Section VIII-A: Bacterial Agents

Bacillus anthracis

Bacillus anthracis, a Gram-positive, non-hemolytic, and non-motile bacillus, is the etiologic agent of anthrax, an acute bacterial disease among wild and domestic mammals, including humans. Like all members of the genus *Bacillus*, under adverse conditions, *B. anthracis* has the ability to produce spores that allow the organism to persist for long periods (i.e., years), withstanding heat and drying, until the return of more favorable conditions for vegetative growth.[1] It is because of this ability to produce spores coupled with significant pathogenic potential in humans that this organism is considered one of the most serious and threatening biowarfare or bioterrorism agents.[2] Most mammals are susceptible to anthrax; it mostly affects herbivores that ingest spores from contaminated soil and, to a lesser extent, carnivores that scavenge on the carcasses of diseased animals. In the United States, it occurs sporadically in animals in parts of the West, Midwest, and Southwest. Human case rates for anthrax are highest in Africa and central and southern Asia.[3] The infectious dose varies greatly from species to species and is route-dependent. The inhalation anthrax infectious dose (ID) for humans has been primarily extrapolated from inhalation challenges of non-human primates (NHPs) or studies done in contaminated wool mills. Estimates vary greatly but the median lethal dose (LD50) is likely within the range of 2,500–55,000 spores.[4] It is believed that very few spores (ten or fewer) are required for cutaneous anthrax infection.[5] Anthrax cases have been rare in the United States since the first half of the 20th century. The mortality rates have been reported to be approximately 20% for cutaneous anthrax without antibiotics, 25–75% for gastrointestinal anthrax, and 80% or more for inhalation anthrax. With treatment, <1% of cutaneous anthrax cases are fatal. The fatality rate of a series of inhalation anthrax cases in 2001 was 36% with antibiotics.[6,7] *Bacillus cereus* biovar *anthracis*, if inhaled, can produce symptoms similar to inhalation anthrax. Rapid rule-out tests to differentiate *B. cereus* biovar *anthracis* from other *Bacillus* spp. are currently not available.[6]

Occupational Infections

Occupational infections are possible when in contact with contaminated animals, animal products, or pure cultures of *B. anthracis*, and may include ranchers, veterinarians, and laboratory workers. Although numerous cases of laboratory-associated anthrax (primarily cutaneous) were reported in earlier literature, in recent years, cases of anthrax due to laboratory accidents have been rare in the United States.[8,9]

Natural Modes of Infection

The clinical forms of anthrax in humans that result from different routes of infection include:

1. Cutaneous (via broken skin);
2. Gastrointestinal (via ingestion);
3. Inhalation anthrax;[10] and
4. Injection (to date, identified in heroin-injecting drug users in northern Europe).[11,12]

Cutaneous anthrax is the most common (> 95% of human cases worldwide) and is a readily treatable form of the disease. While naturally occurring disease is no longer a significant public health problem in the United States, *B. anthracis* has become a bioterrorism concern. In 2001, 22 people were diagnosed with anthrax acquired from spores sent through the mail, including 11 cases of inhalation anthrax with five deaths and 11 cutaneous cases.[13] A report of accidental shipment of live organisms highlights the importance of adherence to handling guidelines.[14] The approach to prevention and treatment of anthrax differs from that for other bacterial infections. When selecting post-exposure prophylaxis or a combination of antimicrobial drugs for treatment of anthrax, it is recommended to consider the production of toxin, the potential for antimicrobial drug resistance, the frequent occurrence of meningitis, and the presence of latent spores.[15]

Laboratory Safety and Containment Recommendations

B. anthracis may be present in blood, skin lesion exudates, cerebrospinal fluid (CSF), pleural fluid, sputum, and rarely, in urine and feces.[12] Primary hazards to laboratory personnel are: direct and indirect contact of broken skin with cultures and contaminated laboratory surfaces, accidental parenteral inoculation and, rarely, exposure to infectious aerosols. Spores are resistant to many disinfectants and may remain viable on some surfaces for years.

BSL-3 practices, containment equipment, and facilities are recommended for work involving production quantities or high concentrations of cultures, screening environmental or unknown samples (especially powders) from anthrax-contaminated locations, diagnostics or suspected anthrax samples, and for activities with a high potential for aerosol production. As soon as *B. anthracis* is suspected in the sample, BSL-3 practices are recommended for further culture and analysis. BSL-2 practices, containment equipment, and facilities are recommended for primary inoculation of cultures from potentially infectious clinical materials. ABSL-2 practices, containment equipment, and facilities are recommended for studies utilizing experimentally infected laboratory rodents. It is recommended that all centrifugation be performed using autoclavable, aerosol-tight rotors or safety cups that are opened within the BSC after each run. In addition, it is recommended to collect routine surveillance swabs for culture inside the rotor and rotor lid and, if contaminated, it is recommended to autoclave rotors before re-use.

Special Issues

Be advised of possible misidentification using automated systems. For identification using MALDI-TOF MS, it is recommended to use alternative tube extraction that kills viable organisms in the BSC, followed by filtration through a 0.1–0.2 um filter to remove any remaining viable cells or spores, and not direct spotting of plates in the open laboratory.[15,16]

Vaccines Control of anthrax begins with control of the disease in livestock, and vaccination of livestock has long been central to control programs. Human anthrax is best controlled through prevention, including (a) pre-exposure vaccination for persons at high-risk for encountering aerosolized *B. anthracis* spores, (b) reduction of animal illness by vaccination of livestock at risk for anthrax, and (c) environmental controls to decrease exposure to contaminated animal products, such as imported hair and skins. After a person is exposed to aerosolized *B. anthracis* spores, a combination of antimicrobials and vaccine provides the best available protection.[17] A licensed vaccine for anthrax in humans is available, the anthrax vaccine adsorbed (AVA). AVA is produced from the protective antigen of an attenuated non-encapsulated strain of *B. anthracis*. The vaccine is approved by the Food and Drug Administration (FDA) for at-risk adults before exposure to anthrax. Guidelines for its use in occupational settings are available from the ACIP.[18] CDC has reviewed and updated guidelines for anthrax post-exposure prophylaxis and treatment.[17] Vaccination is not recommended for workers involved in routine processing of clinical specimens or environmental swabs in general clinical diagnostic laboratories. Of interest, Obiltoxaximab, a novel monoclonal antibody directed against the protective antigen of *B. anthracis*, which plays a key role in the pathogenesis of anthrax, has received approval for treatment and prevention of inhalational anthrax.[19] Because of the limited potential of antibiotic treatment once toxemia has already set in, numerous strategies are being explored for therapy directed against the action of anthrax toxins.[20]

Select Agent *B. anthracis* and *Bacillus cereus* biovar *anthracis* are Select Agents requiring registration with CDC and/or USDA for possession, use, storage and/or transfer. See Appendix F for additional information.

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A Department of Commerce (DoC) permit may be required for the export of this agent to another country. See Appendix C for additional information.

Bordetella pertussis

Bordetella pertussis, an exclusively human respiratory pathogen of worldwide distribution, is the etiologic agent of whooping cough or pertussis. The organism

is a fastidious, small, Gram-negative coccobacillus that requires specialized culture and transport media for cultivation in the laboratory.[21] Alternatively, infection may be diagnosed by molecular methodologies on a direct specimen. Its natural habitat is the human respiratory tract.

Occupational Infections

Occupational transmission of pertussis has been reported, primarily among healthcare workers.[22] Outbreaks, including secondary transmission, among workers have been documented in hospitals, long-term care institutions, and laboratories. Nosocomial transmission has been reported in healthcare settings and laboratory-associated pertussis has also been documented.[23,24]

Natural Modes of Infection

Pertussis is highly communicable, with person-to-person transmission occurring via aerosolized respiratory secretions (droplets) containing the organism. The attack rate among susceptible hosts is affected by the frequency, proximity, and time of exposure to infected individuals; however, transmission rates to susceptible contacts may be close to 90% with the infectious dose only around 100 CFU.[21] Although the number of reported pertussis cases declined by over 99% following the introduction of vaccination programs in the 1940s, the incidence of pertussis remains cyclical, with epidemic peaks occurring every three to five years within a given region.[25] In 2015, the World Health Organization reported 142,512 pertussis cases globally and estimated that there were 89,000 deaths attributed to pertussis.[26] However, a recent publication modeling pertussis case and death estimates proposed that there were 24.1 million pertussis cases and 160,700 deaths in children younger than five years in 2014 worldwide.[27] Of significance, *B. pertussis* continues to circulate in populations despite high vaccination of infants and children because protection wanes after several years.[28]

Nevertheless, in vaccinating countries, although pertussis is primarily observed in neonates, infections are found in under-vaccinated or unvaccinated individuals of all ages, including young infants, older school children, adolescents, and adults.[27–29] Adults and adolescents with atypical or undiagnosed *B. pertussis* infections are a primary reservoir. Pertactin is an outer membrane protein and virulence factor for *B. pertussis*, and it should be noted that pertactin-negative strains may evade vaccine-mediated immunity.[30]

Laboratory Safety and Containment Recommendations

The agent may be present in high levels in respiratory secretions and may be found in other clinical material, such as blood and lung tissue.[31,32] Aerosol generation during the manipulation of cultures and contaminated clinical specimens generate the greatest potential hazard. Direct contact is also a hazard with the agent being able to survive a number of days on surfaces such as clothing.

BSL-3 practices, containment equipment, and facilities are appropriate for production operations. BSL-2 practices, containment equipment, and facilities are recommended for all activities involving the use or manipulation of known or potentially infectious clinical material and cultures. ABSL-2 practices and containment equipment are recommended for housing experimentally infected animals. Primary containment devices and equipment, including biological safety cabinets, safety centrifuge cups, or sealed rotors are recommended for activities likely to generate potentially infectious aerosols.

Special Issues

Vaccines A number of pertussis vaccines are available for infants, children, preteens, teens, and adults. DTaP (Diphtheria/Tetanus/Pertussis) is the childhood vaccine, and Tdap (Tetanus/Diphtheria/Pertussis) is the pertussis booster vaccine for preteens, teens, and adults.[33]

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Brucella species

The genus *Brucella* consists of slow-growing, very small, Gram-negative coccobacilli whose natural hosts are mammals. The taxonomy of *Brucella* species remains in flux; however, this genus currently includes 10 recognized species:

- Six terrestrial
  - *B. melitensis* (preferred hosts: sheep, goats, and camels)
  - *B. suis* (preferred hosts: swine and other wild animals)
  - *B. abortus* (natural hosts: cattle and buffalo)
  - *B. canis* (natural host: dogs)
  - *B. ovis* (natural host: rams)
  - *B. neotomae* (natural host: desert and wood rats)
- Three marine
  - *B. delphini*
  - *B. pinnipedialis*
  - *B. ceti*
- One proposed species of unknown origin.[34]

High-risk species for human infections include *Brucella abortus*, *B. melitensis*, and *B. suis*. There is a wide spectrum of clinical manifestations, and patients may have an extended recovery period. Mortality is estimated to be less than 1%.[34,35]

Occupational Infections

Brucellosis is a frequently reported Laboratory-associated infection.[34–38] Airborne and mucocutaneous exposures can produce Laboratory-associated infections. Many cases of laboratory-associated disease appear to be due to mishandling and misidentification of the organism.[39] The need to improve compliance with recommended guidelines was highlighted when 916 laboratory workers were exposed to the RB51 vaccine strain, which is known to cause human illness, due to mishandling of a proficiency test sample.[41] Brucellosis is an occupational disease for workers who handle infected animals or their tissues. Accidental self-inoculation with vaccine strains is an occupational hazard for veterinarians and other animal handlers.

