National Institute of Allergy and Infectious Diseases

CABS ACSB

High-throughput drug discovery screening facility in a high containment BSL-3 laboratory in NIH

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Laboratory of Clinical Immunology and Microbiology,

NIAID, NIH

September 18, 2019

Objectives

1. Implementation of the NIH Biosafety Program

2. High-throughput drug discovery screening facility in the Building of Biodefense (Bldg. 33)

3. Drug discovery efforts in Tuberculosis Research Section, NIH

   - *Mycobacterium tuberculosis*
   - *Middle east respiratory syndrome coronavirus* (MERS-CoV)
   - *Candida auris* (multi-drug resistant strains)

Background of a 'Surety' Program

BIOSECURITY AND BIOTERRORISM: BIODEFENSE STRATEGY, PRACTICE, AND SCIENCE
Volume 2, Number 1, 2004

Implementation of Biosurety Systems in a Department of Defense Medical Research Laboratory

KATHLEEN CARR, ERIK A. HENCHAL, CATHERINE WILHELMSEN, and BRIDGET CARR

ABSTRACT

New biosurety regulations and guidelines were implemented in 2003 because of increased concern for the safety and security of biological select agents and toxins (BSAT) that may be used as weapons of mass destruction. *Biosurety* is defined as the combination of security, biosafety, agent accountability, and personnel reliability needed to prevent unauthorized access to select agents of bioterrorism. These new regulations will lead to increased scrutiny of the use of select biological agents in registered research laboratories, but the regulations may have unintended effects on cost, progress, and perceptions in programs previously considered part of the academic research community. We review the history of biosurety, evolving guidelines, implementation of the regulations, and impacts at the lead research laboratory for medical biological defense for the Department of Defense.

ELSEVIER SAUNDERS

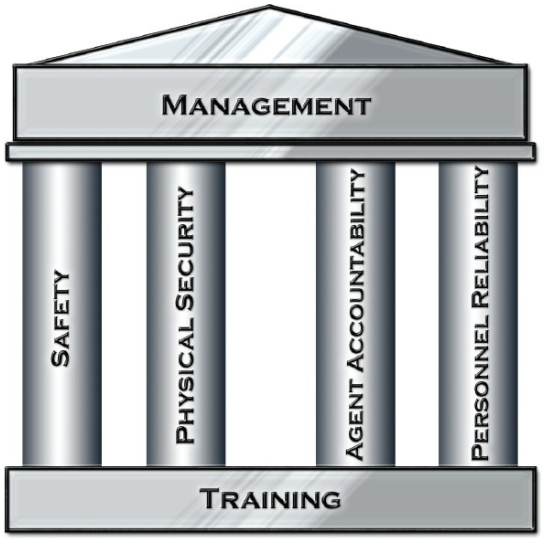
CLINICS IN LABORATORY MEDICINE

Clin Lab Med 26 (2006) 299–312

Clinical Laboratories, the Select Agent Program, and Biological Surety (Biosurety)

Ross H. Pastel, PhD*, Gretchen Demmin, PhD, Grant Severson, MS, Rafael Torres-Cruz, MS, Jorge Trevino, MS, John Kelly, Jay Arrison, Joy Christman

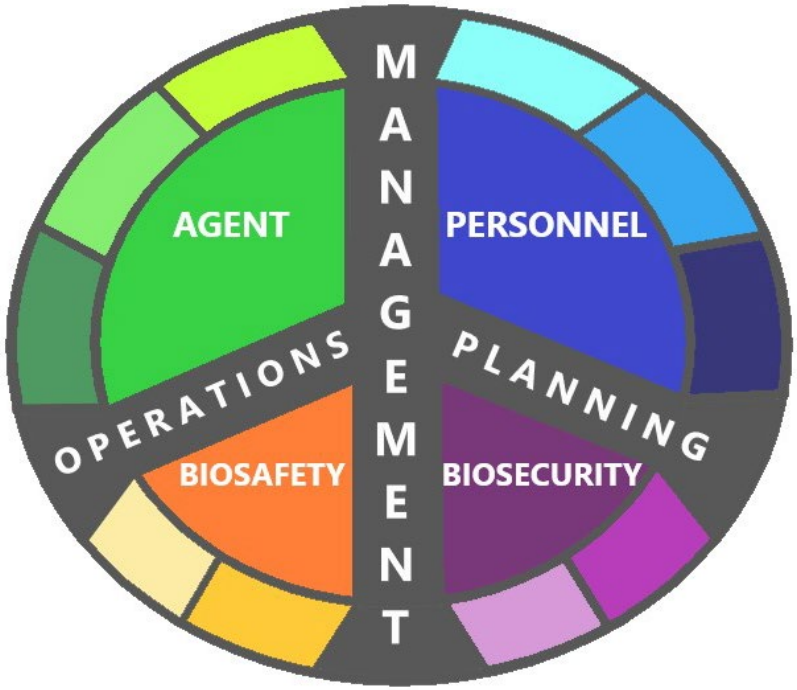
United States Army Medical Research Institute of Infectious Diseases (USAMRIID), 1425 Porter Street, Fort Detrick, MD 21702, USA



- **Biosafety:** methods and systems to minimize risk of infection to self and others via unintentional laboratory exposure.
- **Biosecurity:** physical systems, people and procedures to prevent theft, destruction, or tampering of microbiological pathogens by external influences.
- **Agent Accountability:** combination of inventories, shipping and transfer records, location records, destruction certificates, and other required documents.
- **Personnel Reliability:** systems and procedures to ensure that persons with access to BSAT meet high standards of reliability.

FIGURE 2-1 USAMRIID's Biosurety Program. The program includes systems and procedures to properly safeguard BSAT against theft, loss, diversion, or unauthorized access or use, and to ensure that operations are conducted in a safe, secure, and reliable manner. Source: Skvorak 2009.

