PROTECTING INDIVIDUALS WORKING WITH LAB ANIMALS, FROM A (ALLERGENS) TO Z (ZOONOSES)

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Preventing and Treating Biological Exposures:
An Occupational Health Colloquium
June 19-21, 2013
Regulatory Requirement

- No specific federal regulation addressing Occupational Health and Safety Programs with respect to laboratory animal work
- OSHA standards
  - Blood borne pathogens
  - Occupational exposure to hazardous chemicals in laboratories
  - Compressed gasses
  - PPE
  - Electric systems
Regulatory Requirement

- Public Health Service Policy on Humane Care and Use of Laboratory Animals
  - Requires institutions that receive federal funds for animal research provide an occupational health program for employees with substantial animal contact
  - Outlined in the Guide for Care and Use of Laboratory Animals (Guide)
Regulatory Oversight

• Institutional Animal Care and Use Committee (IACUC)
  – Provision of a safe working environment
  – Responsible for reviewing use of hazardous materials in animals
    • Protocol specific
Requirement

• Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC)
  – Uses *The Guide* as one of it’s standards
  – Occupational Health and Safety programs are still problem spots in many institutions
  – “When problem areas are cited, they most frequently involve: occupational health and safety; the Institutional Animal Care and Use Committee (IACUC) or comparable oversight body; or heating, ventilation and air conditioning systems.”
Components of Program

- Guide is relatively open ended
- Focus = maintaining safe & healthy workplace
- Consistent with federal, state, and local regulations
- Hierarchy of control and prevention strategies
  - Hazard identification
  - Facility design
  - Use of appropriate safety equipment
  - Process and SOP development
  - PPE
Adequate risk assessment must be a prerequisite in selecting appropriate health-care services for employees at risk.
Risk Assessment
Factors to Consider

• Species of Animal
  – Mouse
  – Rat
  – Dog
  – Pig
  – Rabbit
  – Macaques

• Physical and biological hazard presented by the animal
Risk Assessment
Factors to Consider

• Species of Animal
  – Mouse
  – Rat
  – Dog
  – Pig
  – Rabbit
  – Macaques

• Physical and biological hazard presented by the animal
Risk Assessment
Factors to Consider

• Type of contact
  – Veterinarian vs. office worker

• Exposure intensity

• Exposure frequency

• Susceptibility of the employee
Risk Assessment
Factors to Consider

• Occupational-health history of employees doing similar work

• Hazardous properties of the agents used in the research protocols

• Hazard control measures available
Risk Assessment

- Team approach is most effective
  - Principle Investigator
  - Veterinarian
  - Occupational Health and Safety Professionals
  - Environmental Health & Safety Professionals
    - Waste Management
  - Radiation Safety Officer
  - Biosafety Officer
Common Injuries in Animal Facilities

• Burn injuries
  – Cage washers
  – Autoclaves
  – Steam pipes
  – Steam cleaners

• Crush injuries or lacerations
  – moving caging equipment
  – operating sanitation equipment
  – working with intractable large animals
Common Injuries in Animal Facilities

• Musculoskeletal injuries (strains, sprains or fractures) due to
  – the use of improper technique in lifting
  – moving heavy equipment
  – improper restraint and handling of large animals

• Slip and fall injuries from walking on wet flooring
Common Injuries in Animal Facilities

- Hearing impairment resulting from work around loud machinery or animals
- Cage wash\(\geq 85\ \text{dB(A)}\)
- Rodent ventilated cage rack\(80\ \text{dB(A)}\)
- Dog bark (German shepherd)\(120\ \text{dB(A)}\)
- Pig Squeal\(85 - 110\ \text{dB(A)}\)
- Housing rooms
  - Dog\(110\ \text{dB(A)}\)
  - Swine\(80\ \text{dB(A)}\)
  - NHP\(80 - 95\ \text{dB(A)}\)
### OSHA Permissible Noise Exposures

<table>
<thead>
<tr>
<th>Duration per Day (Hours)</th>
<th>Sound level (dBA slow response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>95</td>
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<tr>
<td>3</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>1 ½</td>
<td>102</td>
</tr>
<tr>
<td>1</td>
<td>105</td>
</tr>
<tr>
<td>½</td>
<td>110</td>
</tr>
<tr>
<td>¼ or less</td>
<td>115</td>
</tr>
</tbody>
</table>

- OSHA requires implementing a hearing conservation program when TWA dB(A) \( \geq 85 \).
Common Injuries in Animal Facilities

- Visual impairment from
  - direct trauma (equipment)
  - splash exposure (detergents, disinfectants, or particulate matter)
  - exposure to ultraviolet light resulting in corneal damage
Common Injuries in Animal Facilities

• Skin irritation or contact dermatitis from exposure to chemicals used in cleaning, latex or talc allergy, or in experimental procedures in the animal facility

• Respiratory exposure to irritating vapors, aerosols or particulates from working with disinfectants and bedding materials
Common Injuries in Animal Facilities

• Needle stick exposures
  – attempting to recap hypodermic needles
  – improper injection technique
  – delay or improper disposal of used needles