Natural Modes of Infection

Brucellosis (Undulant fever, Malta fever, Mediterranean fever) is a zoonotic disease of worldwide occurrence. Mammals, particularly cattle, goats, swine, and sheep, act as reservoirs for *Brucella* spp. as animals are generally asymptomatic. Multiple routes of transmission have been identified, including direct contact with infected animal tissues or products, ingestion of contaminated milk, and airborne exposure in animal pens and stables.

Laboratory Safety and Containment Recommendations

Brucella may be found in a wide variety of body tissues, including blood, CSF, semen, pulmonary excretions, placenta, and occasionally urine. Most laboratory-associated cases occur in research facilities and involve exposures to zoonotic *Brucella* organisms grown in large quantities or exposure to placental tissues containing zoonotic *Brucella* spp. Cases have also occurred in clinical laboratory settings from sniffing bacteriological cultures or working on open benchtops.[42,43] Human infections are commonly attributed to exposure to aerosols or direct skin contact with cultures or infectious animal specimens.[43,44] The infectious dose of *Brucella* is 10–100 organisms by aerosol or subcutaneous routes in laboratory animals.[45,46] *Brucella* spp. are environmentally stable, surviving days to months in carcasses and organs, in soil and on surfaces.[45,46]

BSL-3 practices, containment equipment, and facilities are recommended for all manipulations of cultures of pathogenic *Brucella* spp. BSL-3 practices are recommended when handling products of conception or clinical specimens suspected to contain *Brucella*.[12] ABSL-3 practices are recommended for experimental animal studies. BSL-2 practices, containment equipment, and facilities are recommended for routine handling of clinical specimens of human or animal origin.

Special Issues

Be advised of possible misidentification using automated systems. For identification using MALDI-TOF MS, it is recommended to use alternative tube extraction that kills viable organisms and not direct spotting of plates in the open laboratory.

Vaccines Human *Brucella* vaccines have been developed and tested in other countries with limited success.[49] Although a number of successful vaccines are available for immunization of animals, no licensed human vaccines are currently available. Some recently described ribosomal proteins and fusion proteins demonstrate a protective effect against *Brucella* based on antibody and cell-mediated responses, which may prove useful in potential vaccines.[34]

Select Agent *Brucella abortus*, *B. melitensis*, and *B. suis* are Select Agents requiring registration with CDC and/or USDA for possession, use, storage and/or transfer. See Appendix F for additional information.

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Burkholderia mallei

Burkholderia mallei is a non-motile, Gram-negative rod associated with glanders, a disease primarily of equine species, but which can be seen in humans. While endemic foci of infection exist in some areas of the world, glanders due to natural infection is extremely rare in the United States with the last naturally occurring case reported in 1934.[50] Reported mortality rates are over 90% if left untreated, and up to 50% with treatment.[50]

Occupational Infections

Glanders occurs almost exclusively among individuals who work with equine species and/or handle *B. mallei* cultures in the laboratory. *B. mallei* can be very infectious in the laboratory setting. The only reported case of human glanders in the United States over the past 50 years resulted from a laboratory exposure.[51] Modes of transmission may include inhalation and/or mucocutaneous exposure.

Natural Modes of Infection

Glanders is a highly communicable disease of solipeds (such as horses, goats, and donkeys). Zoonotic transmission occurs to humans, but person-to-person transmission is rare. Glanders in solipeds and humans has been eradicated from North America and Western Europe. However, sporadic infections of animals are still reported in Far East Asia, South America, Eastern Europe, North Africa, and the Middle East.[50] Clinical manifestations in humans include localized

infection, pulmonary infection, bacteremia, or chronic infection, characterized by suppurative tissue abscesses. The organism is transmitted by direct invasion of abraded or lacerated skin; inhalation with deep lung deposition; and by bacterial invasion of the nasal, oral, and conjunctival mucous membranes. Occupational exposures most often occur through exposed skin.[50]

Laboratory Safety and Containment Recommendations

B. mallei can be hazardous in a laboratory setting. Laboratory-associated infections have resulted from aerosol and cutaneous exposure. A laboratory-associated infection in 2001 was the first case of glanders reported in the United States in over 50 years.[51,52] The ability of *B. mallei* to survive for up to 30 days in water at room temperature should be a consideration in development and implementation of safety, disinfection, and containment procedures for laboratories and animal facilities handling this agent.

BSL-3 and ABSL-3 practices, containment equipment, and facilities are recommended for all manipulations of suspect cultures, animal necropsies, and for experimental animal studies. BSL-3 practices are recommended for preparatory work on cultures or contaminated materials for automated identification systems. BSL-3 practices, containment equipment, and facilities are appropriate for production operations. BSL-2 practices, containment equipment, and facilities are recommended for primary inoculation of cultures from potentially infectious clinical materials. Primary containment devices and equipment, including biological safety cabinets, safety centrifuge cups, or sealed rotors are recommended for activities likely to generate potentially infectious aerosols.

Special Issues

Be advised of possible misidentification using automated systems. For identification using MALDI-TOF MS, it is recommended to use alternative tube extraction that kills viable organisms and not direct spotting of plates in the open laboratory.

Vaccines Vaccine research and development has been conducted, but there is no available vaccine.[53]

Select Agent *B. mallei* is a Select Agent requiring registration with CDC and/or USDA for possession, use, storage and/or transfer. See Appendix F for additional information.

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Burkholderia pseudomallei

Burkholderia pseudomallei is a motile, Gram-negative, oxidase-positive rod that is found in soil and water environments of equatorial regions, including Southeast Asia, Northern Australia, Madagascar, Africa, India, China, Taiwan, Central America, and South America.[54] This organism, the causative agent of melioidosis, is capable of infecting both humans and animals. A recent study estimates the global incidence of melioidosis is 165,000 cases with 89,000 deaths.[55]

Occupational Infections

Melioidosis is a disease associated with activities that expose people to soil and water such as rice farming or gardening; however, *B. pseudomallei* can be hazardous for laboratory workers, with two possible cases of aerosol transmission of melioidosis in laboratory staff.[56–58]

Natural Modes of Infection

Natural modes of transmission usually occur through direct contact with an environmental source (usually water or soil) by ingestion, percutaneous inoculation, or inhalation of the organism. In endemic areas, a significant number of agricultural workers have positive antibody titers to *B. pseudomallei* in the absence of overt disease.[59] Manifestations include localized disease, pulmonary disease, bacteremia, and disseminated disease. Abscesses can be seen in a variety of tissues and organs. However, the majority of persons exposed to this organism do not develop clinical infection.[54] Latent infection with subsequent reactivation is well recognized. Risk factors for contracting melioidosis include diabetes, liver or renal disease, chronic lung disease, thalassemia, malignancy, and immunosuppression.[54,60,61]

Laboratory Safety and Containment Recommendations

B. pseudomallei can cause systemic disease in human patients. Infected tissues and purulent drainage from cutaneous or tissue abscesses can be sources of infection as can blood and sputum. The ability of *B. pseudomallei* to survive for years in water (as well as soil) should be a consideration in development and implementation of safety, disinfection, and containment procedures for laboratories and animal facilities handling this agent.[62,63]

BSL-3 and ABSL-3 practices, containment equipment, and facilities are recommended for all manipulations of suspect cultures, animal necropsies, and for experimental animal studies. BSL-3 practices are recommended for preparatory work on cultures or contaminated materials for automated identification systems. BSL-3 practices, containment equipment, and facilities are appropriate for production operations. BSL-2 practices, containment equipment, and facilities are recommended for primary inoculation of cultures from potentially infectious clinical materials.

Special Issues

Be advised of possible misidentification using automated systems. For identification using MALDI-TOF MS, it is recommended to use alternative tube extraction that kills viable organisms and not direct spotting of plates in the open laboratory.

Select Agent *B. pseudomallei* is a Select Agent requiring registration with CDC and/or USDA for possession, use, storage and/or transfer.[64] See Appendix F for additional information.

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Campylobacter species

Campylobacters are curved, S-shaped, or spiral Gram-negative rods associated with gastrointestinal infections, bacteremia, and sepsis. Organisms are isolated from stool specimens using selective media, reduced oxygen tension, and elevated incubation temperature (43°C) for some species, or they may be detected by molecular testing of primary clinical specimens.

Occupational Infections

These organisms rarely cause Laboratory-associated infections (LAI), although laboratory-associated cases have been documented.[65–67] Infected animals are also a potential source of infection.[68]

Natural Modes of Infection

Numerous domestic and wild animals, including poultry, pets, farm animals, laboratory animals, and wild birds, are known reservoirs and are a potential source of infection for laboratory and animal care personnel. While the infective dose is not firmly established, ingestion of as few as 350–800 organisms has caused symptomatic infection.[69–71] Natural transmission usually occurs from ingestion of organisms in contaminated food such as poultry and milk products, contaminated water, or from direct contact with infected pets and farm animals—particularly exposure to cow manure.[72] Person-to-person transmission has been documented.[73] Although the illness is usually self-limiting, relapses can occur in untreated cases and in association with some immunocompromised conditions.[74] Although infection can be mild, significant complications can occur in pregnant women, including septic abortion.[75,76]

Laboratory Safety and Containment Recommendations

Pathogenic *Campylobacter* spp. may occur in fecal specimens in large numbers. *C. fetus* subsp. fetus may also be present in blood, exudates from abscesses,

tissues, and sputa. *Campylobacter* spp. can survive for many weeks in water at 4°C. The primary laboratory hazards are ingestion and parenteral inoculation of the organism. The significance of aerosol exposure is not known.

BSL-2 practices, containment equipment, and facilities are recommended for activities with cultures or potentially infectious clinical materials. ABSL-2 practices, containment equipment, and facilities are recommended for activities with naturally or experimentally infected animals.

