 2 (BSL2) Laboratory

Biosafety Level 3 (BSL3) Laboratory

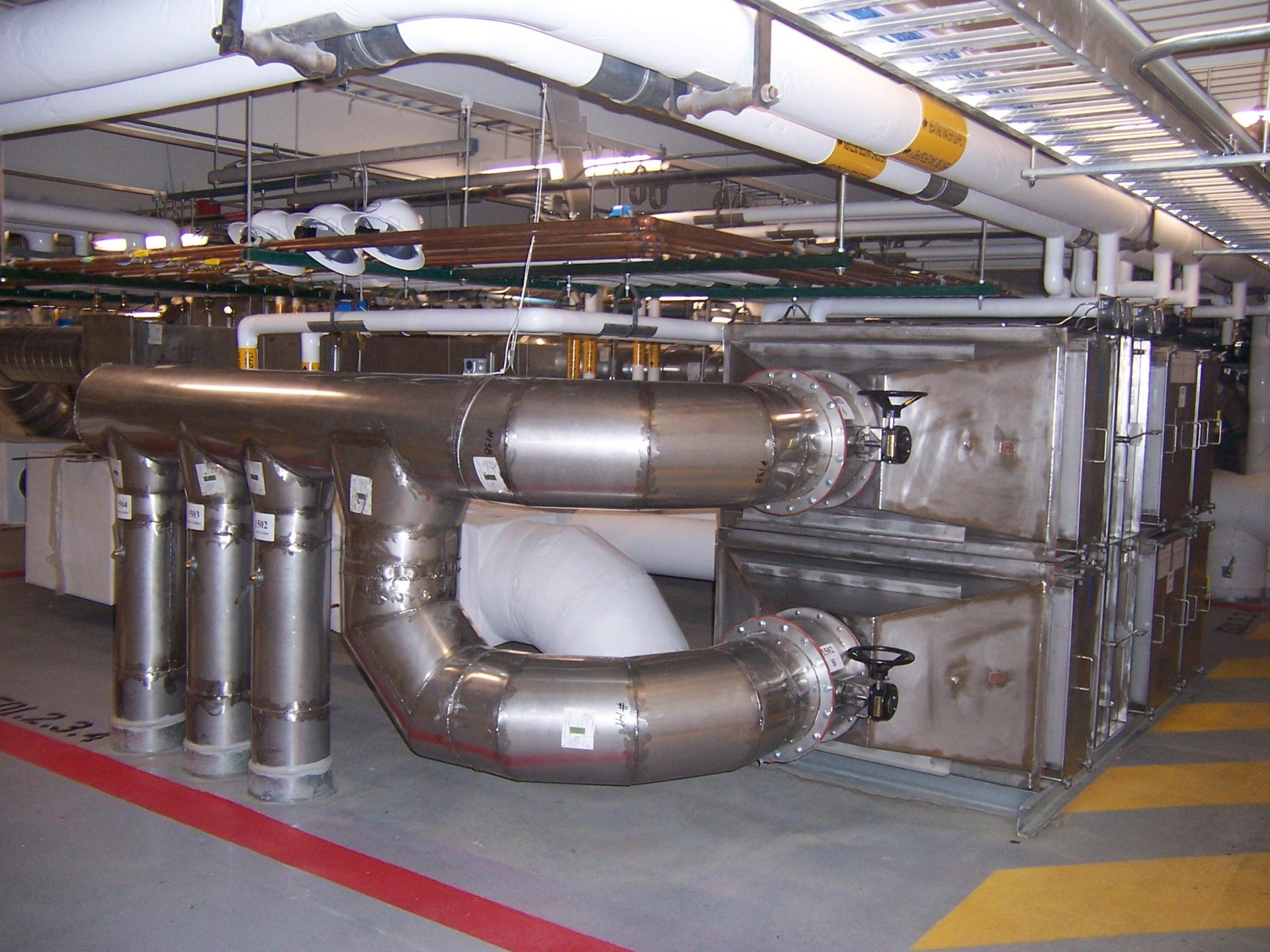
Differential Pressure measured/monitored in real time