Implementation of the Biosafety Program : Step 1



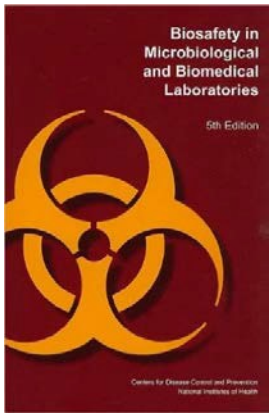
Pathogen registrations

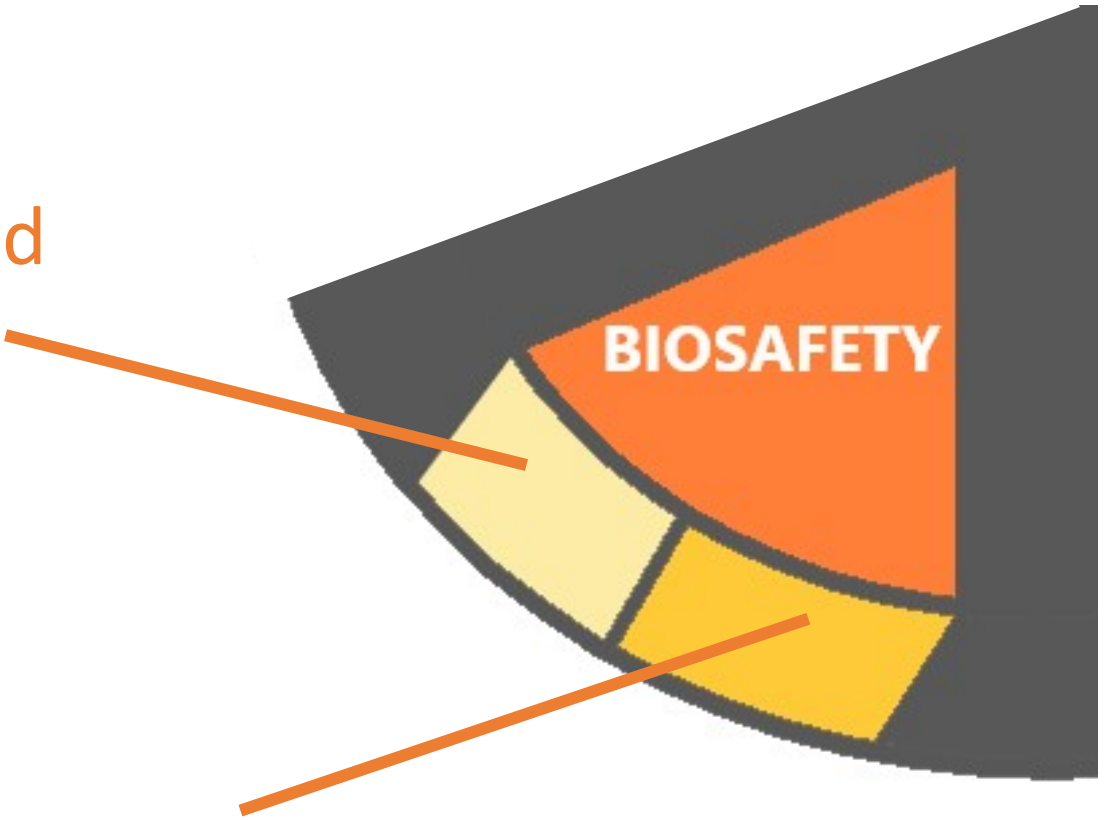
- Risk assessment
- BSL and PPE determination
- IBC approval
- E-sign off by researchers
- Web interface that manages:
  - Protocols
  - Researchers
  - Lab surveys

Implementation of the Biosafety Program

Risk assessment and
risk management

RISK
GROUP
DATABASE
ABSA INTERNATIONAL



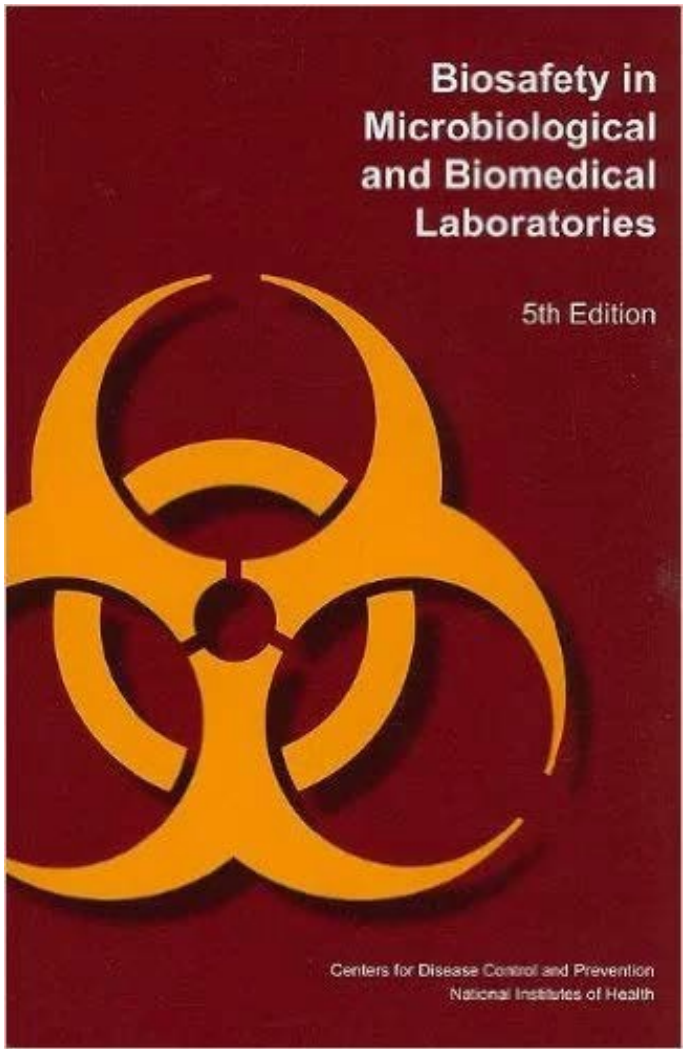


- Follow safe work practices (BMBL)
- Draft lab specific biosafety manuals
- Write lab specific SOPs

The Gold Standard for Biosafety in USA

1984

2007



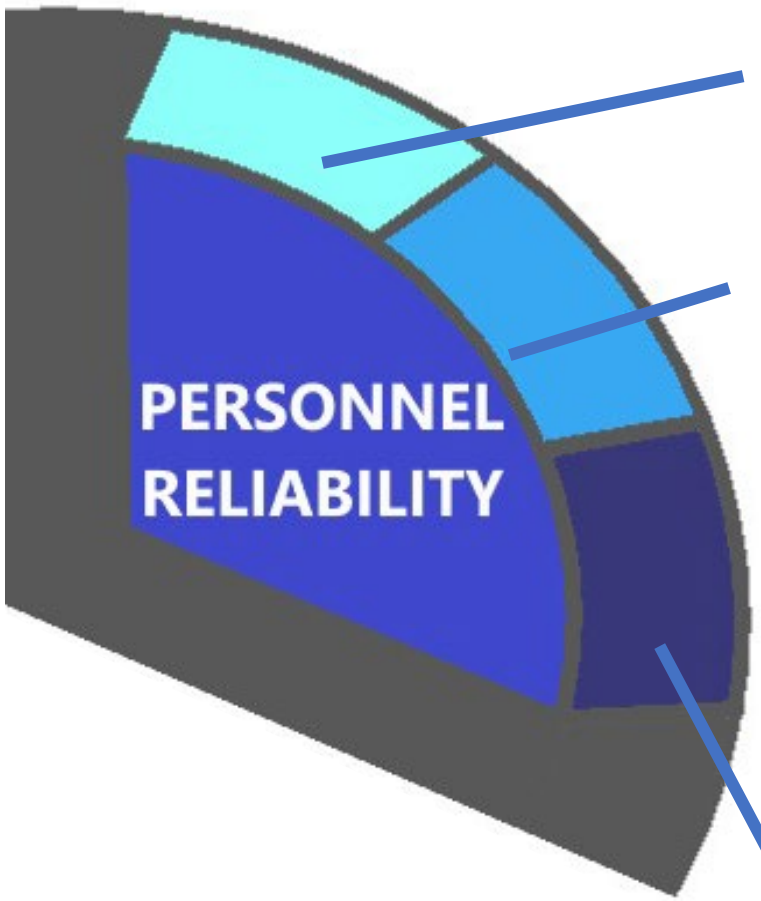
U.S. Department of Health and Human Services
Public Health Service
Centers for Disease Control and Prevention
National Institutes of Health