Special Issues

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Chlamydia psittaci, C. trachomatis, C. pneumoniae

Chlamydia psittaci, C. pneumoniae, and *C. trachomatis* are the three species of *Chlamydia* known to infect humans. Alternative nomenclature may include the names *Chlamydophila pneumoniae* and *Chlamydophila psittaci*. Chlamydiae are non-motile, bacterial pathogens with obligate intracellular life cycles. These three species of *Chlamydia* vary in host spectrum, pathogenicity, and in the clinical spectrum of disease. *C. psittaci* is a zoonotic agent that commonly infects psittacine (i.e., parrot family) birds and is highly pathogenic for humans. With appropriate treatment, the mortality rate for *C. psittaci* is about 1%.[77–79] *C. trachomatis* is historically considered an exclusively human pathogen. *C. pneumoniae* is considered the least pathogenic species, often resulting in subclinical or asymptomatic infections in both animals and humans. Chlamydiae have a biphasic life cycle: elementary bodies form the extracellular stage and are infective, while the reticulate bodies are intracellular and replicate by binary fission in vacuoles.[78–80]

Occupational Infections

Chlamydial infections caused by *C. psittaci* and *C. trachomatis* lymphogranuloma venereum (LGV) strains were at one time among the commonly reported laboratory-associated bacterial infections.[36,83] In cases reported before 1955, the majority of infections were psittacosis, and these had the highest case fatality rate of laboratory-associated infectious agents.[84] The major sources of laboratory-associated psittacosis are contact with and exposure to infectious aerosols in the handling, care, or the necropsy of naturally or experimentally infected birds. Infected mice and eggs also are important sources of *C. psittaci*. Most reports of Laboratory-associated infections with *C. trachomatis* attribute the infection to inhalation of large quantities of aerosolized organisms during purification or sonification procedures. Early reports commonly attributed infections to exposure

to aerosols formed during nasal inoculation of mice or inoculation of egg yolk sacs and harvest of chlamydial elementary bodies. Infections are associated with fever, chills, malaise, and headache; a dry cough is also associated with *C. psittaci* infection. Some workers exposed to *C. trachomatis* have developed conditions including mediastinal and supraclavicular lymphadenitis, pneumonitis, conjunctivitis, and keratitis.[81,85] Seroconversion to chlamydial antigens is common and often striking; however, early antibiotic treatment may prevent an antibody response. Antibiotics are effective against chlamydial infections. A case of Laboratory-associated infection attributed to inhalation of droplet aerosols with *C. pneumoniae* has been reported.[86] There has been a report of an outbreak attributed to exposure to equine fetal membranes.[87,88] With all species of Chlamydia, occupational exposures that can lead to infection most often occur through exposure to mucosal tissues in the eyes, nose, and respiratory tract.

Natural Modes of Infection

C. psittaci is the cause of psittacosis, a respiratory infection that can lead to severe pneumonia requiring intensive care support and possible death. Sequelae include endocarditis, hepatitis, abortion, and neurological complications.[78] Natural infections are acquired by inhaling dried secretions from infected birds. Psittacine birds commonly kept as pets (e.g., parrots, parakeets, cockatiels) and poultry are most frequently involved in transmission. *C. trachomatis* can cause a spectrum of clinical manifestations including genital tract infections, inclusion conjunctivitis, trachoma, pneumonia in infants, and LGV. The LGV strains cause more severe and systemic disease than do genital strains. *C. trachomatis* genital tract infections are sexually transmitted and ocular infections (trachoma) are transmitted by exposure to secretions from infected persons through contact or fomite transmission. *C. pneumoniae* is a common cause of respiratory infection; up to 50% of adults have serologic evidence of previous exposure. Infections with *C. pneumoniae* are transmitted by droplet aerosolization and are most often mild or asymptomatic, although there is research on the possible association of this agent with chronic diseases such as atherosclerosis, asthma, and others.[82,89]

Laboratory Safety and Containment Recommendations

C. psittaci may be present in the tissues, feces, nasal secretions, and blood of infected birds, and in the blood, sputum, and tissues of infected humans. *C. psittaci* can remain infectious in the environment for months and on dry, inanimate surfaces for 15 days.[90] *C. trachomatis* may be present in genital, bubo, and conjunctival fluids of infected humans. Exposure to infectious aerosols and droplets, created during the handling of infected birds and tissues, are the primary hazards to laboratory personnel working with *C. psittaci*.[91,92] The primary laboratory hazards of *C. trachomatis* and *C. pneumoniae* are accidental parenteral inoculation and direct and indirect exposure of mucous membranes of the eyes, nose, and mouth to genital, bubo, or conjunctival fluids, cell culture

materials, and fluids from infected cell cultures or eggs. Infectious aerosols, including those that may be created as a result of centrifugation, also pose a risk for infection.

BSL-3 practices and containment equipment are recommended for activities involving work with cultures, specimens, or clinical isolates known to contain or be potentially infected with the LGV serovars (L1 through L3) of *C. trachomatis*. BSL-3 practices, containment equipment, and facilities are indicated for activities with high potential for droplet or aerosol production and for activities involving large quantities or concentrations of infectious materials.

BSL-3 practices, containment equipment, and facilities are also recommended for activities involving the necropsy of infected birds and the diagnostic examination of tissues or cultures known to contain or be potentially infected with *C. psittaci* strains of avian origin. Wetting the feathers of infected birds with a detergent-disinfectant prior to necropsy can appreciably reduce the risk of aerosols of infected feces and nasal secretions on the feathers and external surfaces of the bird. ABSL-3 practices, containment equipment, and facilities and respiratory protection are recommended for personnel working with naturally or experimentally infected caged birds.

Activities involving non-avian strains of *C. psittaci* may be performed in a BSL-2 facility as long as BSL-3 practices are followed. Laboratory work with the LGV serovars of *C. trachomatis* can be conducted in a BSL-2 facility as long as BSL-3 practices are followed when handling potentially infectious materials.

BSL-2 practices, containment equipment, and facilities are recommended for personnel working with clinical specimens and cultures or other materials known or suspected to contain the ocular or genital serovars of *C. trachomatis* or *C. pneumoniae*. ABSL-2 practices, containment equipment, and facilities are recommended for activities with animals that have been experimentally infected with genital serovars of *C. trachomatis* or *C. pneumoniae*.

Special Issues

C. trachomatis genital infections are reportable infectious diseases.

Vaccines There are no human vaccines against *Chlamydia* spp.

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Clostridium botulinum and neurotoxin-producing species of Clostridia

Clostridium botulinum, and rare strains of *C. baratii* and *C. butyricum*, are anaerobic, spore-forming, Gram-positive bacilli that cause botulism, a life-threatening foodborne illness. The pathogenicity of these organisms results from the production of botulinum toxin under anaerobic conditions in which *C. botulinum* spores germinate. Please refer to Botulinum neurotoxins in Section VIII-G for biosafety guidance in handling toxin preparations.

Laboratory Safety and Containment Recommendations

Neurotoxin producing Clostridia species or its toxin may be present in a variety of food products, clinical materials (serum, feces), and environmental samples (soil, surface water) handled in the laboratory.[93] In addition, bacterial cultures may produce very high levels of toxin.[94] In healthy adults, it is typically the toxin and not the organism that causes disease. Risk of laboratory exposure is primarily due to the presence of the toxin, as opposed to infection from the organism that produces the toxin. Toxin exposure may occur through ingestion, contact with non-intact skin or mucosal membranes, or inhalation. Although spore-forming, there is no known risk from spore exposure except for the potential presence of residual toxin associated with pure spore preparations. It is recommended to use laboratory safety protocols that focus on the prevention of accidental exposure to the toxin produced by these Clostridia species.

BSL-3 practices and containment are recommended for activities with a high potential for aerosol or droplet production or for those requiring routine handling of larger quantities of the organism or toxin. ABSL-2 and BSL-2 practices, containment equipment, and facilities are recommended for diagnostic studies and titration of toxin. Before the collection of specimens, it is recommended to call the designated public health laboratory regarding any case of suspected botulism for guidance on diagnosis, treatment, specimen collection, and investigation.[95] BSL-2 practices, containment equipment, and facilities are recommended for activities that involve the organism or the toxin including the handling of potentially contaminated food.[96]

Special Issues

Select Agent Neurotoxin-producing Clostridia species are Select Agents requiring registration with CDC and/or USDA for possession, use, storage and/or transfer. See Appendix F for additional information. See the *C. botulinum* Toxin Agent Summary Statement in Section VIII-G and Appendix I for additional information.

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent or its toxin to another country. See Appendix C for additional information.

Clostridioides (formerly *Clostridium*) *difficile*

Clostridioides (formerly *Clostridium*) *difficile* is a Gram-positive, spore-forming, obligate anaerobic bacillus, and it is the most common cause of infectious diarrhea in hospitalized patients.[97] The incidence of infection in the United States has increased dramatically since 2000. There were a half a million cases and 29,000 deaths reported in the United States in 2011.[98] Increases in incidence have also been observed worldwide.[99] Clinical presentations range from asymptomatic colonization to mild self-limiting diarrhea to fulminant pseudomembranous colitis, toxic megacolon, and multi-organ failure, requiring emergency colectomy.[100] Because individuals may be asymptomatically colonized with toxigenic or non-toxigenic strains of *C. difficile*, testing in the clinical diagnostic laboratory may involve one of several one, two, or three-step algorithms in an attempt to optimize sensitivity and specificity. Tests include enzyme immunoassays for free toxin or glutamate dehydrogenase, toxigenic culture, and nucleic acid amplification tests for toxin.[101]

Occupational Infections

There is a report of laboratory-associated *C. difficile* infection based on a clinical laboratory survey,[102] but cases are rare.

Natural Modes of Infection

Transmission is primarily via the fecal-oral route through hand-to-hand contact. Airborne environmental dispersal is also a route of transmission.[103,104] Most infections present during or shortly after a course of antimicrobial therapy, which disrupts the intestinal microbial composition, permitting *C. difficile* colonization and toxin production. Clindamycin, other macrolides, third-generation cephalosporins, penicillins, and fluoroquinolones are frequently associated with *C. difficile* infection.[105] Between 20–35% of patients fail initial therapy, and 60% of patients with multiple prior recurrences will fail subsequent therapy. Fecal transplantation has become a successful therapeutic option for many patients.[106,107] Asymptomatic colonization in neonates and infants (<2 years) is quite common. There is concern for an increasing incidence in children beyond this age.[108] *C. difficile* virulence factors include the exotoxins TcdA and TcdB, which bind to receptors on epithelial cells. NAP1, PCR ribotype 027 is a hypervirulent strain of *Clostridioides difficile*, which also contains a binary toxin (CDT) and a deletion in the tcdC gene that affects the production of toxins.[100] It is characterized by high-level fluoroquinolone resistance, efficient sporulation, enhanced cytotoxicity, and high toxin production. There is an associated higher mortality rate, as patients are more likely to develop life-threatening complications.[109,110] Infection or asymptomatic carriage can also occur in domestic, farm, and wild animals. *C. difficile* can be recovered from retail meats.[104]

Laboratory Safety and Containment Recommendations

Infectious fecal specimens are the most common *C. difficile*-containing specimens received in the laboratory. Endospores of *C. difficile* are impervious to desiccation, temperature fluctuations, freezing, irradiation, and many antiseptic solutions, including alcohol-based gels and quaternary ammonium-based agents.[106] Spores can survive in the environment for months to years.[104] Guidelines are available for management of healthcare-associated infections due to *C. difficile* and for cleaning to reduce the spread of the organism.[111]

BSL-2 practices, containment equipment, and facilities are recommended for all activities utilizing known or potentially infected clinical materials or cultures. ABSL-2 facilities are recommended for studies utilizing infected laboratory animals.