• Repetitive motion injuries
  – changing and cleaning cages
    • ~4% of employees at one institution
Specific Animal-Related Hazards

• Zoonotic diseases
  – Though fairly uncommon, can be fatal

• Allergies
  – One of the most wide-spread and serious hazard faced by individuals working with laboratory animals
  – Can ultimately develop into asthma
Specific Animal-Related Hazards

• Hazards associated with research
  – Chemicals
  – Infectious agents
  – Radiation
  – Use of human cells/tissues

• Bites and Scratches
Bites and Scratches

- Significant portion of lab animal associated hazards
  - 35% of veterinarians receive a bite that requires suturing during career
  - 2012 at a Midwestern University
    - 10 mouse bites (60,000+ on census)
    - 1 Rhesus bite with scratch (30 on census)
    - 4 Rhesus scratches
    - 1 squirrel monkey bite (5-10 on census)
Bites and Scratches

- Tissue damage
- Infections
- Anaphylaxis
- Venom
- Psychological distress

http://junglefriends.org/private_sector.shtml
Bites and Scratches

- Expose staff to research materials
  - Biologics
  - Toxins
  - Chemicals

- Salivary shedding
- Grooming
- Coprophagia
- Cannibalism
Tissue Damage

• Severity depends upon
  – Animal species and dentition
    • Dogs
      – Crush injuries, lacerations, abrasions
    • Cats
      – Puncture wounds
      – May appear minor at surface but can penetrate deeply
      – Can puncture bone, joints, tendons
Tissue Damage

• Severity also depends upon
  – Ferocity of attack
  – Anatomical location of the bite
Infection

• Rate differs between species due to differences in oral flora and injury
• Polymicrobial
• Aerobes and Anaerobes
• Organisms may arise from
  – Mouth
  – Victim’s own flora
  – Environment
    • Flora reflective of water environment for aquatic animals
# Oral Flora and Infection Rate

<table>
<thead>
<tr>
<th>Animal</th>
<th>Organism</th>
<th>Infection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs</td>
<td>Pasteurella dagmatis, <em>P. canis</em>, <em>Staphylococcus aureus</em>, <em>S. intermedius</em>, <em>Streptococci</em>, Moroxella spp, Neisseria spp, Capnocytophagia canimorsus, Clostridium spp including <em>C. tetani</em>, Anaerobes</td>
<td>18%</td>
</tr>
<tr>
<td>Cats</td>
<td><em>Pasteurella multocida</em>, mixed aerobes and anaerobes.</td>
<td>28-80%</td>
</tr>
<tr>
<td>Rodents</td>
<td><em>Streptobacillus moniliformis</em>, <em>Spirillium minus</em>, <em>Salmonella</em> spp.</td>
<td></td>
</tr>
<tr>
<td>Pigs</td>
<td>Polymicrobial, <em>Aeromonas</em> spp, <em>P. aerogenes</em>, <em>Actinobacillus</em> spp</td>
<td></td>
</tr>
<tr>
<td>Monkeys</td>
<td>Mixed aerobes and anaerobes, <em>Streptococci</em>, <em>Neisseria</em> sp, <em>Haemophilus influenzae</em></td>
<td>2%</td>
</tr>
</tbody>
</table>

# Zoonotic Organisms

<table>
<thead>
<tr>
<th>Agent</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridium perfringens</em></td>
<td>dog</td>
</tr>
<tr>
<td><em>Bartonella hensela</em></td>
<td>cat</td>
</tr>
<tr>
<td>Macacine Herpes B virus</td>
<td>macaques</td>
</tr>
<tr>
<td>Hantavirus</td>
<td>rodents</td>
</tr>
<tr>
<td>LCMV</td>
<td>rodents</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td>rodents</td>
</tr>
<tr>
<td>Parapox virus</td>
<td>sheep</td>
</tr>
<tr>
<td>Rabies</td>
<td>all mammals</td>
</tr>
</tbody>
</table>
Anaphylaxis

- Relatively Rare
- Patient may or may not be atopic prior to exposure
- Anaphylactic reactions vary from mild generalized urticarial reactions to profound life-threatening reactions.
Anaphylaxis

• Presentation
  – Diffuse itching, hives, and swelling of the face, lips, and tongue or
  – Difficulty in breathing because of laryngeal edema or
  – Asthma with wheezing or
  – Shock leading to loss of consciousness
Anaphylaxis

• Rodents
  – Mice
  – Rats
  – Hamsters
  – Mongolian gerbils
  – Prairie Dogs

• Cats
• Reptiles
  – Gila monsters
• Horses
Management of Bite Wounds

• Lack of evidence on which to base recommendations
• Controversial!!!
  – Closure
    • Primary closure
      – Cosmetic concerns outweigh risk of infection
    • Primary delayed*
  • Healing by secondary intention
  – Antibiotic therapy
Assessment

- Principles of assessing bites in a laboratory setting are the same as when assessing a bite in the general population
- Circumstances of bite
- Was animal exposed to hazardous compounds?
- Tetanus vaccination status
Wound Management

• Gram stain and bacterial cultures
  – Aerobic and anaerobic
  – Indicated if abscess, severe cellulitis, devitalized tissue, or sepsis

