OCCUPATIONAL HEALTH AND SAFETY PLAN
Working with *Mycobacterium tuberculosis* complex organisms, including multidrug resistant (MDR) and extremely drug resistant (XDR) strains in BSL-3 Laboratories
University of Minnesota, Office of Occupational Health and Safety

Background Information

The information in this section is provided as a summary of current guidelines and recommendations from organizations such as NIH and CDC. Specific occupational health and safety requirements for work with these organisms at the University of Minnesota are described further on.

The Mycobacterium tuberculosis complex includes *M. tuberculosis*, *M. bovis*, *M. africanum* and *M. microti*, all of which cause tuberculosis in humans, as well as *M. caprae* and *M. pinnipedii*, which cause tuberculosis in animals. *M. microti* can also infect voles, guinea pigs, rabbits and sometimes bovines. *M. bovis* causes pulmonary disease in bovines and can lead to human infection after ingestion of contaminated milk and milk products. Humans can also contract pulmonary infections from exposure to *M. bovis*-infected animals.

Multidrug resistant tuberculosis (MDR-TB) is caused by strains that are resistant to at least two of the best drug treatments – isonaizid and rifampicin. Extremely drug resistant tuberculosis (XDR-TB) is caused by strains that are resistant to isonaizid, rifampicin, any fluoroquinolone and at least one of three second-line drugs (amikacin, kanamycin, capreomycin). These resistant strains occur when infected individuals fail to follow the complete course of antibiotic treatment, the wrong treatment is prescribed or drugs are not available or of poor quality. Infection by drug resistant organisms occurs in the same manner as for non-drug resistant organisms. Drug resistant organisms pose additional risks to researchers, however, because infections require multiple drugs and longer courses of treatment.

These bacteria are acid-fast staining gram positive rods that do not form spores and are slow growing. Disease may occur after a long incubation period. Inhalation is the most common route of exposure, but ingestion and dermal inoculation can also lead to infection. Infection occurs primarily in the lungs, but other organs can also be infected. *M. tuberculosis* has a very low infective dose (ID_{50} 1-10 bacilli). *M. tuberculosis* and *M. bovis* are highly infectious via inhalation of aerosols from laboratory activities and infected non-human primates. Contaminated litter from other types of infected animal species can also generate infectious aerosols.[1] Direct contact with infected patients or tissues from infected animals can also lead to infection. Infected immunodeficient animals may generate higher levels of aerosols or contaminated litter. Among those laboratory procedures most likely to be associated with aerosol exposures are handling of containers with clinical specimens, centrifugation, pipetting, mechanical homogenization, sonication, heating or boiling, work with bacteriological loops, and preparation and manipulation of frozen sections. Aerosols may also be generated from acid-fast staining, manipulating solid and liquid cultures and flow cytometry.[2]

These bacteria have a thick cell wall that is resistant to alkalis and detergents. The organism can survive up to 8 months in sputum in cool, dark locations, 45 days on clothing, 90-120 days on dust, 45 days on manure and 105 days on paper. It is important to select a disinfectant that is effective for these organisms. [3,4]

[1] Biosafety in Microbiological and Biomedical Laboratories (BMBL), 5th Edition, 2009, p 145 [http://www.cdc.gov/biosafety/publications/bmbl5/index.htm]

[2] Biosafety Recommendations for the Contained Use of Mycobacterium tuberculosis Complex Isolates in Industrialized Countries (Biosafety Recommendations), Division of Biosafety and Technology, P. Herman, Scientific Institute of Public Health, Brussels Belgium, pp 8-9 [www.biosafety.be/CU/PDF/Mtub_Final_DL.pdf]

[3] Biosafety Recommendations, , p 7

[4] See Appendix B in the BMBL for more information on disinfectants.