Special Issues

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Clostridium tetani and Tetanus toxin

Clostridium tetani is an anaerobic, endospore-forming, Gram-positive rod found in the soil and is an intestinal tract commensal. It produces a potent neurotoxin, tetanospasmin, which causes tetanus, an acute neurologic condition characterized by painful muscular contractions. Tetanospasmin is an exceedingly potent protein toxin that consists of a heavy chain subunit that binds the toxin to receptors on neuronal cells and a light chain subunit that blocks the release of inhibitory neural transmitter molecules within the central nervous system. The incidence of tetanus in the United States has declined steadily since the introduction of tetanus toxoid vaccines in the 1940s.[112,113]

Occupational Infections

Although the risk of infection to laboratory personnel is low, there have been some incidents of laboratory personnel exposure recorded.[84,114]

Natural Modes of Infection

Contamination of wounds by soil is the usual mechanism of transmission for tetanus. Of the 233 cases of tetanus reported to CDC from 1998 through 2000, acute injury (puncture, laceration, abrasion) was the most frequent predisposing condition. Elevated incidence rates also were observed for persons aged over 60 years, diabetics, and intravenous drug users.[112,113] When introduced into a suitable anaerobic or microaerophilic environment, *C. tetani* spores germinate

and produce tetanospasmin. The incubation period ranges from three to 21 days. The observed symptoms are primarily associated with the presence of the toxin. Wound cultures are not generally useful for diagnosing tetanus.[95,115] Tetanus is a medical emergency and immediate treatment with human tetanus immune globulin is indicated.[113]

Laboratory Safety and Containment Recommendations

The organism may be found in soil, intestinal, or fecal samples. Accidental parenteral inoculation of the toxin is the primary hazard to laboratory personnel. Because it is uncertain if tetanus toxin can be absorbed through mucous membranes, the hazards associated with aerosols and droplets remain unclear.

BSL-2 practices, containment equipment, and facilities are recommended for activities involving the manipulation of cultures or toxins. ABSL-2 practices, containment equipment, and facilities are recommended for animal studies.

Special Issues

Vaccines It is recommended that vaccination status be considered in a risk assessment for work with this organism and/or toxin. While the risk of laboratory-associated tetanus is low, vaccination is recommended for some following risk assessment, and review of the current recommendations of the ACIP.[116]

Transfer of Agent Importation of this agent or its toxin may require CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Corynebacterium diphtheriae

Corynebacterium diphtheriae is a pleomorphic, Gram-positive rod that is isolated from the nasopharynx and skin of humans. The organism will grow on media containing 5% sheep blood, but it is recommended that primary plating include one selective agar such as cysteine-tellurite blood agar or fresh Tinsdale media incubated in 5% CO2-enriched atmosphere to separate from normal oral flora.[117] *C. diphtheriae* produces a potent exotoxin and is the causative agent of diphtheria, one of the most widespread bacterial diseases of the pre-vaccine era. The exotoxin gene is found on the beta-corynebacteriophage, which can infect non-toxigenic strains of *C. ulcerans* or *C. pseudotuberculosis*, leading to the production of toxin by these species.[118]

Occupational Infections

Laboratory-associated infections with *C. diphtheriae* have been documented.[84,119] Zoonotic infections with *C. diphtheriae* have not been recorded. *C. ulcerans* is a zoonotic pathogen that has been cultured from untreated milk and companion animals and infrequently associated with toxic infections in humans.[120,121]

Inhalation, accidental parenteral inoculation, and ingestion are the primary laboratory hazards.

Natural Modes of Infection

The agent may be present in exudates or secretions of the nose, throat (tonsil), pharynx and larynx, in wounds, blood, and on the skin. *C. diphtheriae* can be present for weeks to months in the nasopharynx and skin lesions of infected individuals and for a lifetime in asymptomatic individuals. *C. diphtheriae* can survive for up to six months on dry inanimate surfaces. Travel to endemic areas or close contact with persons who have returned recently from such areas increases risk.[122] Transmission usually occurs via direct contact with patients or carriers, and more rarely, with articles such as clothing contaminated with secretions from infected people. Naturally occurring diphtheria is characterized by the development of grayish-white, membranous lesions involving the tonsils, pharynx, larynx, or nasal mucosa. Systemic sequelae are associated with the production of diphtheria toxin, and the toxic dose of diphtheria toxin in humans is <100 ng per kg body weight.[123] An effective vaccine is available for diphtheria, and this disease has become a rarity in countries with vaccination programs.

Laboratory Safety and Containment Recommendations

BSL-2 practices, containment equipment, and facilities are recommended for all activities utilizing known or potentially infected clinical materials or cultures. ABSL-2 facilities are recommended for studies utilizing infected laboratory animals.

Special Issues

Vaccines A licensed vaccine is available. The reader is advised to consult the current recommendations of the ACIP.[124] While the risk of laboratory-associated diphtheria is low, the administration of an adult diphtheria-tetanus toxoid at ten-year intervals may further reduce the risk of illness to laboratory and animal care personnel.[124]

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Francisella tularensis

Francisella tularensis is a small, Gram-negative coccobacillus that infects numerous animal species, especially lagomorphs (including rabbits); it is the causal agent of tularemia (Rabbit fever, Deer fly fever, Ohara disease, or Francis disease) in humans. *F. tularensis* can be divided into three subspecies: *F. tularensis* (Type A), *F. holarctica* (Type B), and *F. mediasiatica*. *F. tularensis* subsp. novicida is now considered to be a separate species and referred to as

F. novicida. Type A and Type B strains are highly infectious, requiring only 10–50 organisms to cause disease, and are the main cause of tularemia worldwide.[125] The overall fatality rate of infections is <2%, but can be up to 24% for particular strains.[126] Person-to-person transmission of tularemia has not been documented. The incubation period varies with the virulence of the strain, dose, and route of introduction, but ranges from 1–14 days with most cases exhibiting symptoms in three to five days.[127] Symptoms include sudden fever, chills, headaches, diarrhea, muscle aches, joint pain, dry cough, and progressive weakness, with possible development of pneumonia. Other symptoms may include skin or mouth ulcers, swollen and painful lymph nodes, sore throat, and swollen, painful eyes.

Occupational Infections

Tularemia has been a commonly reported laboratory-associated bacterial infection.[84,128] Most cases have occurred at facilities involved in tularemia research; however, cases have been reported in diagnostic laboratories as well. Occasional cases are linked to work with naturally or experimentally infected animals or their ectoparasites.

Natural Modes of Infection

Arthropod bites (e.g., tick, deer fly, horse fly, mosquito), handling or ingesting infectious animal tissues or fluids, ingestion of contaminated water or food, and inhalation of infective aerosols are the primary transmission modes in nature. Occasionally, infections have occurred from bites or scratches by carnivores with contaminated mouthparts or claws.

Laboratory Safety and Containment Recommendations

The agent may be present in lesion exudates, respiratory secretions, CSF, blood or lymph node aspirates from patients, tissues from infected animals, fluids from infected animals, and fluids from infected arthropods. Direct contact of skin or mucous membranes with infectious materials, accidental parenteral inoculation, ingestion, and exposure to aerosols and infectious droplets have resulted in infection. Infection has been more commonly associated with cultures than with clinical materials and infected animals.[128] According to the Public Health Agency of Canada's (PHAC) Pathogen Safety Data Sheet for *F. tularensis*, the agent can survive for months to years in carcasses, organs, and straw. Additional information is available at https://www.canada.ca/en/public-health/services/laboratory-biosafety-biosecurity/pathogen-safety-data-sheets-risk-assessment/francisella-tularensis-material-safety-data-sheets-msds.html.

BSL-3 and ABSL-3 practices, containment equipment, and facilities are recommended for all manipulations of suspect cultures, animal necropsies, and for experimental animal studies. BSL-3 practices are recommended for preparatory work prior to the use of automatic instruments that involves manipulation of

cultures. Characterized strains of reduced virulence such as LVS and SCHU S4ΔclpB can be handled with BSL-2 practices. *F. novicida* strains can also be handled with BSL-2 practices. BSL-2 practices, containment equipment, and facilities are recommended for initial activities involving clinical materials of human or animal origin suspected to contain *F. tularensis*.

Special Issues

Be advised of possible misidentification using automated systems. For identification of samples suspected of containing *F. tularensis* using MALDI-TOF MS, it is recommended to use alternative tube extraction that kills viable organisms and not direct spotting of plates in the open laboratory.

Vaccines A vaccine for tularemia is under review by the Food and Drug Administration and is not currently available in the United States.[130]

Select Agent *F. tularensis* is a Select Agent requiring registration with CDC and/or USDA for possession, use, storage and/or transfer. See Appendix F for additional information.

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Helicobacter species

Helicobacter species are spiral or curved, Gram-negative rods isolated from gastrointestinal and hepatobiliary tracts of mammals and birds. There are currently 37 recognized species, including at least 14 isolated from humans. *Helicobacter pylori* is the main cause of peptic ulcer disease and a major risk factor for gastric cancer. The main habitat of *H. pylori* is the human gastric mucosa. Other *Helicobacter* spp. (*H. cinaedi*, *H. canadensis*, *H. canis*, *H. pullorum*, and *H. fennelliae*) may cause asymptomatic infection as well as proctitis, proctocolitis, enteritis and extraintestinal infections in humans.[131] Prevalence of *H. pylori* infection is decreasing worldwide, but infection is higher in certain ethnic groups and in migrants.[132]

Occupational Infections

Both experimental and accidental LAIs with *H. pylori* have been reported.[133,134] Ingestion is the primary known laboratory hazard. The importance of aerosol exposures is unknown.

Natural Modes of Infection

Chronic gastritis and duodenal ulcers are associated with *H. pylori* infection. Epidemiologic associations have also been made with gastric adenocarcinoma.[135]

Human infection with *H. pylori* may be long in duration with few or no symptoms or may present as an acute gastric illness. Transmission, while incompletely understood, is thought to be by the fecal-oral or oral-oral route.

Laboratory Safety and Containment Recommendations

H. pylori may be present in gastric and oral secretions and stool. The enterohepatic *Helicobacter* spp. (e.g., *H. canadensis*, *H. canis*, *H. cinaedi*, *H. fennelliae*, *H. pullorum*, and *H. winghamensis*) may be isolated from stool specimens, rectal swabs, and blood cultures.[131] It is recommended to incorporate processes for containment of potential aerosols or droplets into procedures involving homogenization or vortexing of gastric specimens.[136]

BSL-2 practices, containment equipment, and facilities are recommended for activities with clinical materials and cultures known to contain or potentially contain the *Helicobacter* spp. ABSL-2 practices, containment equipment, and facilities are recommended for activities with experimentally or naturally infected animals.

Special Issues

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

***Legionella pneumophila* and other *Legionella* spp.**

Legionella spp. are small, faintly staining, Gram-negative bacteria. They are obligately aerobic, slow-growing, nonfermentative organisms that have a unique requirement for L-cysteine and iron salts for in vitro growth. Legionellae are readily found in natural aquatic bodies and some species (*L. longbeachae*) have been recovered from soil.[137,138] They are able to colonize hot-water tanks at a temperature range from 40 to 50°C. There are currently 59 known *Legionella* species, three subspecies, and over 70 distinct serogroups of Legionella. While 30 species are known to cause human infection, the most frequent cause of human infection is *L. pneumophila* serogroup 1.[137]

Occupational Infections

Although laboratory-associated cases of legionellosis have not been reported in the literature, at least one case due to presumed aerosol or droplet exposure during animal challenge studies with *L. pneumophila* has been recorded.[139] There has been one reported case of probable human-to-human transmission of *Legionella* spp.[140]

Natural Modes of Infection

Legionella is commonly found in environmental sources, typically in man-made, warm water systems. The mode of transmission from these reservoirs is aerosolization, aspiration, or direct inoculation into the airway.[137] *Legionella* spp. may be present in amoebae from contaminated water. *Legionella* spp. have the ability to persist outside of hosts in biofilms, surviving for months in distilled water and for over a year in tap water.[141] The spectrum of illness caused by *Legionella* species ranges from a mild, self-limited, flu-like illness (Pontiac fever) to a disseminated and often fatal disease characterized by pneumonia and respiratory failure (Legionnaires' disease). Although rare, *Legionella* has been implicated in cases of sinusitis, cellulitis, pericarditis, and endocarditis.[138] Legionellosis may be either community-acquired or nosocomial. Risk factors include smoking, chronic lung disease, and immunosuppression. Surgery, especially involving transplantation, has been implicated as a risk factor for nosocomial transmission.

