Risk Assessment in the Clinical and Biological Research Laboratory

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Case Studies

- Case #1
 - The year is 2000
 - Neisseria meningitidis
 - July 15, Alabama microbiologist, 35y/o, evaluated at emergency room for malaise, fever, myalgia
 - Prepared a Gram stain from the blood culture of a patient subsequently shown to have meningococcal disease

Case Studies

- July 16, became tachycardic and hypotensive, died within hours
- Aspiration from blood culture bottles was performed on open bench
 - biosafety cabinets, eye protection, or masks were not used routinely for this procedure

Case Studies

- Case #2
 - The year is 2000
 - Neisseria meningitidis
 - December 24, Michigan State Public Health Laboratory microbiologist, 52yo, acute onset of sore throat, vomiting, headache, and fever; by December 25, the patient had developed a petechial rash on both legs

Case Studies

- Had worked up several *N.* meningitidis serogroup C isolates during the 2 weeks before becoming ill
- Died 25 December of overwhelming sepsis
- performed slide agglutination testing and recorded colony morphology using typical biosafety level 2 precautions; did not use biosafety cabinet

Arnold G. Wedum, M.D., Ph.D

Father of Modern Biosafety "It is true that good engineering design is not a completely adequate substitute for thoughtfully applied good technique, but the reverse also is true. Both are necessary." A.G. Wedum 1976



Risk Analysis

Risk analysis encompasses risk assessment, risk management, and risk communication

Ways to Mitigate Risk

- Anticipate the issues •
- Remove or reduce the hazard
- Increase familiarity with the hazard
- Train to deal with hazard •
- Increase protection from the hazard
- Have a back up plan (in case all of the previous fail)





Hazard Recognition Biological organism

- Pathogenicity
- Mode of transmission
- Work practices •
- Animal work •
- Training •

•

- Personnel •
- Workplace surveys ٠
- Publications/research





- Biohazard
 - A biological agent or condition that constitutes a hazard to man or his environment
 - Also a hazard posed by such an agent or condition

The BMBL

- Outcome-oriented, not prescriptive, but ultimately based on risk assessment
- Laboratory director responsible for assessing risks and setting the biosafety level



The BMBL

- A participatory strategy works best
- Involve workers, safety professionals
- Develop training initiatives
- Vigilant review for effectiveness



Qualitative Risk Assessment

- Identify all applicable risk factors
 - Biological agent
 - Work procedures and practices
 - Personnel
 - Facility
- Review guidelines, regulations, publications

Qualitative Risk Assessment

- Assess available epidemiological and field data
- Consult subject matter experts
- Recognize any available animal data

Over-Arching Principles

- Standard precautions are always advisable
- Be conservative when insufficient information forces subjective judgment
- Everyone is responsible for the risk assessment and management process

 not just the "management"

Risk Communication

- Empathize with those dealing with the situation
 - Have an occasional reality check; acknowledge what is happening
 - Don't tell people not to worry, over-reassure or be "paternalistic"
 - Risk = Hazard + Outrage (to the public)

Risk Communication

- Address the hazard(s) and be the logical information source:
 - Individual threats
 - Community threats
 - Recognize the availability of "outside" messages

Risk Communication

- Address the consequences honestly and concisely:
 - Health
 - Property
 - Financial
- Do not make promises or guarantees
- Consider possible range of reaction

Risk Communication

- Evaluate the process
 - Monitor opinion (inside and outside)
 - Determine need for other information sources
 - Provide feedback

Considerations for Assessing Risk in the Clinical Laboratory Environment

Clinical Environment



Considerations for Assessing Risk in the Clinical Laboratory Environment

- Clinical Environment
 - Demanding constant workload
 - Sample testing volume
 - Unfamiliar with agent (not endemic)
 - May be first to encounter BT agent
 - PT treated like patient specimen
 - Lack of time for training
 - Limited staff

Considerations for Assessing Risk in the Clinical Laboratory Environment

- Clinical Environment
 - "Stat requests"
 - "I didn't think about it"
 - "Boredom" and "routine" (complacency)
 - Over time, rare events are not worried about
 - "Assume" that BSC and PPE are effective