• Irrigate
  – Copious amounts of normal saline with high-pressure jet from syringe

• Debride necrotic tissue and remove foreign objects
Wound Management

• Radiographs, MRI, CT
  – Fracture, bone penetration, rule out osteomyelitis

• Closure
  – Not usually indicated
Antibiotics - Prophylaxis

• Not generally indicated unless serious wound complications or at high risk of infection
  – Amoxicillin and clavulanate

• Factors that place wounds at high risk of infection include
  – Puncture and crush wounds
  – Penetration of bone, joint, tendons, vascular structures, or overlay prosthetic joint
  – Wounds on hands, feet, face, genitals
  – Presence of edema or lymphedema
  – Delayed presentation >8 hours
  – Patient immunocompromised
Antibiotics – Infected Wounds

• Coverage based on patient and specific animal involved

• Should cover beta-lactamase-producing aerobic and anaerobic organisms, including *Pasteurella* species
Antibiotics – Infected Wounds

- Metronindazole and either
  - Amoxicillin/clavulanate
  - Cefotaxime
  - Ceftriaxone
- Avoid fluoroquinolones and aminoglycosides before culture results
  - Ineffective against anaerobes
Hospitalization

• Multiple and severe injuries
• Systemic signs of infection
  – Fever, sepsis
• Cellulitis if severe or rapid spread past one joint
• Involvement of bone, joint, tendon, nerve
• Refractory to oral antibiotic therapy
Hospitalization

- Wound requires surgical intervention
  - Debridement, drainage, reconstruction
- Significant bites to hand
- Cranial bites
- Immunocompromised host
- Noncompliance
Immunization

- Tetanus
- Rabies
Prevention

- Proper handling technique
  TRAINING!
  TRAINING!
  TRAINING!
Restraint

- Chemical
- Restraint Devices
PPE

- Gloves
- Long sleeved clothing
- Protective Sleeves
Prevention

• Maintaining focus while working
  – Avoid complacency

• Proper first aid
  – Helps decrease secondary complications and decreases exposure to lab-related compounds/organisms in mouth
Exposure to Research Materials

• Don’t forget to assess the risk!

• Is the experimental agent reportable?
  – Infectious agent with public health significance
    • CDC
    • State Health Departments
    • County Health Department
  – Select Agent
    • CDC or USDA
  – Recombinant DNA
    • OBA
Legal Issues Regarding Bites

- Some counties require reporting of ALL animal bites, regardless of animal source
  - Cook County, IL
    - Includes bites from research mice
    - 10 day quarantine
    - Not permitted to use animal in research during this time frame
    - Report at beginning and end of 10 day period
  - Los Angeles County, CA
    - Legal requirement to report all bites except those from rodents and rabbits
Scratches

• May not appear as severe as bites, but can be significant
• Small puncture wounds sometimes present
• Nails often contain fecal organisms
• Encourage reporting even if appear minor
  – Herpes B virus
B Virus

• Causative Agent
  – Macacine Herpesvirus 1 (MHV-1)
    • Formerly Cercopithecine Herpesvirus 1
    • Alpha herpesvirus
    • Similar to Herpes Simplex virus

• Common names
  • Herpes B
  • Monkey B virus
  • Herpesvirus B
  • Herpesvirus simiae
  • Herpes B virus
B Virus

• Herpesviruses generally cause subclinical or mild disease in host species

• Can cause serious disease in other species
Disease in Macaques

• Usually asymptomatic
  – latent in carrier (ganglia)

• Fluid filled vesicles => Ulcers and fibronecrotic scabs
  – Primarily at mucocutaneous junctions and mucous membranes
  – Tongue and buccal surfaces of mouth
  – Conjunctiva
  – Genitalia

• Systemic illness
  – Rare
  – Ulcerative lesions in mouth, esophagus, stomach
  – Necrosis of liver, spleen, adrenal glands
Animal Hosts

• Natural host = old world monkeys of genus *Macaque*
  – Asia
  – Rhesus monkey
  – Long tailed or Cynomolgus monkey
  – Japanese Macaque
  – Pig Tailed Macaque

• Captive and wild populations have high incidence of infection
  – 70-100% as age
Hosts

- Other species of NHP
  - Causes fatal disease
- Humans
  - ~80% fatality rate
- Colony of Brown Capuchin NHPs that were infected
  - New World Monkeys
    - South and Central America
  - Subclinical disease
Pathophysiology in Humans

• Inoculation =>
  – Local infection in the skin at the inoculation site with local and regional inflammatory changes
    • Hemorrhagic and focally necrotic lymph nodes
  – Spreads to nerve ganglia by axonal transport
  – Spreads along peripheral nervous system to spinal cord to brain
    • Necrosis in the spinal cord
  – Progression of disease depends on site and size of exposure
B Virus Infection - Humans

• Incubation
  – Typically 5 days to 1 month before symptomatic
  – Once develop, symptoms usually progress over 7-10 days

• May become latent in humans
  – At least one case in which disease occurred years after exposure

• Self limited aseptic meningitis has been reported, but almost all cases produce substantial morbidity and mortality
Disease