Laboratory Safety and Containment Recommendations

The agent may be present in respiratory tract specimens (i.e., sputum, pleural fluid, bronchoscopy specimens, lung tissue) and in extrapulmonary sites. A potential hazard may exist for the generation of aerosols containing high concentrations of the agent.

For activities likely to produce extensive aerosols or when large quantities of *Legionella* spp. are manipulated, BSL-2 with BSL-3 practices are recommended. BSL-2 practices, containment equipment, and facilities are recommended for all activities involving materials or cultures suspected or known to contain *Legionella* spp.

ABSL-2 practices, containment equipment, and facilities are recommended for activities with experimentally-infected animals. Routine processing of environmental water samples for *Legionella* may be performed with standard BSL-2 practices.

Special Issues

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Leptospira

The genus *Leptospira* is composed of spiral-shaped bacteria with hooked ends. Leptospires are ubiquitous in nature; they are either free-living in freshwater or associated with renal infection in animals. Historically, these organisms have been classified into pathogenic (*L. interrogans*) and saprophytic (*L. biflexa*)

groups, but recent studies have identified more than 21 species based on genetic analysis, nine of which are definitive pathogens.[142] These organisms also have been characterized serologically, with more than 200 pathogenic and 60 saprophytic serovars identified.[142] These organisms are the cause of leptospirosis, a zoonotic disease of worldwide distribution. Growth of leptospires in the laboratory requires specialized media and culture techniques, and cases of leptospirosis are usually diagnosed by serology.

Occupational Infections

Leptospirosis is a well-documented, laboratory hazard. In older literature, 70 LAIs and ten deaths have been reported.[36,84] Direct and indirect contact with fluids and tissues of experimentally or naturally infected mammals during handling, care, or necropsy are potential sources of infection.[143,144] A laboratory-associated case caused by percutaneous exposure to broth cultures of *Leptospira* was reported in 2004.[145] It is important to remember that rodents are natural carriers of leptospires. Animals with chronic renal infection shed large numbers of leptospires in the urine continuously or intermittently for long periods of time. *Leptospira* spp. may persist for weeks in soil contaminated with infected urine. Rarely, infection may be transmitted by bites of infected animals.[143]

Natural Modes of Infection

Human leptospirosis typically results from direct contact with infected animals, contaminated animal products, or contaminated water sources. Common routes of infection are abrasions, cuts in the skin or via the conjunctiva. Higher rates of infection are observed in agricultural workers and workers in other occupations associated with animal contact. Human-to-human transmission is rare. Leptospirosis can cause the following symptoms: fever, headache, chills, muscle aches, vomiting, jaundice, red eyes, abdominal pain, diarrhea, and rash. After an initial phase of illness, the patient may recover, then become ill again with another more severe phase that can involve kidney failure, liver failure, or meningitis (Weil's Disease).[146]

Laboratory Safety and Containment Recommendations

The organism may be present in urine, blood, and tissues of infected animals and humans. Asymptomatic infection may occur in carrier animals and humans. Ingestion, parenteral inoculation, and direct and indirect contact of skin or mucous membranes, particularly the conjunctiva, with cultures or infected tissues or body fluids are the primary laboratory hazards. The importance of aerosol exposure is unclear, but occasional cases of inhalation of droplets of urine or water have been suspected.[147]

BSL-2 practices, containment equipment, and facilities are recommended for all activities involving the use or manipulation of known or potentially infective

tissues, body fluids, and cultures. ABSL-2 practices are recommended for the housing and manipulation of infected animals.

Special Issues

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Listeria monocytogenes

Listeria monocytogenes is a Gram-positive, catalase-positive, non-spore forming, aerobic bacillus that is weakly beta-hemolytic on sheep blood agar.[148] The organism has been isolated from soil, animal feed (silage), and a wide range of human foods and food processing environments. It may also be isolated from symptomatic/asymptomatic animals (particularly ruminants) and humans.[149] This organism is the causative agent of listeriosis, a foodborne disease of humans and animals.

Occupational Infections

Cutaneous listeriosis, characterized by pustular or papular lesions on the arms and hands, has been described in veterinarians and farmers.[150] Asymptomatic carriage has been reported in laboratorians.[151]

Natural Modes of Infection

Most human cases of listeriosis result from eating contaminated foods, notably soft cheeses, ready-to-eat meat products (e.g., hot dogs, luncheon meats), pâté, and smoked fish/seafood.[149] Listeriosis can present in healthy adults with symptoms of fever and gastroenteritis; pregnant women and their fetuses; newborns; and persons with impaired immune function are at greatest risk of developing severe infections including sepsis, meningitis, and fetal demise. In pregnant women, *L. monocytogents* infections occur most often in the third trimester and may precipitate labor. Transplacental transmission of *L. monocytogenes* poses a grave risk to the fetus.[152]

Laboratory Safety and Containment Recommendations

Listeria monocytogenes may be found in feces, CSF, and blood, as well as numerous food and environmental samples.[149] *L. monocytogenes* is somewhat heat-resistant, can tolerate (and replicate in) cold temperatures, can survive at low pH conditions, and can be resistant to some disinfectants such as quaternary ammonium compounds.[153,154] Naturally or experimentally infected animals are a source of exposure to laboratory workers, animal care personnel, and other animals. While ingestion is the most common route of exposure, Listeria can also cause eye and skin infections following direct contact with the organism.

BSL-2 practices, containment equipment, and facilities are recommended when working with clinical specimens and cultures known or suspected to contain Listeria. ABSL-2 practices, containment equipment, and facilities are recommended for activities involving experimentally or naturally infected animals. Due to potential risks to the fetus, it is recommended that pregnant women be advised of the risk of exposure to *L. monocytogenes*.

Special Issues

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Mycobacterium leprae

Mycobacterium leprae is a Gram-positive bacterium and is the causative agent of leprosy, also called Hansen's disease. *M. leprae* are intracellular bacteria that cannot be cultured using laboratory medium. Bacteria can be recovered from infected tissues and propagated in laboratory animals, specifically the nine-banded armadillo. *M. lepromatosis* are related bacteria that have now been identified to cause similar disease.[155]

Occupational Infections

There are no cases of occupational acquisition of *M. leprae* reported as a result of working in a laboratory or being in contact with clinical materials of human or animal origin.

Natural Modes of Infection

Leprosy is transmitted from person-to-person following prolonged exposure, presumably via contact with respiratory secretions from infected individuals or animals. Naturally-occurring leprosy has been reported in armadillos, with both humans and armadillos recognized as reservoirs for infection.[156,157] Although transmission from armadillos to humans has not been definitively proven, it is likely since contact with armadillos is a significant risk factor for acquisition of human disease.[158,159] Cases in the United States have recently been seen in Texas, Florida, and Louisiana.[160,161] Endemic animal forms of the disease have been described due to related organisms.[162]

Laboratory Safety and Containment Recommendations

M. leprae may be present in tissues and exudates from lesions of infected humans and experimentally or naturally infected animals. Direct contact of the skin and mucous membranes with infectious materials and parenteral inoculation are the primary potential laboratory hazards associated with handling infectious clinical materials.

Selection of an appropriate disinfectant is an important consideration for laboratories working with mycobacteria. See Appendix B for additional information.

BSL-2 practices, containment equipment, and facilities are recommended for all activities with known or potentially infectious materials from humans and animals. It is recommended to use extraordinary care to avoid accidental parenteral inoculation with contaminated sharp instruments. ABSL-2 practices, containment equipment, and facilities are recommended for animal studies utilizing rodents, armadillos, and NHPs.

Special Issues

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Mycobacterium tuberculosis complex

The *Mycobacterium tuberculosis* complex includes the species *M. tuberculosis*, *M. bovis, M. africanum, M. caprae, M. microti, M. canettii, M. pinnipedii*, and the recently described species *M. mungi* and *M. orygis*.[163,164] *M. tuberculosis* grows slowly, typically requiring several weeks for formation of colonies on solid media. Incubation in broth culture can at times reduce the incubation time to less than one week if the inoculum is sufficient.[163] The organism has a thick, lipid-rich cell wall that renders bacilli resistant to harsh treatments including alkali and detergents. Mycolic acid in the cell wall results in a positive acid-fast stain.

Occupational Infections

M. tuberculosis and *M. bovis* infections are a proven hazard to laboratory personnel and others who may be exposed to infectious aerosols in the laboratory, autopsy rooms, and other healthcare facilities.[36,84,165–169] The incidence of tuberculosis in health care personnel working with *M. tuberculosis*-infected patients has been reported to be significantly higher than that of those not working with the agent.[170] Multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains are of particular concern.[109,171] Naturally or experimentally infected NHPs are a proven source of human infection.[172] Experimentally-infected guinea pigs and mice do not pose the same hazard because droplet nuclei are not produced by coughing in these species; however, litter from infected animal cages may become contaminated and serve as a source of infectious aerosols.

Natural Modes of Infection

M. tuberculosis is the etiologic agent of tuberculosis, a leading cause of morbidity and mortality worldwide. Infectious aerosols produced by coughing spread disease from person to person. Some individuals will develop active disease

within months of infection, and some of those will clear the infection completely. Others will achieve immunological control with latent (but viable) organisms, with potential for reactivation later upon immunosuppression. Approximately 5–10% of latent infections progress to active infections. The primary focus of infection is the lungs, but extra-pulmonary disease does occur, primarily in immunocompromised individuals. Miliary (disseminated) tuberculosis has the most serious consequences with meningitis developing in 50% of cases, along with a high fatality rate if not treated effectively. HIV infection is a serious risk factor for the development of active disease. *M. bovis* is primarily found in animals but can also infect humans. It is spread to humans, primarily children, by consumption of non-pasteurized milk and dairy products, by handling of infected carcasses, or by inhalation. Human-to-human transmission of *M. bovis* via aerosols is possible.

Laboratory Safety and Containment Recommendations

Tubercle bacilli may be present in sputum, gastric lavage fluids, CSF, urine, and in a variety of tissues. Exposure to laboratory-generated aerosols is the most important laboratory hazard encountered. Tubercle bacilli may survive in heat-fixed smears and, if present, may be aerosolized in the preparation of frozen tissue sections.[171] Because of the low infective dose of *M. tuberculosis* (<10 bacilli), it is recommended that sputa and other clinical specimens from suspected or known cases of tuberculosis be considered potentially infectious and handled with appropriate precautions. Mycobacteria can be resistant to disinfection and may survive on inanimate surfaces for long periods. Needlesticks are also a recognized hazard. Selection of an appropriate disinfectant is an important consideration for laboratories working with mycobacteria. See Appendix B for additional information.