Both a code of practice and an authoritative reference "guidance document"

Table 2. Summary of Recommended Biosafety Levels for Infectious Agents

BSL	Agents	Practices	Primary Barriers and Safety Equipment	Facilities (Secondary Barriers)
1	Not known to consistently cause diseases in healthy adults	Standard microbiological practices	▪ No primary barriers required. ▪ PPE: laboratory coats and gloves; eye, face protection, as needed	Laboratory bench and sink required
2	▪ Agents associated with human disease ▪ Routes of transmission include percutaneous injury, ingestion, mucous membrane exposure	BSL-1 practice plus: ▪ Limited access ▪ Biohazard warning signs ▪ "Sharps" precautions ▪ Biosafety manual defining any needed waste decontamination or medical surveillance policies	Primary barriers: ▪ BSCs or other physical containment devices used for all manipulations of agents that cause splashes or aerosols of infectious materials ▪ PPE: Laboratory coats, gloves, face and eye protection, as needed	BSL-1 plus: ▪ Autoclave available
3	Indigenous or exotic agents that may cause serious or potentially lethal disease through the inhalation route of exposure	BSL-2 practice plus: ▪ Controlled access ▪ Decontamination of all waste ▪ Decontamination of laboratory clothing before laundering	Primary barriers: ▪ BSCs or other physical containment devices used for all open manipulations of agents ▪ PPE: Protective laboratory clothing, gloves, face, eye and respiratory protection, as needed	BSL-2 plus: ▪ Physical separation from access corridors ▪ Self-closing, double-door access ▪ Exhausted air not recirculated ▪ Negative airflow into laboratory ▪ Entry through airlock or anteroom ▪ Hand washing sink near laboratory exit
4	▪ Dangerous/exotic agents which post high individual risk of aerosol-transmitted laboratory infections that are frequently fatal, for which there are no vaccines or treatments ▪ Agents with a close or identical antigenic relationship to an agent requiring BSL-4 until data are available to redesignate the level ▪ Related agents with unknown risk of transmission	BSL-3 practices plus: ▪ Clothing change before entering ▪ Shower on exit ▪ All material decontaminated on exit from facility	Primary barriers: ▪ All procedures conducted in Class III BSCs or Class I or II BSCs in combination with full-body, air-supplied, positive pressure suit	BSL-3 plus: ▪ Separate building or isolated zone ▪ Dedicated supply and exhaust, vacuum, and decontamination systems ▪ Other requirements outlined in the text

Implementation of the Biosafety Program



Background investigations

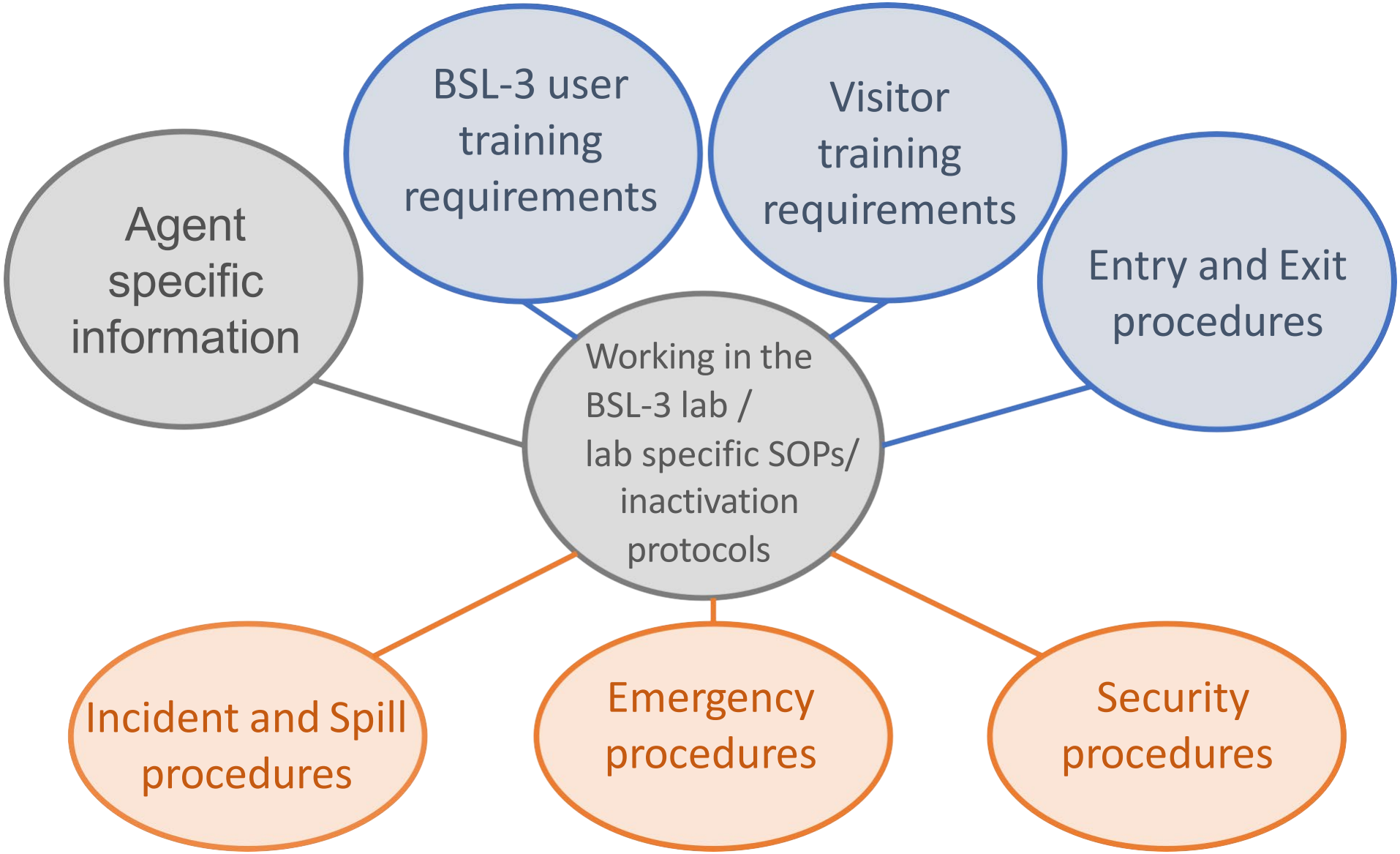
Safety trainings

- Lab biosafety / Bloodborne pathogens
- Agent Specific Training
- Incident and spill procedures
- BSL-3 hands-on training