The period to primary lesion or significant skin reaction can be 4 to 12 weeks following exposure. The risk of developing disease is highest in the first 1 to 2 years after infection.[5] Most infections are latent and asymptomatic; one in ten infections will progress to active disease, which has a greater than 50% mortality rate if not treated. Symptoms include chronic cough with blood-tinged sputum, fever, night sweats and weight loss. A wide range of symptoms may occur if organs other than the lung are infected. Chest radiographs, a tuberculin skin test, blood tests, body fluid culturing and microscopy are all utilized for diagnosis. Treatment may require long courses of multiple antibiotics, depending on drug resistance.

Annual or semi-annual purified protein derivative (PPD) skin testing for skin-test-negative personnel can be used as a surveillance tool. An attenuated live vaccine is available but is not used in the United States, because it offers limited protection.[6]

The treatment of tuberculosis is complex. It is important that individuals who are exposed to infected animals or who have skin testing that goes from positive to negative be seen for treatment. Persons with increased risk for developing tuberculosis include those who have had recent infection with *Mycobacterium tuberculosis* and those who have clinical conditions that are associated with an increased risk for progression from latent tuberculosis infection to active disease. Such conditions include diabetes, chronic renal disease, gastrectomy, solid organ transplant (i.e., kidney, heart) and immune disorders. Pregnancy has minimal influence on the pathogenesis of tuberculosis or the likelihood of latent infection progressing to disease. Treatment for latent or active tuberculosis will be carried out according to guidelines set forth by the Centers for Disease Control or based upon clinical findings at the time of diagnosis.

Work that may result in aerosols must be performed in a biosafety cabinet and respiratory protection is strongly recommended by CDC. [7] Care must also be taken to prevent infection by percutaneous injury and secondary transmission via contaminated gloves or surfaces. Every effort should be made to minimize creation of aerosols, even when working in a biosafety cabinet. Animal cages should be manipulated inside a biosafety cabinet.[8] Higher levels of precaution and personal protection should be used for research involving multidrug and extremely drug resistant organisms.

Occupational Health Requirements for ALL Work in BSL-3 Laboratories

The following summarizes the general requirements for all BSL-3 work. **Refer to the BSL-3 Laboratory Operations Manual as well as the facility's manual and laboratory safety plan for more details on occupational health and safety policies and procedures.** Prior to starting research, a Principal Investigator (PI) is responsible for completing risk assessments for biological, chemical and physical hazards as well as project-specific protocols, in consultation with the Laboratory and BSL-3 Facilities Managers. Decisions about methods for ensuring employee health and safety should be made in consultation with the Office of Occupational Health and Safety (OHS). OHS must approve all decisions about personal protective equipment, medical evaluation, treatment and medical surveillance.

Training Prior to beginning work in a BSL-3 facility, research personnel must receive training about the potential health effects of exposure to all biological and chemical hazards, necessary precautions to avoid exposures, initial medical evaluation requirements, vaccine requirements, importance of monitoring and reporting exposures and symptoms, post-exposure medical evaluation and treatments, as appropriate to their research project and activities.

Preliminary Medical Evaluation Prior to beginning research, the BSL-3 Facilities Manager, Laboratory Manager and Supervisor (PI or Facilities Management Team Leader) must complete a BSL-3 Medical Evaluation Authorization Form for each individual requiring access to a BSL-3 facility. Each employee and visitor must enroll in the Office of Occupational Health and Safety (OHS) medical surveillance program and complete a BSL-3 Medical Questionnaire. In some cases the employee will also be required to complete a Respirator Medical Evaluation Form and be medically

[5] Health Canada Material Safety Data Sheet for *M. tuberculosis* and *M. bovis*, 2001 [http://www.phac-aspc.gc.ca/msds-ftss/msds103e-eng.php]
[6] BMBL, page 147
[7] BMBL, page 146.
[8] Biosafety Recommendations, pp 9-10

cleared to wear a respirator. Based upon review of their BSL-3 Medical Questionnaire, some individuals may be required to complete a medical evaluation conducted by an occupational health physician at the occupational health clinic designated by OHS (www.ohs.umn.edu). The occupational health physician will issue a Work Ability Report indicating medical and respirator clearance for work and respirator use; a copy of this report will be sent to the employee, their supervisor, the Office of Occupational Health and Safety, and the BSL-3 Program Manager. Some individuals may be placed on work restrictions or require additional evaluation. Each employee will receive a card that identifies their work with specific organisms, which should be presented to a health care provider if they are seeking medical attention for symptoms or follow-up.