• Three types of disease
  – Symptoms that first appear near the site of exposure then progress
  – Symptoms limited to the peripheral nervous system or CNS
  – Flulike illness
    • no symptoms near exposure site
    • fever, chills, myalgias, and other nonspecific symptoms
    • may later be followed by the abrupt onset of CNS symptoms.
Early Symptoms

- Variable
- Pain or pruritus at exposure site
- Vesicles or ulcers at or near exposure site
- Local lymphadenopathy
- +/- Keratoconjunctivitis
Intermediate symptoms

- Variable
- Fever
- Malaise
- Diffuse myalgias
- Headache
- Nausea, acute abdominal pain, diarrhea
- Numbness or paraesthesia at or near exposure site
- Persistent hiccups
- Chest pain and difficulty breathing
Late Manifestations

- Persistent headache
- Alteration of mentation
- Focal neurological symptoms
  - Itching or tingling at or near the exposure site
  - Numbness
  - Double vision
  - Difficulty swallowing
- Dizziness
- Confusion
- Can progress to fatal encephalitis
- Can also cause damage to liver, spleen, lymph nodes, and adrenal glands.
Differential Diagnosis

• Rabies
B Virus Infection - Humans

• Incidence
  – ~50 cases reported since 1934
  – Between 30-35 well documented

• Susceptibility low

• Mortality high
  – ~80% of patients die if untreated
  – ~20% die with treatment
  – As of 2007 more than 2 dozen fatal cases
Potentially infectious tissues & secretions

- Secretions
  - Ocular
  - Oral
  - Genital
- Primary cell cultures from monkey kidneys
- CNS tissues
- CSF
- Urine
- Feces
- Peripheral blood has not been reported to cause infection in humans
- Will survive on contaminated surfaces
Exposure Routes in Well-Documented Cases of Herpes B Virus Infection

<table>
<thead>
<tr>
<th>Exposure</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monkey bite</td>
<td>10</td>
</tr>
<tr>
<td>Monkey scratch</td>
<td>2</td>
</tr>
<tr>
<td>Wound contamination with monkey saliva</td>
<td>1</td>
</tr>
<tr>
<td>Tissue culture-bottle cuts(^a)</td>
<td>1</td>
</tr>
<tr>
<td>Needlestick injury(^b)</td>
<td>2</td>
</tr>
<tr>
<td>Possible aerosol(^c)</td>
<td>2</td>
</tr>
<tr>
<td>Cleaned monkey skull</td>
<td>1</td>
</tr>
<tr>
<td>Needle scratch and monkey bite</td>
<td>1</td>
</tr>
<tr>
<td>Cage scratch</td>
<td>2</td>
</tr>
<tr>
<td>Possible reactivation of B virus</td>
<td>1</td>
</tr>
<tr>
<td>Human-to-human contact(^d)</td>
<td>1</td>
</tr>
<tr>
<td>Mucosal splash(^e)</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>26</strong></td>
</tr>
</tbody>
</table>

\(^a\) Cultures involved monkey kidney cells.

\(^b\) In one case, a needle had been used to inject the tissues around the eye, and, in the other case, a needle “may have been used previously to inject monkeys” [4, p. 974].

\(^c\) In one case, aerosol may have been generated during autopsies performed on macaques, and, in the other case, the patient presented with respiratory symptoms.

\(^d\) The patient applied cream to her husband’s herpes vesicles and to areas of her own skin that were affected by contact dermatitis.

\(^e\) The patient was splashed in the eye with material, possibly feces, from a macaque.

Keys to Controlling Human B Virus Infection

• Per the CDC
  – Diligence in the recognition of possible exposures
  – Recommended first aid
  – Rapid diagnosis of B virus infection
  – Must be done well
  – Must be done in a timely fashion
First – Cleanse Exposed Area

• **BEGIN IMMEDIATELY!**
• Thoroughly wash and scrub wound
• Soap, concentrated solution of detergent, povidone-iodine, or chlorhexidine and water
• 0.25% hypochlorite solution followed by detergent solution
• Irrigate the washed area with running water for 15-20 minutes
2nd – Diagnostics

• Patient:
  – Culture wound site (“as applicable”) and send for PCR
    • Controversial
    • Collect as soon as possible after injury
    • **Do NOT collect PCR specimen before washing!**
  – Serology
    • At time of injury
    • 3 weeks following injury
2nd – Diagnostics

• NHP:
  – Physical Exam
    • Note lesions consistent with MHV-1
  – Swab buccal mucosa, conjunctiva, and urogenital area
    • Also controversial since viral shedding can be intermittent
  – Culture fomite if involved in exposure
  – Serology recommended
    • At time of injury and 3 weeks later
    • MHV-1 animals may be seronegative (latency)
2nd - Diagnostics

- Send swabs to reference laboratory
  - MHV-1 must be handled at BSL4
- Send serology to reference laboratory
  - Minimizes cross-reacting HSV antibodies
  - PCR
Early Detection is IMPORTANT

・B virus zoonosis can be effectively managed with early detection
・Early detection can translate into prevention of morbidity and mortality as a result of an inadvertent exposure to this uniquely pathogenic herpesvirus.
3rd - Therapy