Evaluations

- Occupational Health
- Behavioral Health

Agent Specific Training: Objectives



Personal protection equipment (PPE)

Head			Head cover
Eye			Eye protection goggles
Respiratory system			N95 (Annual fit test) PAPR (Monthly validation)
Body			Coverall suit with integrated booties
Hand			Double gloves
Foot			Shoe covers

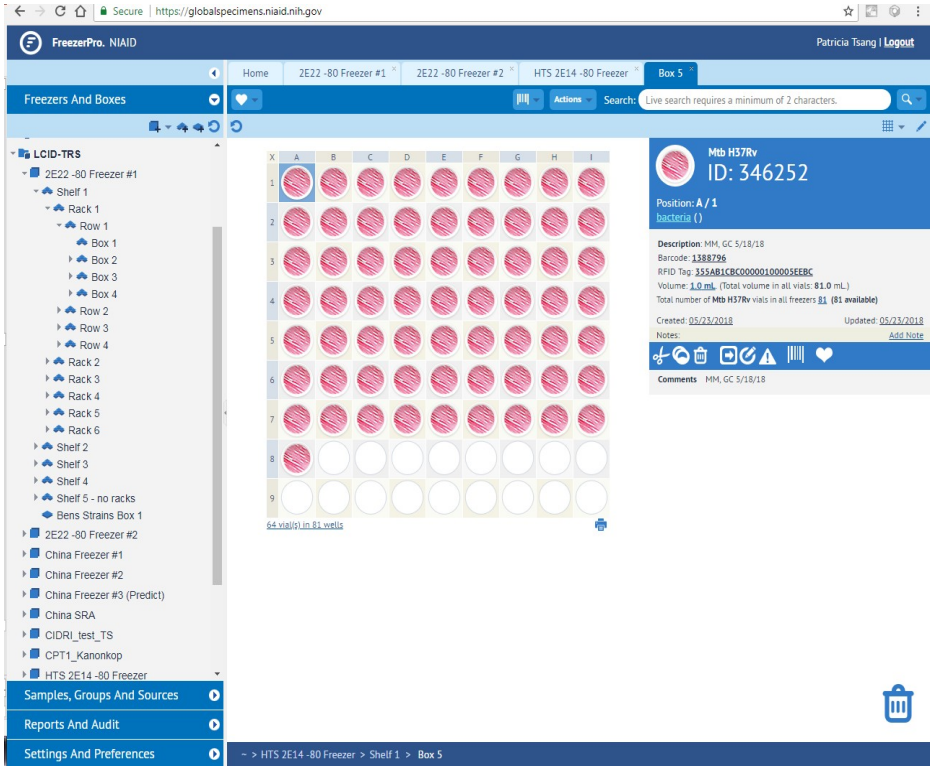
Implementation of the Biosafety Program : Agent accountability

Limited access

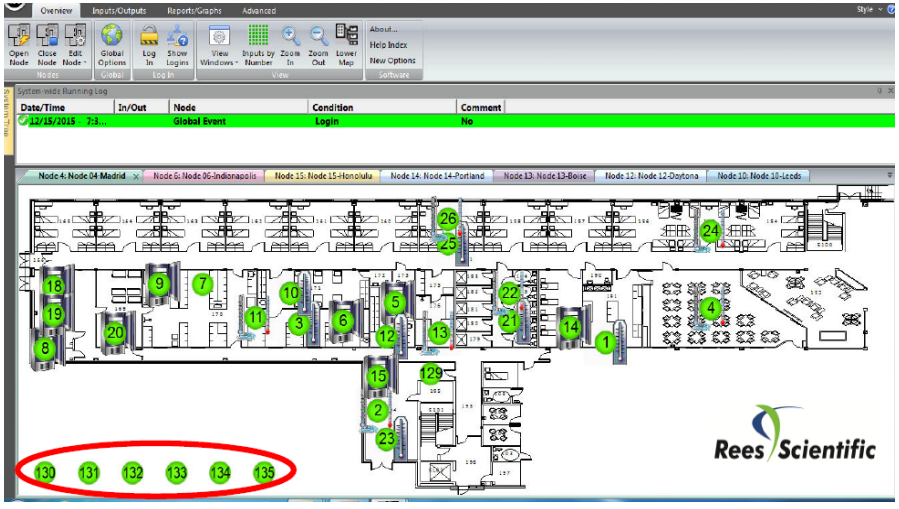
Inventory management

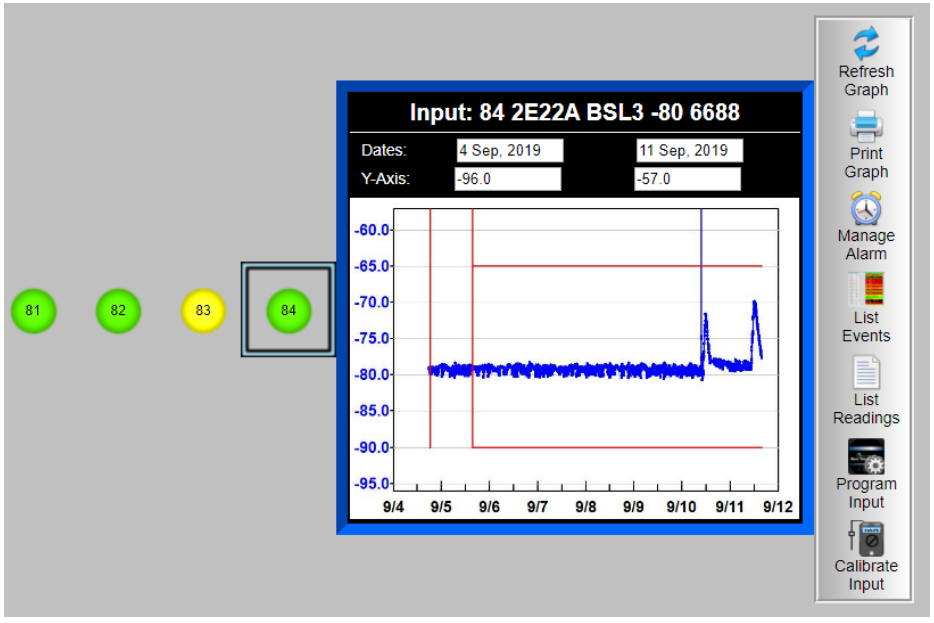
- Location records
- Traceable records
- Transfer records