Considerations for Assessing Risk in the Clinical Laboratory Environment

- Clinical Environment
- Lack of "hands-on" training
 Lack of communication/information
- flow between PHL and hospital labs
- How to track training for staff on off-shifts
- Part-time staff
- New and automated technology
- Requires sustained vigilance

Considerations for Assessing Risk in the Clinical Laboratory Environment

- Clinical Environment
 - Lack of policies, occupational health programs
 - Lab left out of routine hospital surveillance and not represented on committees
 - Lack of skilled MT/microbiologists in small hospitals
 - Small hospitals do not receive patient information

Considerations for Assessing Risk in the Clinical Laboratory Environment

- Clinical Environment
 - Hospital emphasis on patients (infection control), not lab (LAIs)
 - Difficult to differentiate between LAI and community acquired
 - Incorrect facility design, BSC type and placement

Principal Routes of Transmission

- Parenteral inoculations with contaminated sharps
- Spills and splashes on skin & mucous membrane



Principal Routes of Transmission

- Ingestion through pipeting (hand to mouth)
- Cuts and scratches, animal bites
- Inhalation exposures
 to infectious aerosols



Risk Assessment for the Clinical Lab

 Assessment of risk focuses primarily on the prevention of

laboratory-acquired infections (LAI)

- Spills/Splashes
- Aerosol exposures
- Cuts/Lacerations
- Needle sticks
- Animal bites







Aerosol Issues

- Procedures that impart energy into a microbial suspension are a potential source of aerosol (Chatigny, 1974)
- Laboratory procedures having potential of releasing aerosols are ubiquitous
 - Opening vials, centrifugation, mixing, sonication, blending, grinding, shaking, vortexing, spills, pipetting, etc.

Agent Considerations

Agent	Estimated Infectious Dose	
Ebola virus	1	
M. tb	1 – 10	
Tularemia	10	
Brucella	10 – 100	
Anthrax	2,500 – 55,000 viable	
	spores	
Cholera	10^8	
Salmonella typhi	10^3	
E. coli	10^8	
E. Coli 0157:H7	10 – 100	
Shigella spp.	10 – 100	

Viable Particles Recovered from Air					
Procedure	# Particles/ft3 of air				
Sonic oscillator	6				
Mixing w/pipette	7				
Overflow from mixer	9				
Opening lyophilized vial	135				
Top removed after blending	1500				
Dropping flask of culture	1551				
Dropping lyophilized culture	4839				

Other Clinical Microbiological Procedures Presenting Risk in Lab

- Diagnostic/Culture technique
 - Streaking plates
 - Spreading material on slides
 - Cooling loop in media
 - Heating loop in bunsen burner flame

Other Clinical Microbiological Procedures Presenting Risk in Lab

- Sniffing plates
- Rapid test kits/automated liquid dispensing
- Catalase tests

Pipetting

- No mouth pipetting
- Disposable plastic pipettes
- Don't expel last drop
- All samples handled in biosafety cabinet
- Collect pipettes
 inside biosafety
 cabinet



Sharps Hazards

- Syringes and needles, scalpels and broken glass
 - Auto-inoculation
 - Mishandling
 - Separation from syringe
 - Inoculating blood tubes and bottles
 - Inappropriate disposal
 - Poor work practices

Sharps Precautions

- Specific locations for sharps in lab
- Never fill sharps containers all the way
- Use self-retracting needles and other engineering controls
- Substitute plastic for glass when
 possible



Sharps Precautions

- Avoid glass Pasteur pipettes and capillary tubes
- Practice "infectious spill with glass" clean-up procedures
- Immediate collection/disposal
- File and/or trim animal "sharps"





Risks in the Clinical Lab

- Dealing with many types of infectious organisms (at the same time)
- Set ups
 - Fixing slides
 - Any other aerosol generating manipulation (inoculating blood culture bottles, sterilizing loops)

Risks in the Clinical Lab

- Use and training for PPE
- Leaky specimens
- Identifying isolates
 - Face close to open plates (sniffing cultures?)
 - Suspicious plates not sealed
 - Catalase tests
- Using automated systems