- Per the CDC, the risk of infection can NOT be considered zero, regardless of circumstances.
- Treatment recommendations based on exposure details.
- The decision to treat with antivirals should be
  - made at the health care provider’s discretion based on individual case
    - Should be experienced with Herpes B virus infection
  - with liberal consideration of the patient’s wishes and concerns.
  - take into account the following…
Exposure Risks
Physical Condition of Animal

• Species of nonhuman primate

• Presence of lesions
  – Healthy macaques typically don’t shed virus
    • Latent in the trigeminal ganglia
      – False negative serologic test
    • 0-2% shedding at any given time
Exposure Risks
Physical Condition of Animal

• Presence of stress
  – Virus reactivated when animal stressed
  – Psychological stress
  – Pharmacological stress
  – Physical stress
    • Breeding
    • Illness

• Immune status
  – Reactivated if diminished immunocompetence.
Exposure Risks

• Nature of wound
  – Bites or scratches that penetrate the skin
  – Deep puncture wounds that are difficult to clean*
  – Inadequately cleaned wounds
Exposure Risks

• Location
  – Wounds on the face (esp. to eye), neck, throat, torso
    • Provide rapid access to CNS
    • Prophylaxis recommended regardless of severity
  – Superficial wounds to the extremities are less likely to lead to fatal disease, and antiviral treatment is considered less urgent in such exposures.
Risk Assessment

• Nature of the exposure
  – Higher risk
    • Accidental needle sticks with needles that have come into contact with the CNS, eyelids, or mucosa
    • Direct contact with tissues known to harbor live virus
      – Monkey CNS tissues, Saliva, Monkey kidney cell cultures
    • Exposure of eyes or mucous membranes with infected fluids
  – Lower risk
    • Punctures from needles exposed to the peripheral blood of macaques
    • Scratches resulting from contact with possibly contaminated objects
Exposure Risks

• Thoroughness and timeliness of wound cleansing procedure
  • Less likely to be infected
    – cleansed within 5 minutes of exposure
    – cleansed for at least 15 full minutes
  • Increased risk of infection
    – Delay in cleansing or inadequate cleansing of the wound
Exposure Risks

• Viability
  – Media/tissues
    • Up to 7 days at 37°C
    • Weeks at 4°C
    • Stable at −70°C
  – Dry surfaces
    • Presumed 3–6 hours
      – Specific studies have not been performed
      – Based on other mammalian herpes viruses
Treatment Recommended when

- Skin exposure with loss of skin integrity or mucosal exposure +/- injury to a high risk source
  - Macaque
    - Ill
    - Immunocompromised
    - Known to be shedding virus
    - Lesions compatible with B virus infection
Treatment Recommended when

- Inadequately cleaned skin or mucosal exposure +/- injury
- Laceration of the head, neck, or torso
- Deep puncture bite
- Needle stick associated with tissue or fluid from the nervous system, lesions suspicious for B virus, eyelids, or mucosa.
Treatment Recommended when

• Puncture or laceration after exposure to objects
  – contaminated either with fluid from monkey oral or genital lesions or with nervous system tissues or
  – known to contain B virus

• Post-cleansing culture is positive for B virus
Consider Treatment when

• Mucosal splash that has been inadequately cleaned.
• Laceration (loss of skin integrity) that has been adequately cleaned.
• Needle stick involving blood from an ill or immunocompromised macaque.
• Puncture or laceration occurring after exposure to
  – objects contaminated with body fluid (other than that from a lesion) or
  – a possibly infected cell culture.
Treatment Not Recommended when

- Skin exposure in which the skin remains intact.
- Exposure associated with other non-human primates other than macaques, unless they were in a situation where they could have been infected by a macaque.
Treatment Considerations

• Initiate therapy as soon as possible to attempt prevention of disease progression or when prophylaxis is indicated
  – Early treatment successful in modifying infection in some animal models
  – Human data mixed
    • Ability to prevent herpes B virus infection is not documented
    • Progression of complications seems to be limited in some human reports
Treatment Considerations

• Prophylactic therapy may complicate diagnosis
  – May suppress shedding
  – May suppress seroconversion

• Adequate length of effective prophylaxis is uncertain
Prophylaxis

• Prophylaxis for exposure to B virus
  – Valacyclovir*—1g by mouth every 8 hours for 14 days
  – Acyclovir—800 mg by mouth 5 times daily for 14 days
  – Successful in rabbits experimentally inoculated with lethal doses, but no comparable studies of efficacy in humans have been possible
  – Dosing not clearly delineated
Treatment of Exposure

• With no CNS symptoms
  – Acyclovir—12.5–15 mg/kg intravenously every 8 hours, or
  – Ganciclovir—5 mg/kg intravenously every 12 hours

• With CNS symptoms
  – Ganciclovir—5 mg/kg intravenously every 12 hours
Antiviral Drugs

• FEAU (2’-fluoro-5-ethyl-Ara-U)
  – Experimental drug
  – Higher potency than conventional antiviral drugs
  – Compassionate use?
Prognosis