Electronic inventory management system

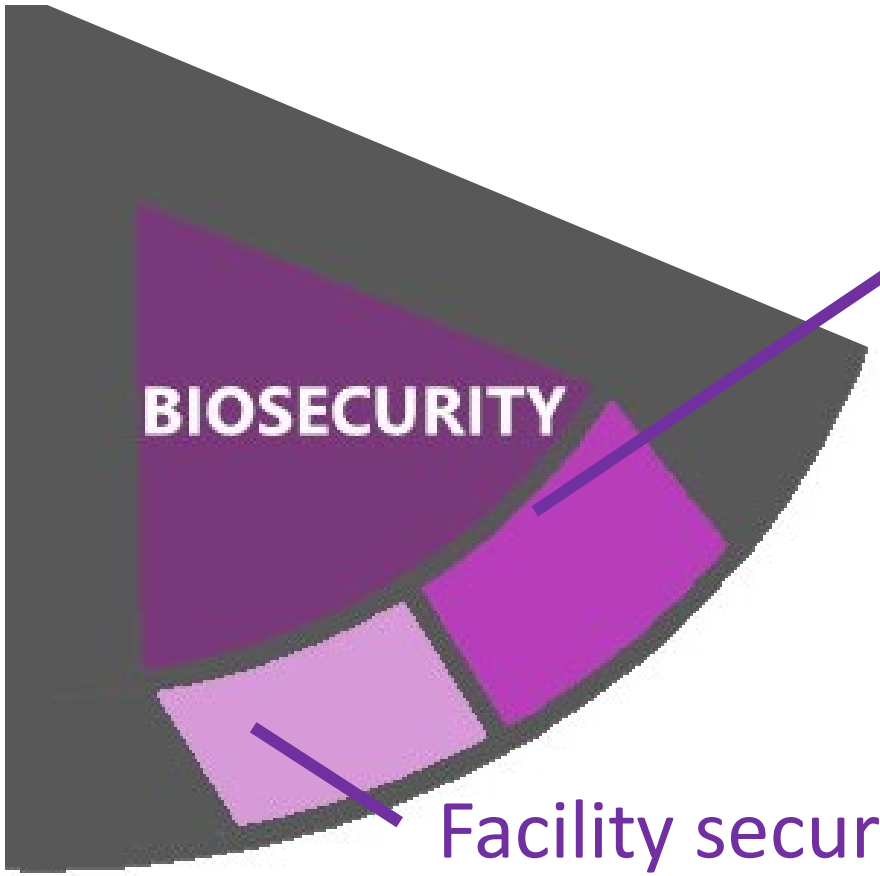


Real-time equipment monitoring system





Implementation of the Biosafety Program: Biosecurity



Facility access

- Authorized access
- Dual-authentication system

Facility security

- Internal monitoring
- External monitoring
- Lab inspections and spot checks

The C.W. Bill Young Center for Biodefense and Emerging Infectious Diseases (Bldg 33)

Biodefense Research Program Fast-Tracked

New Bldg. 33 Complex To Focus on Infectious Diseases

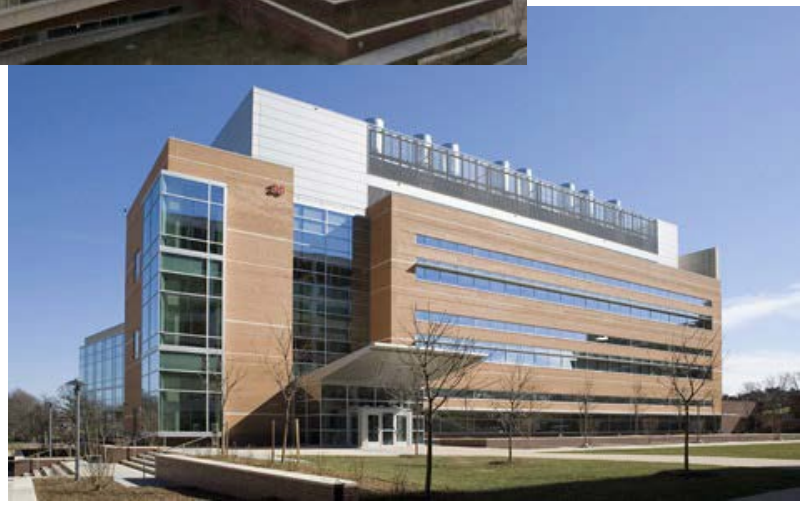
By Carla Garnett

If all goes as planned over the course of the next 2 years, by November 2005 the northeastern corner of NIH's Bethesda campus will be the site of a new 150,000 gross-square-foot lab facility, 1,230-space multilevel parking garage, underground storm water management system and a plaza/courtyard. Currently dubbed the Bldg. 33 Complex, the project will be completed in several stages with the first stage set in motion in late September.

An artist's rendering of how the new Bldg. 33 complex will look once complete in 2005.

The lab facility, Bldg. 33, will be occupied by scientists working at the National Institute of Allergy and Infectious Diseases, which