Risks in the Clinical Lab

- Crowded lab
- Equipment and PPE shortages
- Cracked hands from latex or multiple hand washing
- Workload, stress
- Routine. Complacency
- Lack of training
- New personnel / rotating trainees

Considerations for Assessing Risk in the <u>Clinical</u> Laboratory Environment



- Most patients have "something"
- Most organisms seen spread by hand-mouth, bloodborne and aerosol

Considerations for Assessing Risk in the <u>Clinical</u> Laboratory Environment

- Poor technique can contribute to large
 LAI outbreaks
- Trusting automated Dx equipment with slow growing isolates
- Training for techs an laboratorians needs to be focused and fit schedule

Considerations for Assessing Risk in the <u>Clinical</u> Laboratory Environment

- PPE available, used properly?
 Containment equipment training and use
- Understand aerosol generating
 manipulations, how to reduce/eliminate
- Reinforce hand washing and disinfectant use

Considerations for Assessing Risk in the <u>Clinical</u> Laboratory Environment

- Sickness, injury, exposure reporting
- Reminders to clinicians and pathologists to notify lab if dangerous organism is suspected

Considerations for Assessing Risk in the <u>Biological</u> Research Laboratory



Agent

- Unusual characteristics? Spore former, exotic agent?
- Hard to kill or easy to acquire? Low Infectious Dose?

Considerations for Assessing Risk in the <u>Biological</u> Research Laboratory

- How much will I be working with? How will these quantities be contained?
- Information available? Community issues?
- Animal hosts used in any part of the research? Host range? Permissive species?

Considerations for Assessing Risk in the <u>Biological</u> Research Laboratory

- PPE available, used properly? Prophylaxis or treatment availability
- Mode of transmission? Aerosol, fomites
- Can use surrogate organism? Reduced virulence or killed?

Considerations for Assessing Risk in the <u>Biological</u> Research Laboratory

- Receiving from another facility or group? Safety testing prior to beginning?
- Recombinant DNA or GMO issues? (risk assessment may be different)
- Environmental risk, presence of competent vectors?
- Availability of treatment/vaccines

Considerations for Assessing Risk in the <u>Biological</u> Research Laboratory Personnel

- Researcher experienced with the agent? Aware of special characteristics of the research organism?
- Trained? Competent? Selected based on prior experience?

Considerations for Assessing Risk in the <u>Biological</u> Research Laboratory

- Job analysis performed?
- Emergency response, sharps and spill control training?
- Immune status? Able to recognize symptoms, unusual issues, protocol changes

Considerations for Assessing Risk in the <u>Biological</u> Research Laboratory

- Attitude towards safety, authority, laboratory and research standards (invested in the work?)
- Properly selected PPE for work? Personnel comfort? Animal work?
- Comfort with the work

Work Hazard Analysis

- List major procedure or process
- Break procedure down into individual components
- Determine hazard(s) associated with individual component
- Identify way to deal with each hazard (hazard mitigation)

Work Hazard Analysis

NAME OF PROCEDURE: <u>BSL-4 Suckling Mouse Brain</u> <u>Inoculation for Antigen Production</u> <u>DEPARTMENT: Virology</u> LOCATION: <u>BSL-4</u> <u>Laboratory</u>, <u>Building 123</u>, <u>Room 456</u> All operations with live virus and/or infected animals will be conducted under BSL-4 containment (Protective Suit Laboratory). All individuals involved in inoculation and harvest procedures will be appropriately trained in BSL-4 operations and associated concepts. All individuals handling BSL-4 infected mice will have prior training to handle mice under BSL-4 containment conditions. All individuals involved in these procedures will be trained to handle sharps under BSL-4 containment prior to involvement in these procedures.