• Case fatality 70-80% fatality rate
• Many survivors have substantial residua
• Reported cases seem to have a lower case-fatality rate
  – Earlier diagnosis
  – Earlier treatment
  – Better supportive care
Prevention

• Preventing worker exposure to biohazardous material is the best protection against infection

• No vaccines available
Prevention - PPE

• PPE Program
  – Written and comprehensive
  – Based on thorough risk assessment
  – Clearly identifies PPE required for each specific task or working area
  – Training
  – Inspection and maintenance of PPE
  – Periodic assessment of program effectiveness
  – Certified

Prevention - PPE

• Eye Protection
  – Goggles
  – Face shields
  • Commonly considered secondary eye protectors
  • Ocular exposures have occurred to workers wearing face shields
  • Must prevent droplet splashes to head from running down into eyes
  • Must prevent mucous membrane exposures around edges
Prevention - PPE

• Eye protection recommended when
  – Entering areas containing macaques
  – Conducting captures
  – Transporting caged macaques
  – Other activities as determined by risk assessment
Prevention - PPE

- Protective suits or lab coats
- Tyvek sleeves
- Gloves
  - Nitrile/Latex
  - Leather gauntlet
- Bonnets
- Shoe covers
Equipment

• Free of sharp edges
• In good repair
• Easy to use
  – Avoid difficult to open or clasps that can easily pinch fingers
• Designed appropriately
Specific Pathogen-Free Colony

- Some success in US
- Demand exceeds supply
- Very Difficult
  - False negative animals may shed if virus reactivated
Prevention

• Training
  – Herpes B and other biohazards associated with NHP work
  – Required PPE
• Reporting
  • Known exposures
  • Clinical signs consistent with exposure
• First aid procedures
• Avoiding high risk behaviors
• NHP behavior
Prevention

• Training
  – Before working with NHPs
  – Annual refresher training
  – Change in job responsibilities
  – Whenever an exposure
  – Should include practice in or demonstration of eye washing and wound cleansing

• DOCUMENT!
Prevention

- C
- R
- A
- P
Prevention

- Call for help
- R
- A
- P
Prevention

• Call for help
• Rinse wound
• A
• P
Prevention

• **C**all for help
• **R**inse wound
• **A**lert veterinary staff
• **P**
Prevention

• Call for help
• Rinse wound
• Alert veterinary staff
• Proceed to occupational health and safety
Exposure Kits

• Facilitates rapid response following exposure

• Contents
  – First aid supplies
  – Specimen collection supplies
  – Copies of written instructional materials
  – Treatment protocols for exposures

• Signage to direct people to kits where NHP work occurs
Prevention

• Occupational Health care system in place ahead of time
  – Documentation of exposure
  – Wound care
  – Treatment
  – Follow-up
  – Patient Counseling
Prevention

• Wallet Card
  – Symptoms of infection
  – Contact info
    • Knowledgeable local health care worker
    • Expert clinical and lab consultation
    • Reference for prophylaxis and therapy guidelines
Resources
National B Virus Resource Laboratory

• Funded by NIH National Center for Research Resources
• Diagnostic Services
  – Both nonhuman primates and humans suspected to be infected with B virus.
  – Provide service on a 24/7
  – Emergency basis 365 days/year
  – Emergency and routine screening
Specific Animal-Related Hazards

• Bites and Scratches
• Zoonotic diseases
  – Though fairly uncommon, can be fatal
• Allergies
  – One of the most wide-spread and serious hazard faced by individuals working with laboratory animals
  – Can ultimately develop into asthma
• Hazards associated with research
Zoonoses

• From Greek
  zoion = animals
  nosos = diseases

• Any disease or infection that is naturally transmissible from vertebrate animals to humans.
Significance
Laboratory Animal Workers

• Survey of laboratory workers in 2005 (Weigler et al)
  – 1367 people participated
  – During the last 5 years did you
    • Acquire a zoonotic disease from your work?
    • Go to a doctor to have it diagnosed?
    • Report it to your supervisor/occupational health physician?
  – Calculated the Incidence of zoonotic disease acquired from research animals at the workplace during previous 5 years

• Results:
  – 23 persons (~1.7%) reported 28 cases of infection
  – 6 cases were medically confirmed
  – Annual incidence rate = 45 cases per 10,000 worker-years at risk
Significance
Laboratory Animal Workers

• Annual incidence rate = 45 cases per 10,000 worker-years at risk

• Significance
  – Similar to the rate for Occupational Safety & Health Administration (OSHA)-recordable nonfatal occupational illnesses during 2002 for
    • all full-time workers in the agricultural production-livestock industry
      – 43.9 cases per 10,000 worker-years
    • those employed broadly within health services industries
      – 50.9 per 10,000 worker years
Most common sources

• Rodents
• Dogs
• Cats
• Nonhuman Primates
Relative odds of acquiring a zoonotic disease

- Veterinarians
- Veterinary technicians
- Research technicians
- Animal facility supervisory staff
- Animal technicians
- Research investigators