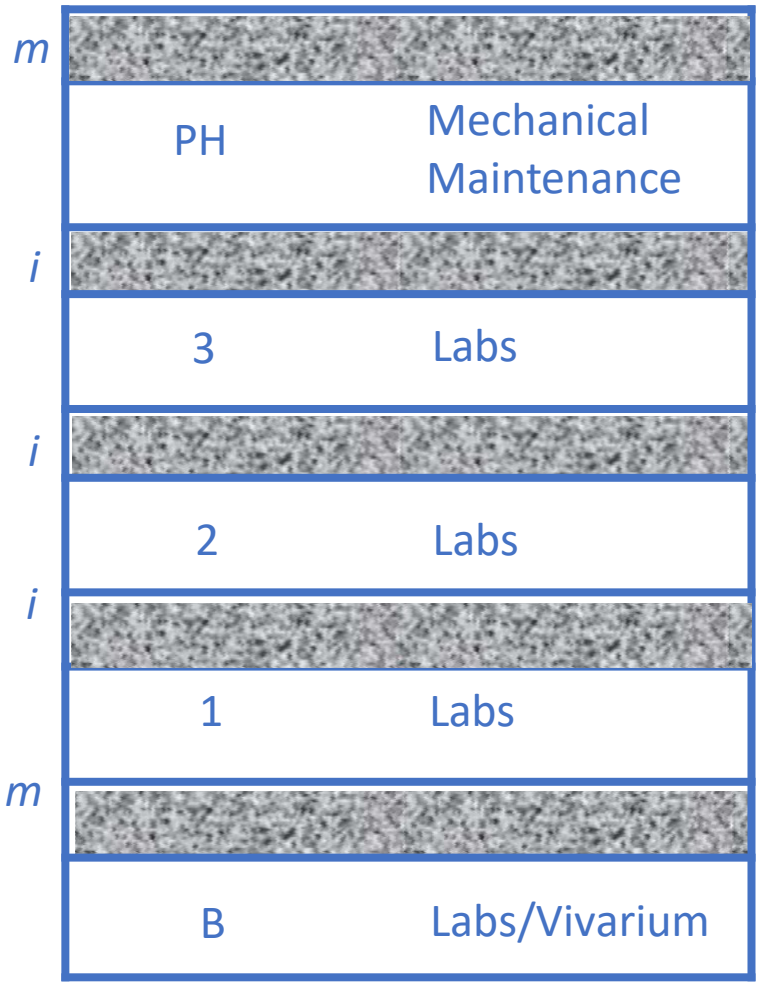
SEE **BLDG. 33 COMPLEX**, PAGE 8



http://www.whiting-turner.com/portfolio/industry/federal/9770/9770.html

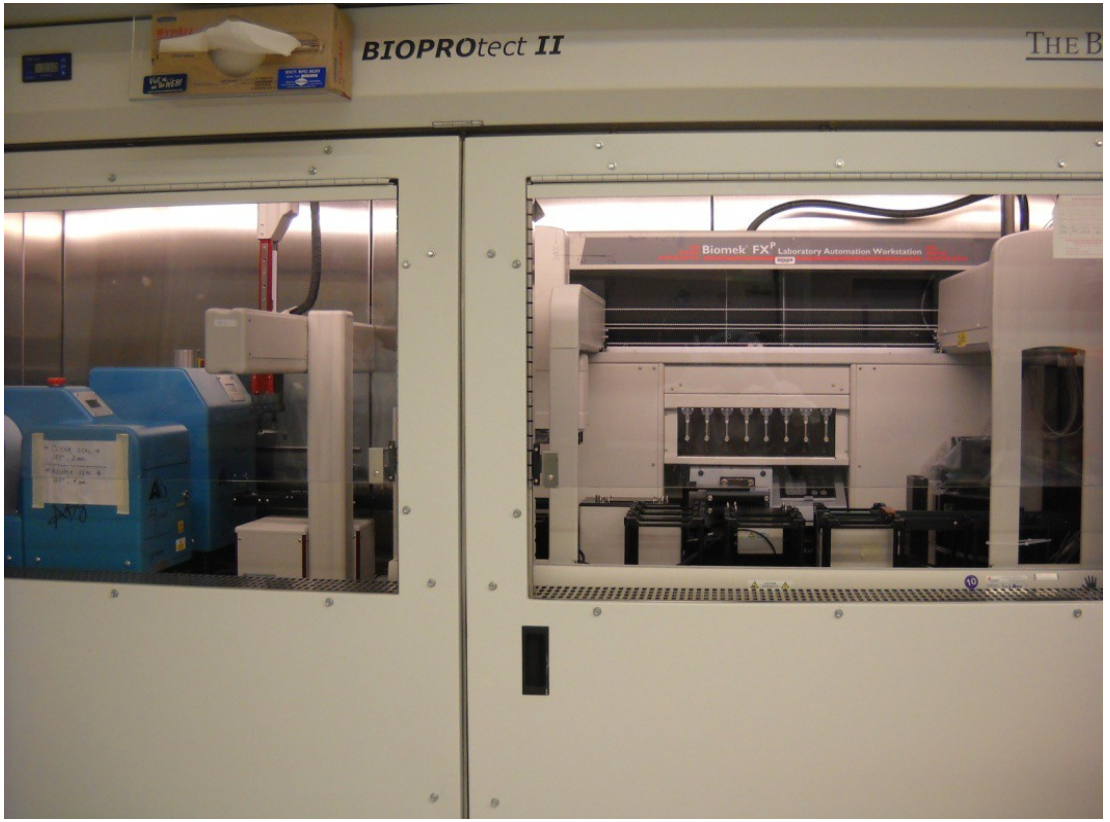
https://nihrecord.nih.gov/newsletters/10_14_2003/story01.htm

The C.W. Bill Young Center for Biodefense and Emerging Infectious Diseases (Bldg 33)



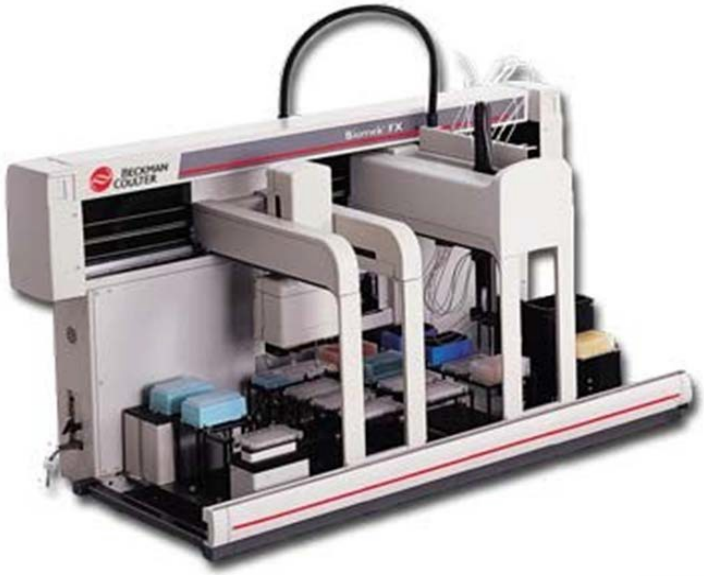
http://www.thebellcompany.com/projects/11/building-33-national-institues-of-health/

High-Throughput drug discovery screening facility



BioPROTECT walk-in and reach-in equipment containment safety enclosure (Class II, Type A2), 164-cubic foot

High-Throughput drug discovery screening facility



Biomek Fx liquid handler

Viaflo 96 liquid dispenser

EnVision microplate reader

High-Throughput drug discovery screening facility

Fully automated HTS system

High-throughput drug discovery efforts in TRS, NIH

- Whole-cell screening approach
  - Determination of compound activity against live cells
  - All physiologically available targets explored at once
  - A true hit always exhibits antibacterial activity
  - Quick and dirty
  - Target has to be identified

- Main pathogen of interest: *Mycobacterium tuberculosis*
- Other emerging pathogens that require BSL-2+/3 labs