A tetanus vaccine is recommended for all personnel. Depending on the research activities, employees will require additional immunizations and, in some cases, periodic follow-up blood titers to measure antibody production. Employees choosing not to receive recommended vaccines or follow-up titers must sign a declination form. **Declination may prevent work with a BLS-3 agent or result in work restrictions from the occupational health physician. In many instances University policy does NOT permit an individual who declines immunization to work in some specified environments.**

Ongoing Medical Evaluations It is required that BSL-3 employees complete the BSL-3 Medical Questionnaire, and a medical re-evaluation conducted by the occupational health physician if indicated, at least every two years. If a respirator is required, an initial respirator medical evaluation must be completed and must be repeated at least every two years. More frequent re-evaluations may be necessary, depending on the organism or a change in the health of the employee. Updated medical evaluations may be required if there are changes in research processes as identified by an updated risk assessment. Any medical condition that increases risk following exposure (e.g. immunosuppression, pregnancy, significant injury) must be reported to the Office of Occupational Health and Safety to ensure appropriate evaluation.

Specific Occupational Health Requirements for Work with *Mycobacterium tuberculosis* complex organisms

The following are specifically required for an employee to be cleared to work with *Mycobacterium tuberculosis* complex organisms and resistant strains and apply to all employees whose job duties may involve their presence in the laboratory when the organism is being used in research activities. These requirements do not apply to individuals who may encounter the organism only during a medical or other emergency or to individuals whose job duties involve their presence when research activities are not being conducted. An occupational health physician will make the final determination about the application of these requirements for each individual. Changes in these requirements may be made only for **compelling** medical reasons and with approval from the OHS Director.

Preventing Exposures Possible routes of infection include inhalation, accidental parenteral inoculation, direct contact with mucous membranes and ingestion. In addition to the required facility-specific personal protective equipment, nitrile gloves and a gown with tight wrists and ties in back must be worn when manipulating cultures. At minimum an N95 filtering facepiece respirator and goggles or a full facepiece respirator equipped with N95 filters must be worn.

All direct manipulation of organisms must be performed in a biosafety cabinet. When handling sharps, multiple layers of gloves (minimum of two) must be worn. Tasks must be performed in a manner that prevents or minimizes the generation of aerosols. If aerosol-generating procedures are involved, a Powered Air Purifying Respirator (PAPR) with N100 filters must be worn by all personnel in the room. If MDR- or XDR-TB strains are being used, a PAPR with N100 filters must be worn by all personnel in the room and work should be contained within a single suite or room. If work requires the use of shared equipment, all personnel working in the shared equipment room must wear a PAPR with N100 filters.

Anyone responding to a medical or other emergency where there is potential for exposure must wear personal protective equipment that prevents both skin and respiratory system exposures.

Preliminary Medical Evaluation All employees working with *M. tuberculosis* complex organisms are required to obtain a baseline tuberculin skin test (TST). This requirement can be met by:

1) A negative symptom screen within the past year and a negative chest radiograph within the last two years
2) A two-step skin test (PPD/Mantoux) with two tests no less than 7 days and no more than 3 weeks apart, both of which demonstrate no tuberculosis infection *or*

3) A negative Quantiferon-gold test.

Individuals who have previously received any of the above can release the results to OHS by completing the form found at http://www.ohs.umn.edu/prod/groups/ahc/@pub/@ahc/@ohs/documents/asset/ahc_asset_175797.pdf. New employees who cannot provide a record of a negative TB skin test within the last year must complete the two-step TB skin test process. For individuals who previously tested positive through a TB skin test and have not undergone treatment for tuberculosis, a Quantiferon-gold test is required. Individuals who have received a BCG vaccination should take the Quantiferon-gold test. If the two-step skin test is positive, a Quantiferon-gold test may be undertaken or the individual may receive a chest radiograph, symptom screen and physical exam with an occupational health physician. If the Quantiferon-gold test is positive, the occupational health physician may require a chest radiograph and physical exam.