BSL-3 practices, containment equipment, and facilities are recommended for laboratory activities in the propagation and manipulation of cultures of any of the subspecies of the *M. tuberculosis* complex. Use of a slide-warming tray, rather than a flame, is recommended for fixation of slides. ABSL-3 practices are recommended for animal studies using experimentally or naturally infected NHPs or immunocompromised mice, as high titers may be found in organs from immunocompromised animals. Animal studies using rodents (e.g., guinea pigs, rats, rabbits, mice) can be conducted at ABSL-2 with ABSL-3 practices.[174] All airborne infections of rodents using *M. tuberculosis* must be performed in an appropriate ABSL-3 laboratory.

BSL-2 practices and procedures, containment equipment, and facilities are recommended for non-aerosol-producing manipulations of clinical specimens. Manipulation of small quantities of the attenuated vaccine strain *M. bovis* Bacillus Calmette-Guérin (BCG) can be performed at BSL-2 in laboratories that do not

culture *M. tuberculosis* and do not have BSL-3 facilities. However, considerable care is suggested to verify the identity of the strain and to ensure that cultures are not contaminated with virulent *M. tuberculosis* or other *M. bovis* strains.

Special Issues

Be advised of possible misidentification using automated systems. For identification using MALDI-TOF MS, it is recommended to use alternative tube extraction that kills viable organisms in the BSC, and not direct spotting of plates in the open laboratory.

Surveillance Annual or semi-annual skin testing with purified protein derivative (PPD) or FDA-approved Interferon-Gamma Release Assay (IGRA) of previously skin-test-negative personnel can be used as a surveillance procedure.[175]

Vaccines The attenuated live BCG is available and used in other countries but is not generally recommended for use in the United States.

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Mycobacterium spp. other than *M. tuberculosis* complex and *M. leprae*

There are over 150 *Mycobacterium* species including both slowly and rapidly growing species.[163] In the past, mycobacterial isolates that were not identified as *M. tuberculosis* complex were often called atypical mycobacteria, but these are now more commonly referred to as nontuberculous mycobacteria (NTM) or mycobacteria other than tuberculosis (MOTT). The majority of mycobacterial species are common environmental organisms. There has been a perceived increase in NTM isolated from hospitalized patients over the past 20 years.[176,177] Approximately 25 species are associated with human infections, with a number of additional species associated with infections in immunocompromised persons.[178] All of these species are considered opportunistic pathogens in humans, and they are not considered generally communicable; however, there is evidence of transmission between some individuals with chronic diseases.[179] The most common types of infections and causes are:

1. Pulmonary disease with a clinical presentation resembling tuberculosis caused by *M. kansasii, M. avium*, and *M. intracellulare*;
2. Lymphadenitis associated with *M. avium, M. scrofulaceum*, and other rapidly growing mycobacteria;[180]
3. Disseminated infections in immunocompromised individuals caused by *M. avi*um and *M. intracellulare*;

4. Pulmonary infection or colonization of patients with cystic fibrosis caused by *M. avium* complex, *M. kansasii, M. abscessus*, and other rapidly growing mycobacteria;[181,182] and
5. Skin ulcers and soft tissue wound infections including Buruli ulcer caused by *M. ulcerans*, granulomas caused by *M. marinum* associated with exposure to organisms in freshwater and saltwater and fish tanks, and tissue infections resulting from trauma or surgical procedures caused by *M. fortuitum, M. chelonae*, and *M. abscessus*.

Occupational Infections

A Laboratory-associated infection with *Mycobacterium* spp. other than *M. tuberculosis* complex was reported when a laboratory worker injected bacteria into his thumb while performing experiments on mice.[183]

Natural Modes of Infection

Person-to-person transmission is not considered common, but there is evidence for transmission in some populations.[179] Presumably, pulmonary infections are most often the result of inhalation of aerosolized bacilli, most likely from the surface of contaminated water. Mycobacteria are widely distributed in the environment and in animals, and zoonoses have occurred.[184,185] They are also common in potable water supplies, perhaps as the result of the formation of biofilms.

Laboratory Safety and Containment Recommendations

Various species of mycobacteria may be present in sputa, exudates from lesions, tissues, and in environmental samples. Mycobacteria can be resistant to disinfection and survive on inanimate surfaces and for long periods in natural and tap water sources. Direct contact of skin or mucous membranes with infectious materials, ingestion, and parenteral inoculation are the primary laboratory hazards associated with clinical materials and cultures. Aerosols created during the manipulation of broth cultures or tissue homogenates of these organisms also pose a potential infection hazard.

BSL-2 practices, containment equipment, and facilities are recommended for activities with clinical materials and cultures of *Mycobacterium* other than *M. tuberculosis* complex. Clinical specimens may also contain *M. tuberculosis* and laboratory workers are advised to exercise caution to ensure the correct identification of mycobacterial isolates. Special caution is recommended in handling *M. ulcerans* and *M. marinum* to avoid skin exposure. ABSL-2 practices, containment equipment, and facilities are recommended for animal studies. Selection of an appropriate tuberculocidal disinfectant is an important consideration for laboratories working with mycobacteria. See Appendix B for additional information.

Special Issues

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Neisseria gonorrhoeae

Neisseria gonorrhoeae is a Gram-negative, oxidase-positive diplococcus associated with gonorrhea, a sexually transmitted disease of humans. The organism may be isolated from clinical specimens and cultivated in the laboratory using specialized growth media.[186] Infection is often diagnosed using molecular methods on direct clinical specimens.

Occupational Infections

Laboratory-associated gonococcal infections have been reported in the United States and elsewhere.[187–189] These infections have presented as conjunctivitis, with either direct finger-to-eye contact or exposure to splashes of either liquid cultures or contaminated solutions proposed as the most likely means of transmission.

Natural Modes of Infection

Gonorrhea is a sexually transmitted disease of worldwide importance. The 2016 rate of reported infection for this disease in the United States was 145.8 per 100,000 population, a steady increase from a low of 98.1 infections per 100,000 population recorded in 2009.[191] The natural mode of infection is through direct contact with exudates from mucous membranes of infected individuals. This usually occurs by sexual activity, although newborns may also become infected during birth.[186]

Laboratory Safety and Containment Recommendations

The agent may be present in conjunctival, urethral and cervical exudates, synovial fluid, urine, feces, blood, and CSF. Parenteral inoculation and direct or indirect contact of mucous membranes with infectious clinical materials are known primary laboratory hazards. Laboratory-associated illness due to aerosol transmission has not been documented.

Additional primary containment and personnel precautions such as those described for BSL-3 may be indicated when there is high risk of aerosol or droplet production and for activities involving production quantities or high concentrations of infectious materials. BSL-2 practices, containment equipment, and facilities are recommended for all activities involving the use or manipulation of clinical materials or cultures. Animal studies may be performed at ABSL-2.

Special Issues

Neisseria gonorrhoeae has gained resistance to several classes of antimicrobials over the last few decades, making the organism increasingly difficult to treat. Fluoroquinolones, oral cephalosporins such as cefixime, and doxycycline are no longer recommended for treatment of uncomplicated gonorrhea. An extensively drug-resistant (XDR) strain has been reported and is being monitored, and currently, there are no other effective treatments for XDR gonorrhea.[192]

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Neisseria meningitidis

Neisseria meningitidis is a Gram-negative diplococcus which can cause serious invasive bacterial infections, with clinical manifestations including serious acute meningitis and septicemia in humans. Virulence is associated with the expression of a polysaccharide capsule. Among the thirteen defined *N. meningitidis* capsular serogroups, six are the main causes of invasive meningococcal disease (serogroups A, B, C, W, X and Y). The handling of *N. meningitidis* isolates, particularly from sterile body sites, and/or clinical specimens containing live *N. meningitidis* may increase the risk of transmission for microbiologists.[193]

Occupational Infections

Manipulating suspensions of *N. meningitidis* outside a BSC is associated with a high risk for contracting meningococcal disease.[193,194] Microbiologists have been shown to have a much higher infection rate compared to that of the United States' general population aged 30–59 years, and a case fatality rate of 50%—substantially higher than the 12–15% associated with disease among the general population. Almost all the microbiologists identified as having an LAI had manipulated invasive *N. meningitidis* isolates on an open laboratory bench.[195] Rigorous protection from droplets or aerosols (including the use of a BSC) is recommended when microbiological procedures are performed on all *N. meningitidis* isolates. Although there are some molecular assays that can detect *N. meningitidis* directly in clinical specimens, cultures are still routinely performed.

Natural Modes of Infection

The human upper respiratory tract is the natural reservoir for *N. meningitidis*. Invasion of organisms from the respiratory mucosa into the circulatory system causes infection that can range in severity from subclinical to fulminant fatal disease. Transmission occurs from person-to-person and is usually mediated by direct contact with respiratory droplets from infected individuals.

Laboratory Safety and Containment Recommendations

N. meningitidis may be present in pharyngeal exudates, CSF, blood, saliva, sterile body sites (most commonly CSF and blood), and in rare cases, urine or urethral (genital) discharge. Parenteral inoculation, droplet exposure of mucous membranes, infectious aerosol generation and ingestion are the primary hazards to laboratory personnel. Based on the mechanism of natural infection and the risk associated with the handling of isolates on an open laboratory bench, exposure to droplets or aerosols of *N. meningitidis* is the most likely risk for infection in the laboratory. Although *N. meningitidis* does not survive well outside of a host, the organism is able to survive on plastic and glass from hours to days at room temperature.

BSL-3 practices and procedures are indicated for activities with a high potential for droplet or aerosol production and for activities involving production quantities or high concentrations of infectious materials. BSL-2 practices, containment equipment, and facilities are recommended for handling bacterial cultures and inoculation of clinical materials. It is recommended to handle all *N. meningitidis* cultures within a BSC. ABSL-2 conditions are recommended for animal studies.

Special Issues

Vaccines For protection against *N. meningitidis* serogroups A, C, Y, and W-135, there are commercially available polysaccharide and conjugate vaccines. These are recommended to be administered to otherwise healthy children in adolescence with a booster in late adolescence.[193] Recently, a meningococcal serogroup B vaccine has become available. Both vaccines are necessary for full protection as one does not confer immunity for the other.[196] Vaccination with both vaccines is recommended for laboratorians who handle live bacteria and may be exposed to *N. meningitidis*.[193,197,198]

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Salmonella serotypes, other than *S. enterica* serotype Typhi (*S.* Typhi)

Salmonellae are Gram-negative, enteric bacteria associated with diarrheal illness in humans. They are motile oxidase-negative organisms that are easily cultivated on standard bacteriologic media, although enrichment and selective media may be required for isolation from clinical specimens. *Salmonellae* can easily be isolated using selective and differential media or may be detected by molecular testing of primary clinical specimens. Taxonomic studies have organized this genus into two species, *S. enterica* and *S. bongori*, containing more than 2,500 antigenically distinct serotypes.[199,200] *S. enterica* contains the vast majority of

serotypes associated with human disease. *S. enterica* serotypes Typhimurium and Enteritidis are the serotypes most frequently encountered in the United States. This summary statement covers all serotypes except *S*. Typhi.