Dampers

- Bubble Tight Isolation Dampers



- Bubble tight at maximum operating pressure
- No bubbles seen on down stream side



Equipment Decontamination

- 2 walk-in autoclaves
- VHP Decon

Animal Holding Rooms

Aerosol Exposure Room

- Class III Biological Safety Cabinet
- Aerosol delivery of pathogen to animals
- Mimics natural exposure
- Uses a HEPA-filtered cart to safely transport animals too and from animal housing rooms

BSL3 Personal Protective Equipment

- HEPA PAPR
- Scrubs
- Facility shoes
- Back-closing lab coat
  - Disposable
- Facility Shoes
- TYVEC Sleeves
- Double Gloves

Biosecurity

Site Security

- HTRL monitored continuously (24/7)
  - CCTV (60+), exterior and interior
  - Only locker rooms and individual offices are not monitored
- Perimeter access control
  - Proximity card and biometric
  - Individual PIN codes for all authorized personnel

Biometric Access Control

Biosecurity

- Stocks stored in locked freezers.
- Inventories reconciled on monthly basis
  - Stocks in long-term storage
  - Working cultures (records updated daily)
  - Animals (records updated continuously)
- Electronic access records reconciled against written sign in records.

Insider Threat

- Insider threat is most common but underrated
- Primary threat on most organizations' list of threats

Biosurety

- Background checks
- Credential checks
- FBI/DOJ Clearance
- *Two person rule*
- Annual Performance Evaluations
- Annual interviews
- Annual *Code of Conduct* attestation

Code of Conduct

Individual Code of Conduct for the University of Chicago
Select Agent Program and the Howard Taylor Ricketts Laboratory

For the individual scientist, an ethical code of conduct centers on personal integrity. It embodies, above all, a commitment to intellectual honesty and personal responsibility for one's actions, and to a range of practices that characterize the responsible conduct of research, including:

- Intellectual honesty in proposing, performing, and reporting research;
- Accuracy in representing contributions to research proposals and reports;
- Fairness in peer review;
- Collegiality in scientific interactions, including communications and sharing of resources;
- Transparency in conflicts of interest or potential conflicts of interest;
- Protection of human subjects in the conduct of research;
- Humane care of animals in the conduct of research; and
- Adherence to the mutual responsibilities between investigators and their research teams.

In the realm of research involving the study of Select Agent pathogens and toxins, additional responsibilities include:

- Awareness of and adherence to all safety protocols associated with research conducted at the H.T. Ricketts Laboratory. In addition to standard operating procedures for work in BSL2 and BSL3 labs and in the ABSL3 vivarium, this includes the following:
  - Knowledge and awareness of Select Agent and agent profiles for non-Select Agent organisms as described in the HTRL Agent Profile Summaries.
  - Knowledge and awareness of Health Watch Protocols as described in the HTRL Biosafety Plan.
  - Knowledge and awareness of spill and exposure protocols as described in the HTRL Biosafety Plan.
  - Knowledge of and adherence to reporting requirements related to spills, exposures, potential releases from containment and near misses related to of Select Agents or related to spills, exposures or near misses involving non-Select Agent organisms in a BSL2 or BSL3 lab.
  - Knowledge and awareness of all emergency response protocols (e.g., fire, tornado, inclement weather) as described in the HTRL Emergency Response Plan.
- Completion of all training requirements associated with the Select Agent Program, whether required annually (or periodically) or on a one-time basis.
- Completion of all proficiency training requirements as outlined in the "Escorted Access" Program of the HTRL.
- Completion of all Occupational Health requirements, including documentation of required physicals, medical clearances, and/or vaccinations.
- Immediate reporting to the Principal Investigator and Responsible Official of any situation that compromises an individual's ability to perform as required in a BSL3 or ABSL3 laboratory, including physical or psychological issues.
- Immediate reporting to the Principal Investigator and Responsible Official of behavior or activities that are inconsistent with HTRL Safety and Security Plans.
- Awareness of and adherence to security protocols necessary to protect and secure the Select Agents with which an individual works. Included in this responsibility to maintain security are the following:
  - Awareness of, and adherence to, all security protocols required by the Protective Force of Argonne National Laboratories. These procedures are found in the HTRL Security Plan.
  - Participation in all required training programs and drill exercises conducted at the H.T. Ricketts as instructed by the Responsible Official or Alternate Responsible Official.
  - Protection of all access mechanisms, including identification/access cards, personal identification codes or numbers, and/or keys.
  - Immediately reporting to the Responsible Official/Alternate Responsible Official of lost keys, identification cards, and/or compromised access codes.
  - Immediate reporting to the Responsible Official/Alternate Responsible Official of Select Agent loss or release, theft, or any evidence of inventory tampering or suspicious activity.
  - Protection of potentially sensitive information and awareness of reporting and publication requirements associated with research with dual use potential.