On-Going Medical Evaluation Two-step skin and Quantiferon-gold testing of negative personnel should occur at least annually; the occupational health physician will determine if more frequent testing is required on an individual basis. The occupational health physician will determine the frequency and type of screening needed for personnel with positive skin or Quantiferon-gold tests. Quantiferon (QFT-GIT and T-Spot) testing should be used for individuals who have prior immunization with Bacille Calmette-Guerin (BCG). In general, estimates of sensitivity for Quantiferon are about the same as those for tuberculin skin testing. In general, testing using both methods is not recommended.

Post-Exposure Reporting and Medical Evaluation Any known or suspected exposure to *M. tuberculosis* complex organisms or resistant strains must be reported immediately to the designated occupational health physician. The employee should show their BSL-3 card, the agent hazard information sheet and this occupational health and safety plan to the medical provider. Within 24 hrs of medical care, a BSL3 Incident Report form must be completed and submitted to the IBC, BSL3 Program and OHS.A First Report of Injury form must also be completed and submitted to the University's Risk Management Office.

In the case of organism exposure by needle stick or cut, allow the wound to bleed, express the wound, wash the area with disinfectant followed by soap and water, and call the BSL-3 Pager (612-650-5571). Seek immediate medical attention and bring the agent hazard identification sheet and this plan to the occupational health physician.

Personnel with a documented negative PPD within the three months preceding the exposure do not need to have the baseline PPD repeated. All other exposed personnel, except those previously known to have a positive PPD in the past, should receive a Mantoux tuberculin skin test as soon as possible after exposure. If the initial skin test is negative, a test should be repeated 12 weeks after the initial exposure for assessment of secondary conversion.

Exposed persons with newly positive tuberculin skin test reactions or with symptoms suggestive of tuberculosis should receive chest radiographs. Routine chest radiographs are not required for asymptomatic skin test negative individuals. After the initial chest radiograph, personnel with a positive PPD need a repeat chest radiograph unless symptoms develop. Persons with previously known positive tuberculin skin tests do not require a chest radiograph unless they have symptoms of tuberculosis.

If tuberculosis is diagnosed, appropriate therapy should be instituted. Personnel with a positive skin test or skin test conversions but without active disease should be evaluated for prophylactic chemotherapy. Anyone with a history of tuberculosis or a positive skin test should be counseled concerning their risk for reactivation of tuberculosis in the future. Any symptoms must be promptly reported to and evaluated by an occupational health physician.

Symptom Monitoring and Reporting Employees must continuously self-monitor for symptoms that may indicate exposure, seek immediate medical care and show their BSL-3 card to the medical provider. Symptoms of pulmonary tuberculosis may include cough (sometimes with phlegm), coughing up blood, excessive sweating (especially at night), fatigue, fever, unintentional weight loss. Other symptoms that may occur with this disease include breathing difficulty, chest pain and wheezing. Within 24 hrs of treatment for symptoms consistent with tuberculosis exposure, a BSL3 Incident Report form must be completed and submitted to the IBC, BSL3 Program and OHS. A First Report of Injury form must also be completed and submitted to the University's Risk Management Office. All symptoms consistent with possible

tuberculosis exposure must be reported to a supervisor and OHS. If symptoms occur after completing or leaving the project, this should be reported to OHS.

Describing an Occupational Health Plan in a Project-Specific Standard Operating Procedure

The Principal Investigator must include the following information in the Occupational Health Plan Appendix as part of their Project-Specific Standard Operating Procedure(s) for a BSL-3 workplan:

1. Identify the type of respiratory protection that will be worn by all personnel.
2. List by name and job title all personnel who will receive:
    a. Health and safety training
    b. Medical evaluation
    c. Respirator clearance
3. Identify who has responsibility for conducting health and safety training and describe how training records will be maintained.
4. Identify who has responsibility for reporting exposures (suspected or real).