Occupational Infections

Salmonellosis is a documented hazard to laboratory personnel.[114,201–204] Primary reservoir hosts include a broad-spectrum of domestic and wild animals, including birds, mammals, and reptiles, all of which may serve as a source of infection to laboratory personnel. Case reports of LAIs indicate a presentation of symptoms similar to those of naturally-acquired infections.[205]

Natural Modes of Infection

Salmonellosis is a foodborne disease of worldwide distribution. An estimated one million foodborne cases of salmonellosis occur annually in the United States, and the global burden of non-typhoidal disease is estimated to be 94 million cases and 155,000 deaths annually.[206–208] A wide range of domestic and feral animals (e.g., poultry, swine, rodents, cattle, iguanas, turtles, chicks, dogs, cats, and others) may serve as reservoirs for this disease, as well as humans.[209,210] Some human carriers shed the bacteria for years and some patients recovering from *S. enterica* infections may shed the bacteria for months. Animals can also have a latent or carrier state with long-term shedding of the bacteria. The most common mode of transmission is by ingestion of food from contaminated animals or contamination during processing. The disease usually presents as acute enterocolitis (fever, severe diarrhea, abdominal cramping), with an incubation period ranging from six to 72 hours, most often lasting four to seven days and patients tend to recover without treatment. Antimicrobial therapy is not recommended for uncomplicated *Salmonella*-related gastroenteritis.[206] Bacteremia occurs in 3–10% of individuals infected with *S. enterica*. Antimicrobial resistance of *Salmonella* spp. is becoming a problem worldwide, and this is a concern for invasive disease.[211]

Laboratory Safety and Containment Recommendations

The agent may be present in feces, blood, urine, food, feed, and environmental materials. Some *Salmonella* spp. may survive for long periods in food, feces, water, and on surfaces. Ingestion and parenteral inoculations are the primary laboratory hazards. Naturally or experimentally infected animals are a potential source of infection for laboratory and animal care personnel and for other animals.

BSL-2 practices, containment equipment, and facilities are recommended for activities using clinical materials and diagnostic quantities of infectious cultures. It is recommended that special emphasis be placed on personal protective equipment, handwashing, manipulation of faucet handles, and decontamination of work surfaces to decrease the risk of LAI. For work involving production quantities or high concentrations of cultures, and for activities with a high potential for

aerosol production, it is recommended that a BSC be used and that centrifugation be performed using autoclavable, aerosol-tight rotors and safety cups. ABSL-2 facilities and practices are recommended for activities with experimentally infected animals.[199]

Special Issues

Vaccines Human vaccines against non-typhoidal strains are not available.[212]

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Salmonella enterica serotype Typhi (*S.* Typhi)

The genus *Salmonella* is divided into two species, *S. enterica* and *S. bongori*, containing more than 2,500 antigenically distinct subtypes or serotypes.[200] *S. enterica* contains the vast majority of serotypes associated with human disease. *S. enterica* serotype Typhi, commonly designated *S*. Typhi, is the causative agent of typhoid fever. Untreated case mortality for typhoid fever is >10%.[213] *S*. Typhi is a motile, Gram-negative, enteric bacterium that is easily cultivated on standard bacteriologic media, although enrichment and selective media may be required for isolation of this organism from clinical materials. *S*. Typhi can easily be isolated using selective and differential media, or it may be detected by molecular testing of primary clinical specimens. *S. enterica* serotype Paratyphi (*S.* Paratyphi) is also considered a typhoidal serovar causing a similar illness.

Occupational Infections

Typhoid fever is a demonstrated hazard to laboratory personnel and students working with *S*. Typhi in teaching laboratories with many Laboratory-associated infections and several resulting fatalities being reported.[84,114,203] Ingestion and, less frequently, parenteral inoculation are the most significant modes of transmission in the laboratory. Secondary transmission to other individuals outside of the laboratory is also a concern. Laboratory-associated *S*. Typhi infections usually present with headache, abdominal pain, high fever, and possible septicemia.[203]

Natural Modes of Infection

Typhoid fever is a serious, potentially lethal, bloodstream infection associated with sustained high fever and headaches. It is common in the developing world with 25 million infections and >200,000 deaths annually but rare in the United States with only 400 cases annually.[214–216] Less than 1% of cases in the U.S. are lethal, and these cases are often associated with foreign travel. Humans are the sole reservoir, and asymptomatic carriers may occur. The infectious dose is low

(<1000 organisms), and the incubation period may vary from one to six weeks depending upon the dose of the organism. The natural mode of transmission is by ingestion of food or water contaminated by feces or urine of patients or asymptomatic carriers.[199,206] Antimicrobial resistance of *S.* Typhi is a significant global concern.[217]

Laboratory Safety and Containment Recommendations

The agent may be present in feces, blood, bile, and urine. Humans are the only known natural reservoir of infection. Ingestion and parenteral inoculation of the organism represent the primary laboratory hazards. The importance of aerosol exposure in previous cases is not known. To avoid possible secondary transmission related to contaminated surfaces and clothing in teaching laboratories, the use of nonpathogenic strains is recommended.

BSL-3 practices and equipment are recommended for activities likely to produce significant aerosols or for activities involving production quantities of organisms. BSL-2 practices, containment equipment, and facilities are recommended for activities using clinical materials and diagnostic quantities of infectious cultures. It is recommended that special emphasis be placed on personal protective equipment, handwashing, manipulation of faucet handles, and decontamination of work surfaces to decrease the risk of LAI.

It is recommended that centrifugation be performed using autoclavable aerosol-tight rotors or safety cups. ABSL-2 facilities, practices, and equipment are recommended for activities with experimentally infected animals.

Special Issues

Vaccines Vaccines for *S*. Typhi are available and it is recommended that personnel regularly working with potentially infectious materials consider vaccination. The reader is advised to consult the current recommendations of the Advisory Committee on Immunization Practices (ACIP).[218]

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Shiga toxin (Verocytotoxin)-producing *Escherichia coli*

Escherichia coli (*E. coli*) is one of six species in the Gram-negative genus *Escherichia*. This organism is a common inhabitant of the bowel flora of healthy humans and other mammals and is one of the most extensively studied prokaryotes. An extensive serotyping system has been developed for *E. coli* based on the O (somatic) and H (flagellar) antigens expressed by these organisms. Certain

pathogenic clones of *E. coli* may cause urinary tract infections, bacteremia, meningitis, and diarrheal disease in humans, and these clones are associated with specific serotypes.[199]

The diarrheagenic *E. coli* strains have been characterized into at least five basic pathogenicity groups: Shiga toxin (Verocytotoxin)-producing *E. coli* (a subset are referred to as enterohemorrhagic *E. coli*), enterotoxigenic *E. coli*, enteropathogenic *E. coli*, enteroinvasive E. coli, and enteroaggregative *E. coli*.[199] In addition to clinical significance, *E. coli* strains are routinely used as hosts for cloning experiments and other genetic manipulations in the laboratory. This summary statement only provides recommendations for safe manipulation of Shiga toxin-producing *E. coli* strains.

Occupational Infections

Shiga toxin-producing *E. coli* strains, including strains of serotype O157:H7, are a demonstrated hazard to laboratory personnel with the majority of reported Laboratory-associated infections being caused by enterohemorrhagic *E. coli*.[219–223] Sources of infection include ingestion from contaminated hands and contact with infected animals. The infectious dose is estimated to be low, similar to that reported for *Shigella* spp., at 10–100 organisms.[223]

Natural Modes of Infection

Cattle represent the most common natural reservoir of Shiga toxin-producing *E. coli*, but it has also been detected in wild birds and rodents in close proximity to farms.[224] Transmission usually occurs by ingestion of contaminated food, including raw milk, fruits, vegetables, and particularly ground beef. Human-to-human transmission has been observed in families, daycare centers, and custodial institutions. Waterborne transmission has been reported from outbreaks associated with swimming in a crowded lake and drinking unchlorinated municipal water.[225–227] *E. coli* has the ability to survive from hours to months on inanimate surfaces. In a small number of patients (usually children) infected with these organisms, the disease progresses to hemolytic uremic syndrome or death.

Laboratory Safety and Containment Recommendations

Shiga toxin-producing *E. coli* are usually isolated from feces. However, a variety of food specimens contaminated with the organisms including uncooked ground beef, unpasteurized dairy products, and contaminated produce may present laboratory hazards. This agent may also be found in blood or urine specimens from infected humans or animals. Ingestion is the primary laboratory hazard. The importance of aerosol exposure is not known.

BSL-2 practices, containment equipment, and facilities are recommended for activities using clinical materials and diagnostic quantities of infectious cultures.

It is recommended that special emphasis be placed on personal protective equipment, handwashing, manipulation of faucet handles, and decontamination of work surfaces to decrease the risk of LAI. For work involving production quantities or high concentrations of cultures, and for activities with a high potential for aerosol production, it is recommended that a BSC be used and that centrifugation be performed using autoclavable aerosol-tight rotors and safety cups. ABSL-2 facilities and practices are recommended for activities with experimentally infected animals.

Special Issues

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Shigella

The genus *Shigella* is composed of non-motile, Gram-negative bacteria in the family *Enterobacteriaceae*. There are four subgroups that have been historically treated as separate species including: subgroup A (*Shigella dysenteriae*), subgroup B (*S. flexneri*), subgroup C (*S. boydii*), and subgroup D (*S. sonnei*). Members of the genus *Shigella* have been recognized since the late 19th century as causative agents of bacillary dysentery, or shigellosis.[199] Shigella can easily be isolated using selective and differential media, or it may be detected by molecular testing of primary clinical specimens.

Occupational Infections

Shigellosis is one of the most frequently reported Laboratory-associated infections in the United States.[102,114] A survey of 397 laboratories in the United Kingdom revealed that in 1994–1995, four of nine reported Laboratory-associated infections were caused by *Shigella*.[228] The direct handling of isolates and animal work, such as experimentally infecting guinea pigs, other rodents, and NHPs are proven sources of Laboratory-associated infection.[114,229]

Natural Modes of Infection

Humans and other large primates are the only natural reservoirs of *Shigella* bacteria. Most transmission is by the fecal-oral route; infection also is caused by ingestion of contaminated food or water.[199] Infection with *Shigella dysenteriae* type 1 causes more severe, prolonged, and frequently fatal illness than does infection with other *Shigella* spp., with a fatality rate up to 20%. Complications of shigellosis can include hemolytic uremic syndrome and reactive arthritis (Reiter's syndrome).[230]

Laboratory Safety and Containment Recommendations

The agent may be present in feces and, rarely, in the blood of infected humans or animals. The organism can be shed for weeks after infection and it is communicable as long as the organism is present in the feces. *Shigella* spp. can survive for days in feces and water. Ingestion is the primary laboratory hazard and to a lesser extent, parenteral inoculation of the agent and person-to-person transmission are potential laboratory hazards. Although rare, experimentally-infected guinea pigs and other rodents can transmit infection to laboratory staff. The 50% infectious dose (oral) of Shigella for humans is only 180 organisms.[114] The importance of aerosol exposure is not known.