STEPS	OR HEALTH HAZARDS	CONTROLS	TO BE USED	INSPECTION REQUIREMENTS	TRAINING REQUIREMENT
Virus Dilution	Spill, aerosol generation	Perform all dilutions in Class II biosafety cabinets (BSC); Use mechanical / automatic pipettors; disinfectant	BSC; Virus stock vial; dilution tubes; diluent; automatic pipettors; tube holders; appropriate disinfectant; wet ice	Laboratory exhaust filter and BSC filter testing; BSC annual certification; training records; agent accountability records	Basic BSL-4 operations; BSC usage; pipet handlin technique
Preparation for virus inoculation	Aerosol generation, auto-inoculation	Fill syringes in Class II BSC or on downdraft table; fill syringe barrel, using forceps or a hemostat, attach needle just prior to inoculation; use sterile 15ml centrifuge tube to keep syringe sterile before adding needle	BSC; Dilution tubes; wet ice; tube holders, 15ml sterile centrifuge tubes; 0.5 ml syringes, #28 gauge single use, Luer- Lock needle and syringe combination (or similar engineered sharps safety inoculation device); sharps disposal containers; appropriate disinfectant	Training records	Basic BSL-4 operations; BSC usage; sharps handling un BSL-4 containment aerosol containment pipet handli technique



Some Factors That Affect the Perception of Risk

- Choice
- Scale
- Familiarity
- Origin
- History
- Media



Some Factors That Affect the Perception of Risk

- Communication (or lack there of)
- Proximity and/or Location
- Time
- Reversibility
- Equitability



Risk Management

- In the modern world, the availability and access to information complicates issues of risk assessment
- The general public, whether qualified or not, can have an impact on risk acceptability
- Necessitates having a plan for Risk Communication

Risk Communication

- Prepare an overall communication plan (have one before you need one)
 - Determine roles and responsibilities
 - Strategic coordination
 - Identify partners and populations
 - Know what is important to stakeholders
 - Identify communication channels and delivery methods

Risk Communication

- Decide who will be the spokesperson(s)
 - Ideally with proper background and training
 - Credibiliity
 - -Relatability
 - Backup capability

Risk Communication

- Develop scenarios, realistically train for the worst
 - -What happened?



- -What does it mean?
- -Nothing is ever off the record

Case Study: Rocky Mountain Spotted Fever

- Location: CDC Atlanta, 1977
- 2 laboratory glassware workers
- Picked up improperly marked glassware for cleaning
- Opened waste pan and aerosolized culture of RMSF

Case Study: Rocky Mountain Spotted Fever

- The two men died
- CENTERS FOR DISEASE CONTROL
 1977 Fatal Rocky Mountain spotted
 fever Georgia . Morb Mort Wkly Rep
 26: 84

Case Study: Burkholderia mallei

- Location: Maryland, May 2000
- Experienced microbiologist, USAMRIID
- Diabetic, developed painful mass under left axilla in March
- Febrile presentation at Baltimore hospital. Despite antibiotic course, fever increased, fatigue, weight loss, abdominal pain

Case Study: Burkholderia mallei

- Aspirates of abdominal abscesses yielded small, Gm–rods, then isolated systemically
- Initial automated bacterial identification system indicated *Pseudomonas sp.*

Case Study: Burkholderia mallei

- "He <u>neither reported nor recalled</u> any laboratory mishaps, although on occasion he had handled without wearing gloves laboratory equipment containing live Burkholderia strains."
- No association with horses or other farm animals

Case Study: Burkholderia mallei

 CENTERS FOR DISEASE CONTROL Laboratory-Acquired Human Glanders
 --- Maryland, May 2000. Morb Mort Wkly Rep 49: 24

Case Study: Sabia virus

- Location: Yale University, BSL-3 Laboratory, 1994
- Experienced virologist was centrifuging cells infected with Sabia virus (an arenavirus) (6x250ml bottles)
- Noticed leaking bottle at end of run, so cleaned up spill with bleach (no PAPR), continued work for another 3 hours

Case Study: Sabia virus

- Became ill 8 days later, symptoms resembled malaria
- Treated himself before deciding it was time to go to the hospital – did not recall any "serious" lab exposure at the time
- Treated with ribavirin, and recovered

Case Study: Sabia virus

- Issues
 - Lack of training and reporting for incidents
 - Introductory training inadequate
 - Questionable risk assessment of work
 - Previous arenaviruses accidents (1 death and one serious infection with Lassa fever)