Mycobacterium tuberculosis

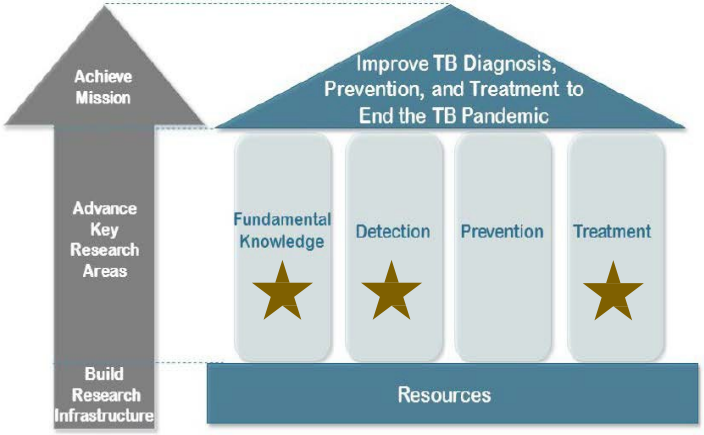


Figure 1. The NIAID Strategic Plan for TB Research proposes to build on an existing foundation of research and resources to advance five TB research priorities targeted at 1) improving fundamental knowledge, 2) advancing diagnosis, 3) preventing initial infection or progression to active disease, 4) improving treatment for all forms of TB in all populations and age groups, and 5) building resources to advance understanding and tool development in priorities 1 through 4.

Tuberculosis Research Section (TRS), NIH

Bacteria | Genus **Mycobacterium** | Species **tuberculosis**

NIH (2016): 3
BMBL (2009)*:
Australia/New Zealand (2010): 3 **notes:** c: Vaccination, sec Clause 2.6.4.; d: Respiratory protection should be considered.; e: Greater than 5000 cultures per year, susceptibility testing, known multi-drug resistant strains. See references in Clause 3.3.2.1.
Belgium (2008): 3
Canada (2015): 3
Canada PSDS: https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment/mycobacterium-tuberculosis-complex.html#footnote28
EU (2000): 3 **notes:** V
Germany (2013): 3 **notes:** AR
Japan: 3
Singapore: 3 **notes:**
Singapor Schedule: First Schedule Part I
Switzerland: 3 **notes:** (Including subsp. caprae and subsp. tuberculosis)
UK (2013): 3 **notes:** Vaccine available
Human Pathogen: y **Animal Pathogen:** y **Plant Pathogen:** n
Select Agent CDC: n **Select Agent USDA:** n

RISK GROUP DATABASE
ABSA INTERNATIONAL

Collaborative efforts in accelerating drug discovery for *Tuberculosis*

What is the TB Drug Accelerator?

The TBDA is a groundbreaking partnership between eight pharmaceutical companies, eight research institutions, and a product development partnership that seeks to develop a new TB drug regimen through collaboration in early-stage drug discovery research.

NIH National Institute of Allergy and Infectious Diseases

University of Cape Town • iYunivesithi yaseKapa • Universiteit van Kaapstad

Drug Discovery Unit

Weill Cornell Medical College • Cornell University

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

IDRI

Lilly

MERCK & CO., INC.
Kenilworth, N.J., U.S.A.

Calibr
California Institute for Biomedical Research

abbvie

gsk do more feel better live longer

SANOFI

BAYER

RUTGERS
BIOMEDICAL AND HEALTH SCIENCES

Eisai

ATM

AstraZeneca

With Participation From:

BILL & MELINDA GATES *foundation*

Middle east respiratory syndrome coronavirus (MERS-CoV)

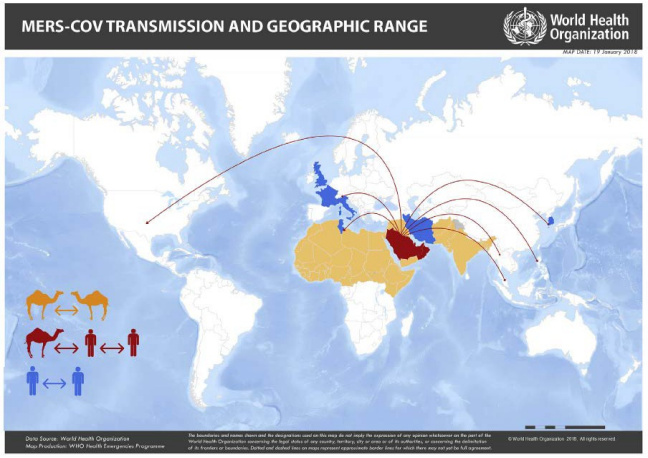
- Middle East respiratory syndrome (MERS) is a viral respiratory disease caused by a novel coronavirus (*Middle East respiratory syndrome coronavirus*, or MERS-CoV) that was first identified in Saudi Arabia in 2012
- Coronaviruses are a large family of viruses that can cause diseases ranging from the common cold to Severe Acute Respiratory Syndrome (SARS)
- Approximately 35% of reported patients with MERS have died

Virus

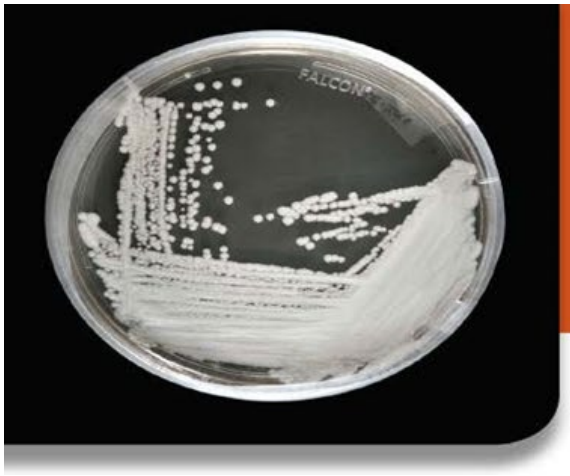
Viral Group	Name
Coronaviridae	**Middle eastern respiratory (MERS)**

NIH (2016): 3
BMBL (2009)*: 2(3). Interim guidelines can be found at http://www.cdc.gov/coronavirus/mers/guidelines-lab-biosafety.html
Australia/New Zealand (2010):
Belgium (2008):
Canada (2015): 3 **notes:** Middle East Respiratory Syndrome Coronavirus (MERS-CoV)
Canada PSDS: https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/biosafety-directives-advisories-nc
syndrome-coronavirus-mers.html
EU (2000):
Germany (2013):
Japan:
Singapore: **notes:** AVA Approval required, Corrosponding AVA Approved Code VVP0V3CORMERS
Singapor Schedule: First schedule part 2
Switzerland:
UK (2013):
Human Pathogen: y **Animal Pathogen:** n **Plant Pathogen:** n
Select Agent CDC: n **Select Agent USDA:** n