I acknowledge that I have read, understood and will honor my responsibilities under this Code of Conduct. I acknowledge that I have been provided the informational documents referred to above and have reviewed these documents.

NAME: _____
SIGNATURE: _____
DATE: _____

Occupational Medicine: Health Watch

SELECT AGENT EXPOSURES and Rule-Out LABORATORY-ACQURIED INFECTIONS

The purpose of this protocol is to provide instructions to UC investigators (p. 1), PIs (and/or supervisors), Biosafety personnel (p.2), and clinicians (pp. 3-4) in the event of possible exposures to biological agents at the HTRL.

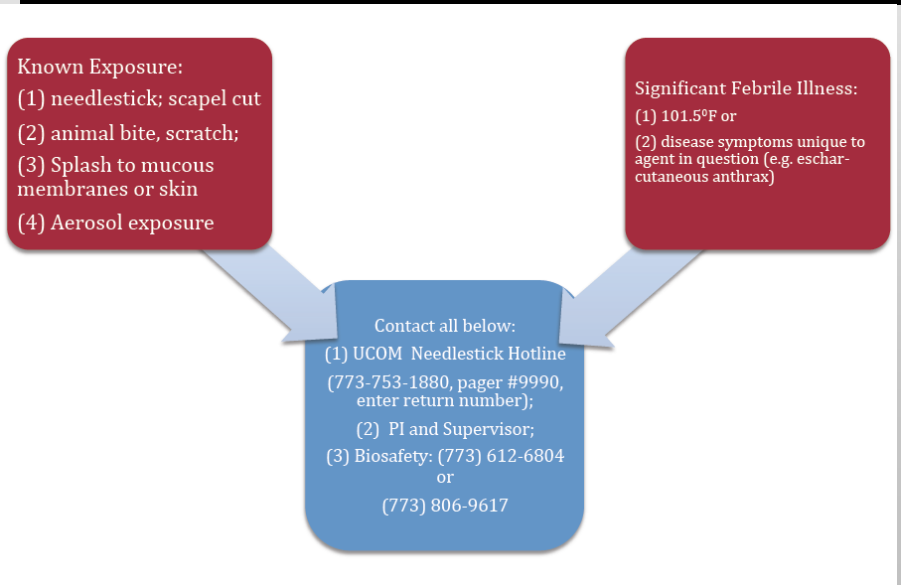
For Investigators

If **you** experience either of the following:

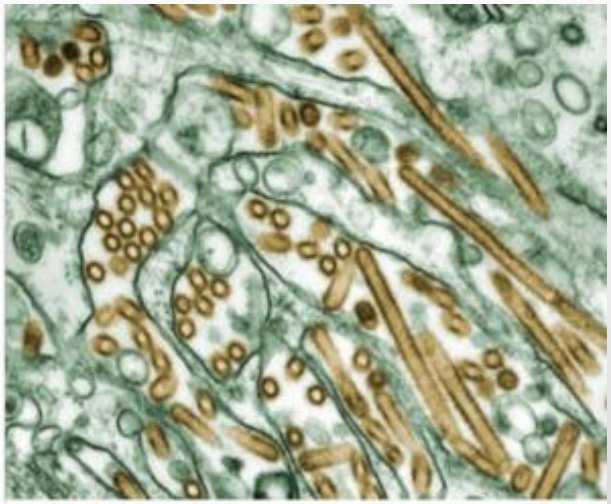
1. An overt or potential exposure to a select agent, or
2. A significant febrile illness (usually a temperature of 101.5° F) and have been working in an area with select agents,