Case Study: Sabia virus

- Issues
 - Incorrect clean up procedures and respiratory protection
 - No medical monitoring of staff

Risk Assessment Review

- There is risk in everything that we do
- Never underestimate biological agents
- Don't underestimate the value of good training
- Assume that any unknown illness in your lab is a potential LAI until proven otherwise

Risk Assessment Review

- Be conservative when dealing with unknowns or unfamiliar agents
- Have a plan to deal with unrecognized illness
- Develop an overall communication
 plan

Risk Assessment Exercise



Risk Assessment Exercise

- Synopsis
 - Sample given to 1 med tech student in hospital micro lab for unknown isolate identification exercise
 - 6 of 19 med tech students working in same lab develop symptoms of Shigellosis (abdominal cramps, diarrhea, back pain, chills, and headache)

Risk Assessment Exercise

- Synopsis
 - Some also developed myalgia, vomiting, fever and malaise
 - Two had bloody stools (hematochezia)
 - PFGE of stool cultures from ill students determined that all had same strain of *Shigella sonnei* (all stool isolates obtained had same antibiogram as well)

Risk Assessment Exercise

- Synopsis
 - Most recent clinical Shigella isolate handled in the lab was from 22 days prior to first symptoms of illness and had different antibiogram sensitivities than that from the stricken students

Risk Assessment Exercise

- Synopsis
 - PFGE and antibiogram from isolates from ill technologists matched the unknown isolate that was being handled by the student
 - Student handling the unknown did not get sick

- What happened?
- Lab bench where student was characterizing unknown was closest to sink used for hand washing in the area
- Just prior to the outbreak, the lab sink faucet control was switched from foot operated (hands-free) to faucet handle (????)

Risk Assessment Exercise

 Student handling the unknown recalled contaminating his gloves with a heavy concentration of agent from a titer well

Risk Assessment Exercise

- Pathogenic Agent?
- "Agent: Shigella spp."
 - Shigellosis is a demonstrated hazard to laboratory personnel, with dozens of cases reported in the United States and Great Britain alone (90)(91)(92)(93)

Risk Assessment Exercise

- "Agent: Shigella spp."
 - While outbreaks have occurred in captive nonhuman primates, humans are the only significant reservoir of infection
 - However, experimentally infected guinea pigs, other rodents, and nonhuman primates are also proven sources of infection

Risk Assessment Exercise

- Laboratory Hazards:
 - The agent may be present in feces and, rarely, in the blood of infected humans or animals
 - Ingestion and parenteral inoculation of the agent are the primary laboratory hazards

Risk Assessment Exercise

- Laboratory Hazards:
 - The oral 25%-50% infectious dose of S. flexneri for humans is approximately 200 organisms (94)
 - The importance of aerosol exposure is not known

- Recommended Precautions:
 - Biosafety Level 2 practices, containment equipment, and facilities are recommended for all activities utilizing known or potentially infectious clinical materials or cultures

Risk Assessment Exercise

- **Recommended Precautions:**
- Animal Biosafety Level 2 facilities and practices are recommended for activities with experimentally or naturally infected animals
- Vaccines are currently not available for use in humans

Risk Assessment Exercise

"The Shigella isolate given to the student was a quality control strain stocked in the laboratory. Transmission appears to have resulted from contamination of the faucet handles of the single sink used for hand washing by technologists in the work area. The student working with the unknown isolate admitted that heavy glove contamination had occurred when he placed his gloved finger in a titer well containing a high concentration of S. sonnei during the typing process. This occurred at the bench closest to the hand washing sink and farthest from the processing sink (bench 6). It is believed that the **Student broke laboratory protocol** and used the hand washing sink, rather than the sink that he had been instructed to use for processing, to discard the concentrated *Shigella* suspension in the titer wells and to wash off the reusable titer wells following disinfection with Lysol. This activity likely led to contamination of the sink and faucet handles."

Risk Assessment Exercise

Assuming that this outbreak was not caused intentionally, if you are the Laboratory Supervisor or Biosafety Officer, what would be your course of action for dealing with this situation?