HIGHEST

LOWEST
### Most Common Lab Acquired Zoonotic Diseases 1999 - 2003

<table>
<thead>
<tr>
<th>Disease</th>
<th>Source</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ringworm</td>
<td>Dog, cat, rabbit, ox</td>
<td>Skin contact</td>
</tr>
<tr>
<td>Q fever</td>
<td>Sheep</td>
<td>inhalation</td>
</tr>
<tr>
<td>Giardia</td>
<td>Dog</td>
<td>Unspecified</td>
</tr>
<tr>
<td><em>Pasteurella</em> sp.</td>
<td>Rabbit, bat</td>
<td>Bite, needle stick</td>
</tr>
<tr>
<td>B virus</td>
<td>Macaque</td>
<td>?</td>
</tr>
<tr>
<td>Cat scratch disease</td>
<td>Cat</td>
<td>Bite</td>
</tr>
<tr>
<td>Ectoparasites</td>
<td>Mouse, rabbit</td>
<td>Skin contact</td>
</tr>
<tr>
<td>Influenza</td>
<td>Ferret, pig</td>
<td>inhalation</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>Chimpanzee</td>
<td>inhalation</td>
</tr>
<tr>
<td>Mycobacterium sp.</td>
<td>Guinea pig</td>
<td>?</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>Sheep</td>
<td>Splash to eyes, nose, mouth</td>
</tr>
<tr>
<td><em>Clostridium difficile</em></td>
<td>Hamster</td>
<td>Bite</td>
</tr>
<tr>
<td>Simian foamy virus</td>
<td>Baboon</td>
<td>Bite or scratch</td>
</tr>
</tbody>
</table>
Agriculture workers?

- Vet schools
- Schools with ag animals
- Significant concern
  - Rabies (all mammals)
  - Anthrax (cattle, horses, pigs)
  - Brucellosis (cattle, ovids, dogs)
  - Swine and Avian Influenza
  - Salmonellosis (cattle, horses)
  - *Campylobacter jejuni* (poultry)
  - Community Acquired MRSA (swine)
Transmission

- Transmission
  - Direct contact
    - Skin contact (1)
    - Splash (mucous membranes)
  - Direct inoculation
    - Bites (2) and scratches
    - Needle sticks
  - Inhalation (3)
  - Fomites
    - Contaminated equipment
  - Ingestion
  - Arthropod vectors
Assessment

• Most knew whom to talk to at their institution for medical evaluation and care
• Occupationally acquired zoonotic diseases were under reported (only 18 of 28 were reported to supervisors)
  – Lack of concern about potential significance to health
  – Worry about punitive consequences
Laboratory Animal Allergy
Significance

• Significant risk for those working with laboratory animals
  – 10-44% of people working with laboratory animals have respiratory allergy
  – up to 73% of persons with pre-existing allergic disease eventually develop allergy to laboratory animals
  – Up to 17% of those with allergy develop asthma
  – Asthma can progress, even in the absence of continuing exposure
    • Symptomatic even after years following exposure
Who is at risk?

• All laboratory animal facility personnel who regularly come in contact with laboratory animals are at risk of developing LAI
  – Technicians
    • Cleaning cages
  – Researchers
  – Cleaning staff
  – Veterinarians
  – Administrative staff
  – Maintenance
Laboratory Animal Allergies

- Antigen concentrations on the order of parts per billion in laboratory facility environments can induce symptoms in sensitized subjects.
Onset of Symptoms

- Symptoms usually evolve over a period of exposure of 1-2 years.

- Occupation-related asthma
  - Acute while worker exposed to allergen
    - Cough, wheezing, and shortness of breath
  - Chronic symptoms persisting for months to years even after exposure ceases.
Surveillance

- For chronic exposure
  - Annual screening
  - Detect those who are developing allergic symptoms
  - Goal to take appropriate intervention measures to prevent long-term difficulties.

- Questionnaire
  - allergic or asthma symptoms

- Skin testing or an *in vitro* test for specific IgE antibodies to identify sensitization.

- Periodic monitoring of pulmonary function is recommended if asthma symptoms appear
# Prevention

<table>
<thead>
<tr>
<th>Control measure</th>
<th>Agent</th>
<th>Process/appliance</th>
<th>Working environment</th>
<th>Work practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination</td>
<td>Total substitution</td>
<td>Different process</td>
<td>Layout change</td>
<td>Automation, robotisation, remote control</td>
</tr>
<tr>
<td>Reduction</td>
<td>Partial substitution, change of form</td>
<td>Adjustment, preventive maintenance, specialised appliance</td>
<td>Good housekeeping</td>
<td>Correct work procedures, training, instruction, motivation, supervision</td>
</tr>
<tr>
<td>Isolation</td>
<td>Enclosure segregation</td>
<td></td>
<td></td>
<td>Ensuring enclosure</td>
</tr>
<tr>
<td>Ventilation</td>
<td>Local exhaust ventilation, push/pull ventilation</td>
<td>Dilution ventilation, air douches, air curtains</td>
<td></td>
<td>Portable jets, low-volume, high-velocity tools</td>
</tr>
<tr>
<td>Exposure avoidance</td>
<td></td>
<td>Booths for operators</td>
<td></td>
<td>Shorter shifts, fewer people, work schedules</td>
</tr>
<tr>
<td>Personal protection</td>
<td></td>
<td></td>
<td></td>
<td>Respiratory protection, gloves, clothing</td>
</tr>
</tbody>
</table>

Building Ventilation

• Eliminating/Reducing Allergen through ventilation
  – Would require extremely high ventilation rates (in excess of 100 air changes per hour)
  – HEPA-filtered laminar-flow units
  – Impractical and extremely expensive
Local Ventilation

• Cage-emptying where loose bedding is used results in particularly high levels of allergen exposure.