You should…

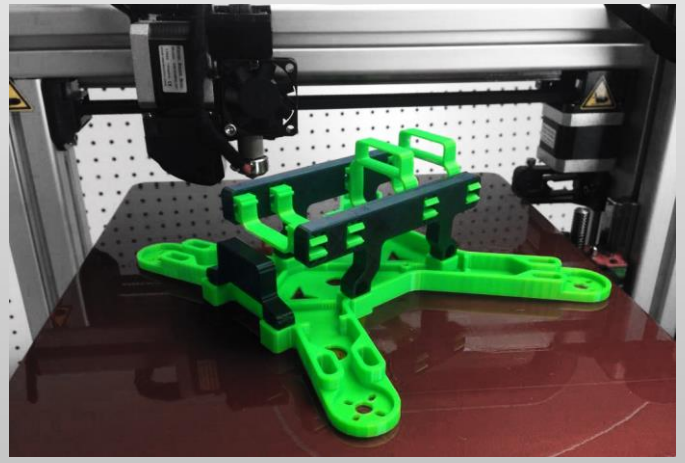
1. Contact your PI and/or immediate supervisor.
2. Contact Biosafety at: 1-773-612-6804 (Joe) or 1-773-806-9617 (John).
3. **Contact University of Chicago Occupational Medicine (UCOM) Needle-Stick Hotline at: 1-773-753-1880, enter pager number: 9990#, enter return number.**
4. Report exposure/symptoms to Hotline attending physician.
5. Report either to UCOM or the UC Emergency Division (UCED) depending upon instruction from Hotline attending physician.
6. When reporting to UCOM, UCED or any health care setting, **you should acknowledge your work involving Select Agent research**. NOTE: It is important that you call in advance of presenting to the health care area. It is inappropriate for a lab worker to show up without advanced warning, and the PI is responsible to make sure this doesn't happen.



Dual-Use Research



H5N1 influenza virus



An era of heightened concern

1990's

- Decade of concern about bioterrorism

2001

- 9/11
- 9/18
- Australian group engineers hyper-virulent mousepox (*J.Virology*)

2002

- *de novo* chemical reconstruction of poliovirus (*Science*).
- PNAS report on increasing vaccinia virulence

2004

- US NAS NRC publishes the Fink Report
- NSABB Established (first meeting in 2005)

2005

- CDC reconstructs 1918 H1N1 Influenza (*Science*).

2011

- Two manuscripts describing mammalian transmission of HPAI submitted for publication (*Science, Nature*).

Dual-Use Research of Concern (DURC): NSABB Definition

"Life sciences research that, based on current understanding, can be reasonably anticipated to provide **knowledge, information, products, or technologies** that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security."

Experiments of Concern:

1. Enhance the harmful consequences of a biological agent or toxin
2. Disrupt immunity or the effectiveness of an immunization without clinical and/or agricultural justification
3. Confer to a biological agent or toxin, resistance to clinically and/or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin, or facilitate their ability to evade detection methodologies
4. Increase the stability , transmissibility, or the ability to disseminate a biological agent or toxin
5. Alter the host range or tropism of a biological agent or toxin
6. Enhance the susceptibility of a host population
7. Generate a novel pathogenic agent or toxin, or reconstitute an eradicated or extinct biological agent

U.S. DURC Policies

The U.S. Government has issued two complementary policies for the oversight of life sciences DURC

1. **USG Policy for Oversight of Life Sciences DURC (2012)**
   - Describes the role of the Federal funding agencies in identifying DURC and implementing risk mitigation strategies as necessary
2. **USG Policy for Institutional Oversight of Life Sciences DURC (2015)**
   - Focuses on the responsibilities of research institutions in identifying DURC and mitigating risks at the institutional level

The Gain-of-Function (GOF) Issue

Gain-of-function is a term used to refer to any modification of a biological agent that confers new or enhanced activity.