Risk Assessment Exercise

- A. Standard Microbiological Practices
 - #2. Persons wash their hands after they handle viable materials, after removing gloves, and before leaving the laboratory

Risk Assessment Exercise

 #7. Work surfaces are decontaminated on completion of work or at the end of the day and after any spill or splash of viable material with disinfectants that are effective against the agents of concern

- B. Special Practices
 - #6. Biosafety procedures are incorporated into standard operating procedures or in a biosafety manual adopted or prepared specifically for the laboratory by the laboratory director. Personnel are advised of special hazards and are required to read and follow instructions on practices and procedures.

Risk Assessment Exercise

- #7. The laboratory director ensures that laboratory and support personnel receive appropriate training on the potential hazards associated with the work involved, the necessary precautions to prevent exposures, and the exposure evaluation procedures. Personnel receive annual updates or additional training as necessary for procedural or policy changes

Risk Assessment Exercise

 #10. Laboratory equipment and work surfaces should be decontaminated with an effective disinfectant on a routine basis, after work with infectious materials is finished, and <u>especially after overt spills,</u> <u>splashes, or other contamination by</u> <u>infectious materials</u>

Risk Assessment Exercise

C. Safety Equipment (Primary Barriers)

 #4. Gloves are worn when hands may contact potentially infectious materials, contaminated surfaces or equipment. Wearing two pairs of gloves may be appropriate. Gloves are disposed of when overtly contaminated, and removed when work with infectious materials is completed or when the integrity of the glove is compromised.

Risk Assessment Exercise

- C. Safety Equipment (Primary Barriers)

 #4 cont'd. Disposable gloves are not washed, reused, or used for touching "clean" surfaces (keyboards, telephones, etc.), and they should not be worn outside the lab. Alternatives to powdered latex gloves should be available. Hands are washed following removal of gloves.
- D. Laboratory Facilities (Secondary Barriers)
 - #3. Each laboratory contains a sink for hand washing.

Risk Assessment Exercise

- B. Special Practices
 - #12. Laboratory equipment and work surfaces should be decontaminated routinely with an effective disinfectant, after work with infectious materials is finished, and especially after overt spills, splashes, or other contamination with infectious materials.

- C. Safety Equipment (Primary Barriers)
 - #3. Frequent changing of gloves accompanied by hand washing is recommended. Disposable gloves are not reused.

Risk Assessment Exercise

- D. Laboratory Facilities (Secondary Barriers)
 - #2. Each laboratory room contains a sink for hand washing. <u>The sink is</u> <u>hands-free or automatically operated</u> <u>and is located near the room exit</u> <u>door.</u>

Risk Assessment Exercise

- Contributing Factors
- No mention in the article if a Biosafety Cabinet was used by the student identifying the unknown
- "For those laboratories with faucet handle controls on sinks, the use of paper towels as barriers may reduce transmission of microbial pathogens in this high-risk environment."

Risk Assessment Exercise

 "As with so many areas of infection control, written protocols and appropriate training in sterile technique may not ensure good practice. <u>This report emphasizes the</u> fact that despite the rigorous training of students and new personnel, close supervision of these individuals is of paramount importance."

Risk Assessment Exercise

"The student did not develop diarrhea or any of the other symptoms described above."

Why???

Risk Assessment Review

- There is risk in everything that we do
- Never underestimate biological agents
- Try to anticipate issues
- Don't underestimate the value of good training
- Be conservative when dealing with unknowns or unfamiliar agents – maintain healthy suspicion

Risk Assessment Review

- Assume that any unknown illness in your lab is a potential LAI until proven otherwise
- Have a plan to deal with unrecognized illness
- Develop an overall communication
 plan

Bottom Line Risk Management Recommendations

- When in doubt, be conservative
- Use Standard Precautions as a starting point
- Complacency and routine can be deadly
- Constantly remind clinicians and pathologists to notify lab personnel if suspicion exists

Bottom Line Risk Management Recommendations

- Risk Assessment requires information about the agent and the work along with good judgment
- Acknowledge and make aware of "close calls"

Risk Management

- Does your risk management solution:
 - Make scientific sense?
 - Make logical sense?
 - Make practical/common sense?

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