• Ventilated hoods or work stations for cage emptying and cage-cleaning with filtered, recirculated air can reduce exposure.
Local Ventilation

• Caging
  – Filter top caging
  – Ventilated caging
    • Negative
    • Positive
    • Building exhaust
    • HEPA filtered local exhaust
Humidity

• Increasing relative humidity from 54% to 77%
  – Substantially reduces airborne rat-allergen concentrations
  – Exceeds the optimal range for animals
  – Uncomfortable for employees
  – Induces mold growth
Administrative Controls

• Removing staff from jobs that have high levels of exposure
  – first step to minimize exposure of people who have become sensitized or have developed symptoms.

• High levels of exposure
  – Cage cleaning

• Low levels of exposure
  – Feeding
  – Weighing
  – Necropsy
Administrative Controls

• Work practices
  – Establishing codes of practice
  – Educational programs
    • Risks
    • Proper measures to control and avoid exposure as much as possible
    • Include maintenance as well as animal care staff
  – Can greatly reduce the incidence
    • 37% to 12% over 4 years
  – Also decreases severity of allergic symptoms
Administrative Controls

• Limiting animal use to the animal facility

• If need to bring up to lab
  – Restricting contaminated PPE to animal facility
  – BSC/fume hood

• Restrict access to the animal facility
Work Practice Controls

• Reducing density of animals
• Cleaning procedures to minimize exposure
• Hand washing/showering
PPE

- Respirators
- Hair Bonnets
- Gloves
- Shoe covers
- Gown, lab coat, or jump suit
- Sleeves
- Work uniform
Respirators

• Strong case for using respirators

• Use of respirators
  – Requires ongoing commitment
    • Selection, cleaning, maintenance, storage, training, fitting, medical monitoring
  – Best when used as interim measure while efforts to control source
What’s new?

• Performance of the halogen immunoassay to assess airborne mouse allergen-containing particles in a laboratory animal facility
What’s new?

• Quantified allergens in rodent facility and correlated it with activities (baseline levels)

• Mice
  – Washing and cleaning cages and the number of mice handled daily were the most important determinants of personal exposure to mouse urinary allergen
  – Exposure levels were associated with day-to-day variation of tasks rather than characteristics of workers.

• Rats
  – Only persons handling rats were exposed to rat urinary allergen

• Joshua T Glueck, Richard B Huneke, Hernando Perez,1 and Igor Burstyn. Exposure of Laboratory Animal Care Workers to Airborne Mouse and Rat Allergens 2012 51(5): 554–560
Hazards Associated with Research

- Chemicals
- Biological Hazards
- rDNA
- Radiation
Risk Assessment

• Procedures should be developed for conducting a health and safety review of research activities that involve hazards.
  – Incorporated into the institutional animal care and use committee (IACUC) project-review process.
  – Recommend that an appropriate environmental health and safety professional serve on the committee
Biological Hazards and rDNA

• Issues specific to animals include
  – Host range
    • Is the animal a natural host?
    • Is the organism going to be able to replicate
    • Is the organism shed and by what route?
  – Management of contaminated bedding?
  – Transportation of infectious agents from the lab to the animal facility
  – Transportation of infected animals to core facilities/labs?
  – Carcass management
Chemical Hazards

• MSDS’s not always useful
  – Small volumes in Vivarium
• Management of contaminated bedding?
  – Disposable cages
• Transportation of chemical agents from the lab to the animal facility
• Transportation of treated animals to core facilities/labs
• Carcass management
Radiological Hazards

• Similar issues
• Decay of isotopes
  – Carcasses
  – Caging
  – Storage?
• Staffing?
Hazard Mitigation

• Strategies are similar to what we have been talking about
  – Facility design
  – Equipment
  – PPE
  – SOPs
Culture of Safety

• Where substantial risks exist, researchers should be encouraged to incorporate health and safety procedures as an integral part of the research plan.
Conclusions

• Though not required by law and Occupational Health and Safety program that covers those with substantial animal contact should be developed.
  – Team approach is best

• Hazards of animal use in research laboratories include bites, scratches, exposure to zoonotic diseases, exposure to allergens, and hazards associated with the specific research (exposure to chemicals, infectious organisms, rDNA, radiation
Conclusions

• Efforts to decrease exposure to these risks include
  – Proper facility design
  – Use of protective equipment
  – PPE
  – Development of appropriate SOPs

• TRAINING IS CRITICAL
Questions?

Photo of Macaque nigra (Sulawesi crested macaque) taken by Karsten Wrobel beside a lake at Tangkoko National Park on the Indonesian island of Sulawesi