Debate has centered around **a specific subset of GOF studies** that involve the **generation of pathogens with pandemic potential**

- Studies that generate certain pathogens with enhanced pathogenicity or transmissibility (by respiratory droplets) in mammals
- The GOF studies that have raised concerns are often cited as an example of DURC
- Ongoing debate about risks and benefits

GOF Studies: Benefits and Risks

Potential Benefits of GOF Studies

- Help define the fundamental nature of human-pathogen interactions
- Enable assessment of the pandemic potential of emerging infectious agents
- Inform public health and preparedness efforts
- Further medical countermeasure development

Potential Risks of GOF Studies

- Involve generating novel engineered pathogens that could pose a pandemic threat if they were to be accidentally or intentionally released
- May generate information that could be misused to threaten public health or national security
- Risks would increase as more labs perform this type of research

GOF Studies Raise Biosafety and Biosecurity Concerns

- **Dual use/biosecurity issues:** Do the studies generate information that could be utilized to create a potentially human-transmissible virus that, in the wrong hands, could be intentionally released to threaten public health and security?
- **Biosafety issues:** Could the engineered pathogens accidentally infect a lab worker or be released into the environment?

Should such research findings be communicated? If so, how can they be responsibly communicated?

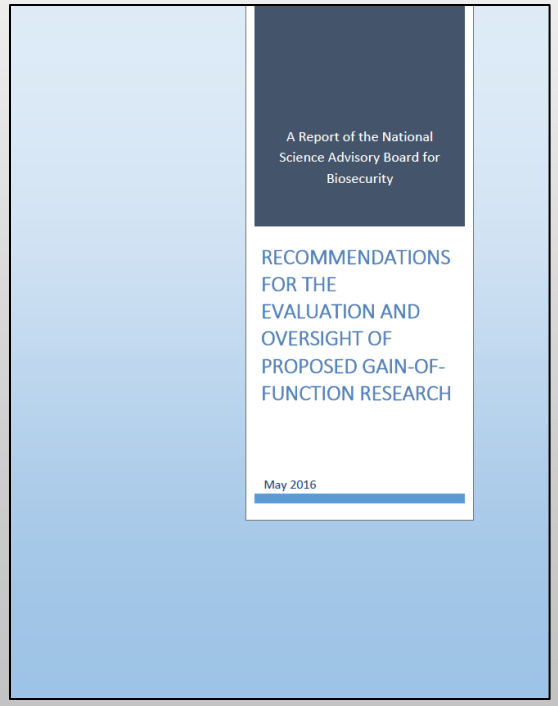
Under what conditions can these studies be safely conducted?

Should this type of research be conducted at all?

NSABB Report on GOF Research

Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research **(May 2016)**

- Guiding principles for NSABB deliberations
- NSABB's framework for conducting RBA
- Analysis and interpretation of the RBA
- Consideration of ethical values and decision-making frameworks
- Analysis of the current policy landscape and potential policy options
- Findings and Recommendations



NSABB Report on GOF Research

*There are many types of GOF studies and not all of them have the same level of risks. Only a small subset of GOF research—**GOF research of concern (GOFROC)**—entail risks that are potentially significant enough to warrant additional oversight.*

*Research proposals involving GOF research of concern entail significant potential risks and **should receive an additional, multidisciplinary review, prior to determining whether they are acceptable for funding.** If funded, such projects should be subject to ongoing oversight at the federal and institutional levels.*

NSABB report, Finding 1 and Recommendation 1

Additional Pre-funding Review: Identifying GOFROC

To be considered GOFROC, the research must, in a single step or over the course of multiple manipulations, be reasonably anticipated to generate a pathogen with both of the following attributes:

1. **The pathogen generated is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations.**
2. **The pathogen generated is likely highly virulent and likely to cause significant morbidity and/or mortality in humans.**

For more description and examples see NSABB report p. 41-42 and Appendix C

Additional Pre-funding Review: Guiding Funding Decisions

Only GOFROC projects that are in line with all of the 8 principles listed should be considered acceptable for funding.