RISK GROUP DATABASE
ABSA INTERNATIONAL

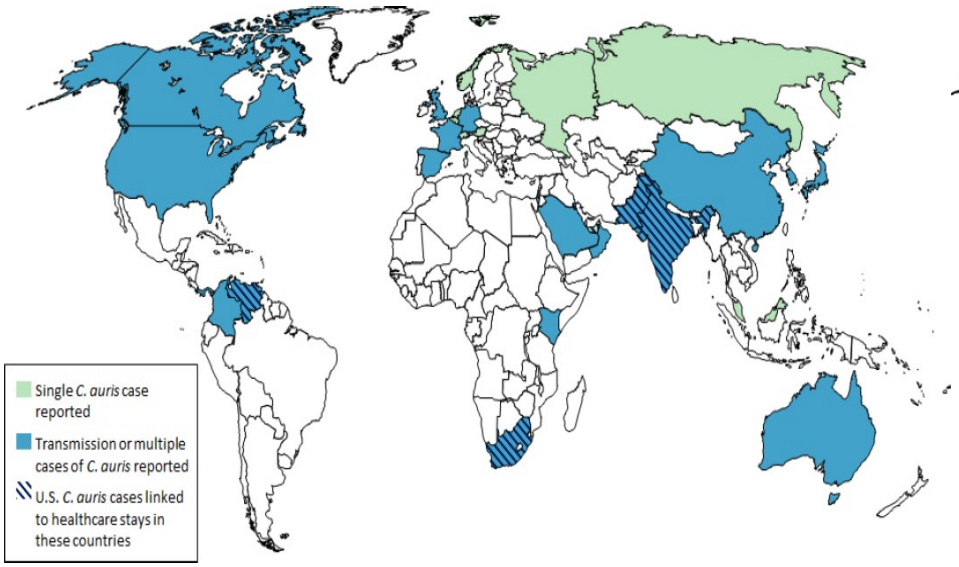


http://www.who.int/en/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov)

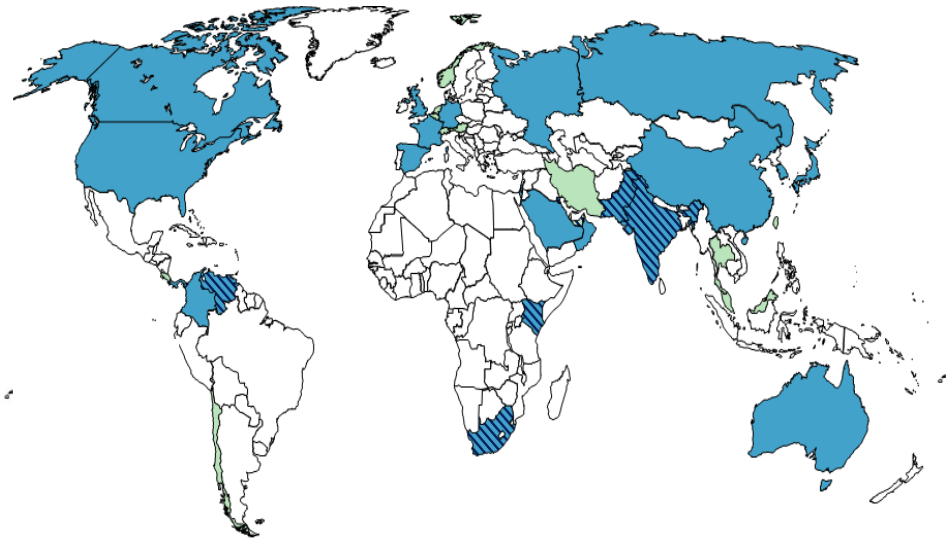


Candida auris:
A drug-resistant germ that spreads in healthcare facilities

Candida auris (also called *C. auris)* is a fungus that causes serious infections. Patients with *C. auris* infection, their family members and other close contacts, public health officials, laboratory staff, and healthcare workers can all help stop it from spreading.



Reported cases as of August, 2018



Reported cases as of July, 2019

https://www.cdc.gov/fungal/candida-auris/index.html

MENU CBCnews

Health

Doctors and scientists mystified by spread of Candida auris superbug

Climate change could be contributing to rise of a potentially deadly fungal pathogen

Amina Zafar - CBC News

Posted: July 25, 2019

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International Journal of Infectious Diseases

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Candida auris: An emerging multidrug-resistant pathogen

David Sears*, Brian S. Schwartz

Division of Infectious Diseases, University of California, San Francisco, USA

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Keywords:
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Multidrug-resistance
Healthcare-associated
Outbreak
Infection control

ABSTRACT

Candida auris is an emerging multidrug-resistant pathogen
traditional biochemical methods. *C. auris* is capable of causin
among hospitalized patients with significant medical comorbid
of choice for *C. auris*, although not all isolates are susceptible
Nosocomial *C. auris* outbreaks have been reported in a numb
control measures are paramount to stopping transmission.

Fungus

Genus	Species
Candida	**spp**

NIH (2016):
BMBL (2009)*: not mentioned
Australia/New Zealand (2010):
Belgium (2008):
Canada (2015):
Canada PSDS:
EU (2000): 2
Germany (2013):
Japan:
Singapore: 2 **notes:**
Singapor Schedule: Fourth Schedule
Switzerland:
UK (2013): 2
Human Pathogen: y **Animal Pathogen:** n **Plant Pathogen:** n
Select Agent CDC: n **Select Agent USDA:** n

RISK GROUP DATABASE
ABSA INTERNATIONAL

Centers for Disease Control and Prevention

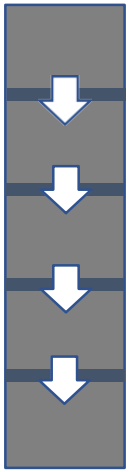
Candida auris

Safety Considerations When Working with Known or Suspected Isolates of *Candida auris*

Important: All safety procedures should conform to your institution's safety policy. These safety steps are recommendations for when the laboratory is working with known or suspected *Candida auris* isolates. They are not meant to supersede your institution's methods and policies.

A successful biosafety program

- Communications
- Recordkeeping
- Operations
- Planning
- Inspections



DOHS, NIH

Responsible Officer (RO)

Investigator (PI)

Lab Manager

Individual

Conclusions

1. Implementation of NIH's Biosafety Program in the lab – involves every stakeholder in the lab, from the PI, researchers, lab manager, IBC committee to approve pathogen registrations, biosafety officers to conduct lab inspections, IT infrastructure to manage inventory and equipment

2. High-throughput drug discovery screening facility in the Building of Biodefense

3. Decide the most appropriate BSLs per recommendation of your institute's safety committee, based on risk assessment and risk group analysis of the pathogens, especially the multi-drug resistant strains

Acknowledgement

Tuberculosis Research Section,

LCIM, NIAID,NIH

Dr Clifton Barry

Dr Helena Boshoff

HTS screen team

Division of Occupational Health and Safety, NIH

Funding

NIH Intramural Research Program
Our Research Changes Lives

BILL & MELINDA GATES *foundation*