1. The research proposal has been evaluated by a peer-review process and determined to be **scientifically meritorious**, with high impact on the research field(s) involved.
2. The pathogen that is anticipated to be generated must be judged, based on scientific evidence, to be **able to arise by natural processes**.
3. An assessment of the overall potential risks and benefits associated with the project determines that the **potential risks as compared to the potential benefits to society are justified**.
4. There are **no feasible, equally efficacious alternative methods** to address the same scientific question in a manner that poses less risk than does the proposed approach.

Additional Pre-funding Review: Guiding Funding Decisions

Only GOFROC projects that are in line with all of the 8 principles listed should be considered acceptable for funding.

5. The investigator and institution proposing the research have the **demonstrated capacity and commitment to conduct it safely and securely**, and have the ability to respond rapidly and adequately to laboratory accidents and security breaches.

6. The **results of the research are anticipated to be broadly shared** in compliance with applicable laws and regulations in order to realize their potential benefits to global health.

7. The research will be supported through funding mechanisms that allow for appropriate **management of risks and ongoing federal and institutional oversight** of all aspects of the research throughout the course of the project.

8. The proposed research is **ethically justifiable**.

Ongoing Oversight: Potential Risk Mitigation Measures

- Enhance biosafety practices or features, as warranted given the specific strains and proposed manipulations
- Enhance security measures around strains, reagents, notebooks, and personnel
- Prohibit certain additional GOFROC experiments without prior approval
- **Treat the research as if subject to the USG DURC policies, if it is not already**
- Identify certain experimental outcomes that would trigger a re-evaluation of the risks and benefits prior to proceeding with a study
- Communicate regularly and coordinate with federal, state, and local public health and safety officials on accident and theft response

Other NSABB Recommendations

- Undertake broad efforts to **strengthen laboratory biosafety and biosecurity** and **seek to raise awareness** about the specific issues associated with GOF research of concern

- **Engage the international community** in dialogue about the oversight and responsible conduct of GOF research of concern

Contribution of DURC to Biosafety/Biosecurity

- State-sponsored* risk (biosecurity-risk based upon information)
- Terrorist/Rogue scientist risk (biosecurity-risk in the form of a pathogen)
- Accidental release risk (biosafety-risk)

Solutions to DURC challenges

It is important to be mindful of the threat we are trying to mitigate (biosafety vs. biosecurity) as the solutions to each are different

Efforts to promote biosafety and biosecurity

- Training and education programs
  - Scientists
  - Facility engineers
- Funding for infrastructure maintenance (especially important in developing countries)
- Raising awareness of DURC among scientists
- Raising public awareness
- Mechanisms for reporting and sharing of best practices

Additional measures :

Establishment of ethical and responsible codes of conduct of life sciences research, including awareness of DURC potential and consideration of alternative, less risky experimental approaches.

- Whenever possible, *gain-of-function* research involving pathogens with pandemic potential should include explicit and documented consideration of alternative approaches and/or the use of surrogate or attenuated pathogen strains.

- Also, it is critical that all research staff involved with these studies are committed to the ethical and responsible conduct of science.

Additional measures:

- **Strengthen biosafety practices and capabilities internationally.**
- **Establish reporting mechanisms, including anonymous reporting pathways, to better catalog and document personnel exposures and/or releases from containment.**
- **When reported, investigations should evolve a root cause analysis and lessons learned that should be shared not only locally, but also across the research enterprise.**

Additional measures:

- Education and outreach to the public at large, particularly to our youth, about the importance of life sciences research to public health and well-being.
- Communication to the public, political leaders, and funding agencies about the rigor being applied to address DURC-related biosafety and biosecurity concerns.

Acknowledgements

- Emmett Barkley, Ph.D.
- Robert Hawley, Ph.D., R.B.P., C.B.S.P.
- Karen Beyers, M.S., R.B.P., C.B.S.P.
- Scott Handley, Ph.D.

Thank you!

THE UNIVERSITY OF CHICAGO | Office of Research Safety