BSL-2 practices, containment equipment, and facilities are recommended for activities using clinical materials and diagnostic quantities of infectious cultures. It is recommended that special emphasis be placed on personal protective equipment, handwashing, manipulation of faucet handles, and decontamination of work surfaces to decrease the risk of LAI. For work involving production quantities or high concentrations of cultures, and for activities with a high potential for aerosol production, it is recommended that a BSC be used and that centrifugation be performed using autoclavable, aerosol-tight rotors and safety cups. ABSL-2 facilities and practices are recommended for activities with experimentally-infected animals.

Special Issues

Vaccines Vaccines are currently not available for use in humans.

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Staphylococcus aureus **(Methicillin-Resistant, Vancomycin-Resistant, or Vancomycin-Intermediate)**

Staphylococcus aureus is a Gram-positive bacterium associated with a wide spectrum of diseases in humans, ranging from minor to severe. *S. aureus* is a catalase-positive coccus that is a non-motile, non-spore forming facultative anaerobe. *S. aureus* isolates express a coagulase factor, which differentiates them from other staphylococci that colonize humans. *S. aureus* is easily cultivated on standard and selective media, such as high mannitol salt agar. Several molecular tests are also available for testing from clinical specimens. Methicillin-resistant *S. aureus* (MRSA) is common in most areas of the world, with a resistance rate of 30% in most of North America. Vancomycin is currently the treatment of choice for MRSA.[231] Vancomycin-resistant *S. aureus* (VRSA) (vancomycin MIC ≥ 16 µg/mL) is rare, with only 14 cases documented in the

United States, in addition to unconfirmed cases in India and Iran.[232] Vancomycin-intermediate *S. aureus* (VISA) (i.e., isolates with reduced susceptibility to vancomycin, defined as a MIC of 4–8 µg/mL) have been documented at a higher rate, but remain uncommon in most hospitals.[233] To date, all isolates of VRSA and VISA have remained susceptible to other FDA-approved drugs.

Occupational Infections

Several cases of laboratory-associated MRSA infections have been documented.[234–236] To date, no laboratory or occupational infections due to VISA or VRSA have been reported. Case reports of Laboratory-associated infections include nasal colonization and minor skin infections. Guidelines have been provided for investigation and control of VRSA in healthcare settings.[235]

Natural Modes of Infection

S. aureus (including MRSA and VISA) is part of the normal human flora, found primarily in the nares and on the skin of primarily the groin and axillae. Approximately 20% of the population is persistently colonized by *S. aureus*, and 60% are colonized intermittently.[238] Animals may act as reservoirs, including livestock and companion animals.[239] *S. aureus* is an opportunistic pathogen that causes a wide variety of diseases in humans. The organism is a leading cause of foodborne gastroenteritis, as a result of consumption of food contaminated with enterotoxins expressed by some strains. Skin conditions caused by *S. aureus* include cellulitis, scalded skin syndrome, furuncles, carbuncles, impetigo, and abscesses. Certain strains of *S. aureus* express toxic shock syndrome toxin-1 (TSST-1), which is responsible for toxic shock syndrome. *S. aureus* is also a common cause of surgical site infections, endocarditis, peritonitis, pneumonia, bacteremia, meningitis, osteomyelitis, and septic arthritis. Infection modes include ingestion of food containing enterotoxins and person-to-person transmission via contact with colonized health care workers to patients. Nasal colonization can lead to auto-infection.

Laboratory Safety and Containment Recommendations

The agent may be present in many human specimens and in food. Primary hazards to laboratory personnel are direct and indirect contact of broken skin or mucous membranes with cultures and contaminated laboratory surfaces, parenteral inoculation, and ingestion of contaminated materials.

BSL-2 practices, containment equipment, and facilities are recommended for all activities utilizing known or potentially infected clinical materials or cultures. ABSL-2 facilities are recommended for studies utilizing infected laboratory animals.

Special Issues

Vaccines Vaccines are currently not available for use in humans.

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Treponema pallidum

Treponema pallidum is a species of extremely fastidious spirochetes that die readily upon desiccation or exposure to atmospheric levels of oxygen and have not been cultured continuously in vitro.[240] *T. pallidum* cells have lipid-rich outer membranes and are highly susceptible to disinfection with common alcohols (i.e., 70% isopropanol). This species contains three subspecies including *T. pallidum* subsp. pallidum (associated with venereal syphilis), *T. pallidum* subsp. *endemicum* (associated with endemic syphilis), and *T. pallidum* subsp. *pertenue* (associated with yaws). These organisms are obligate human pathogens.

Occupational Infections

T. pallidum is a documented hazard to laboratory personnel, but there have been no reported cases since the 1970s.[84,241] Experimentally-infected animals are a potential source of infection. Syphilis has been transmitted to personnel working with a concentrated suspension of *T. pallidum* obtained from an experimental rabbit orchitis.[242] Rabbit-adapted *T. pallidum* (Nichols strain and possibly others) retains virulence for humans, and rabbits are used in both clinical and research laboratories to isolate clinical strains and model venereal syphilis, respectively.[243] A murine model was recently developed to study venereal syphilis.[244]

Natural Modes of Infection

Humans are the only known natural reservoir of *T. pallidum*; though, non-human primates may be a potential reservoir.[245] Transmission occurs via direct sexual contact (venereal syphilis), direct skin contact (yaws), or direct mucous membrane contact (endemic syphilis). Venereal syphilis is a sexually transmitted disease that occurs worldwide, whereas yaws occurs in tropical areas of Africa, South America, the Caribbean, and Indonesia. Endemic syphilis is limited to arid areas of Africa and the Middle East.[246]

Laboratory Safety and Containment Recommendations

The agent may be present in materials collected from cutaneous and mucosal lesions and in blood. *T. pallidum* has a low infectious dose (57 organisms) by injection. Parenteral inoculation and contact of mucous membranes or broken skin with infectious clinical materials are the primary hazards to laboratory personnel.

BSL-2 practices, containment equipment, and facilities are recommended for all activities involving the use or manipulation of blood or other clinical specimens from humans or infected animals. ABSL-2 practices, containment equipment, and facilities are recommended for work with infected animals.

Special Issues

Vaccines Vaccines are currently not available for use in humans.

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Vibrio species

Vibrio species are straight or curved motile Gram-negative rods. Growth of *Vibrio* spp. is stimulated by sodium, and the natural habitats of these organisms are primarily aquatic environments. Though rare in the U.S., cholera is an acute intestinal infection caused by *V. cholerae* with 3–5 million cases and 100,000 deaths each year, globally.[247] There are at least 12 different *Vibrio* spp. isolated from clinical specimens. *V. cholerae* and *V. parahaemolyticus* are common causes of human enteritis, and *V. alginolyticus* and *V. vulnificus* are common causes of extraintestinal infections including wound infections and septicemia.[248] *Vibrio* spp. can easily be isolated using selective and differential media, or can be detected by molecular testing of primary clinical specimens.

Occupational Infections

Rare cases of bacterial enteritis due to Laboratory-associated infections with either *V. cholerae* or *V. parahaemolyticus* have been reported.[84,249–251] Naturally- and experimentally-infected animals and shellfish are potential sources for such illnesses. No other *Vibrio* spp. have been implicated in Laboratory-associated infections.

Natural Modes of Infection

The most common natural mode of infection is the ingestion of contaminated food or water. The human oral infecting dose of *V. cholerae* in healthy, non-achlorhydric individuals is approximately 106–1011 colony-forming units, while that of *V. parahaemolyticus* ranges from 105–107 cells.[252,253] The importance of aerosol exposure is unknown; although, it has been implicated in at least one instance.[251] The risk of infection following oral exposure is increased in persons with abnormal gastrointestinal physiology, including individuals on antacids, with achlorhydria, or with partial or complete gastrectomies. Fatal cases of septicemia may occur in individuals who are immunocompromised or have pre-existing medical conditions such as liver disease, cancer, or diabetes.

Laboratory Safety and Containment Recommendations

Pathogenic *Vibrio* spp. can be present in human fecal samples or in the meats and the exterior surfaces of marine invertebrates such as shellfish. Survival and growth of *Vibrio* spp. in water is dependent on high salinity. Other clinical specimens from which *Vibrio* spp. may be isolated include blood, arm or leg wounds, eye, ear, and gallbladder.[250] LAIs of *V. cholerae* or *V. parahaemolyticus* have been observed in laboratory researchers after the use of syringes, decontamination of a laboratory spill, or the handling of infected animals.[249–251] Exposure of open wounds to *Vibrio* spp. in contaminated seawater or shellfish can result in infections and septicemia.

BSL-2 practices, containment equipment, and facilities are recommended for activities with cultures or potentially infectious clinical materials. ABSL-2 practices, containment equipment, and facilities are recommended for activities with naturally or experimentally infected animals.

Special Issues

Vaccines A cholera vaccine is licensed and available in the United States. It is currently only recommended for adult travelers to areas of active cholera transmission.[254] There are currently no human vaccines against *V. parahaemolyticus*.

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Yersinia pestis

Yersinia pestis, the causative agent of plague, is a Gram-negative bacillus frequently characterized by a “safety pin” appearance on stained preparations from specimens. The incubation period for bubonic plague ranges from two to six days while the incubation period for pneumonic plague is one to six days.

Occupational Infections

Y. pestis is a documented laboratory hazard. A number of LAIs have been reported in the United States, some of which were fatal.[84,255] One lethal case in a laboratory researcher was due to the attenuated strain KIM D27.[256] The condition of hereditary hemochromatosis coupled with diabetes in the researcher is believed to have contributed to the fatal course of disease. Veterinary staff and pet owners have become infected when handling domestic cats with oropharyngeal or pneumonic plague.

Natural Modes of Infection

There is a natural zoonotic cycle of *Y. pestis* between wild rodents and their fleas. Infective fleabites are the most common mode of transmission, but direct human contact with infected tissues or body fluids of animals and humans may also serve as sources of infection.

Plague has a high mortality rate if untreated (50%) and caused three major pandemics, including the Black Death of the 14th century. There are three manifestations of disease: bubonic, septicemic, and pneumonic. Bubonic plague results in tender and painful lymph nodes (buboes). Septicemic plague, which may develop directly or from untreated bubonic plague, can lead to shock and bleeding into the skin and tissues, potentially causing necrosis. Pneumonic plague results in a rapidly developing pneumonia and can be spread from person to person via respiratory droplets. Plague occurs in multiple countries of the world, with the highest incidence in Africa. Most cases in the United States occur in rural, western states. Sporadic cases in the United States average about seven cases per year. Contact with infected sylvatic rodents, such as prairie dogs and ground squirrels, has resulted in human infections.[257]

Laboratory Safety and Containment Recommendations

Y. pestis has been isolated from bubo aspirates, blood, sputum, CSF and autopsy tissues (spleen, liver, lung), depending on the clinical form and stage of the disease; feces, urine or bone marrow samples may be positive for *Y. pestis* DNA or antigen but not the organism itself. Primary hazards to laboratory personnel include direct contact with cultures and infectious materials from humans or animal hosts and inhalation of infectious aerosols or droplets generated during their manipulation. Laboratory animal studies have shown the lethal and infectious doses of *Y. pestis* to be quite low, less than 100 colony-forming units.[258] *Y. pestis* can survive for months in human blood and tissues. Fleas may remain infective for months. It is recommended that laboratory and field personnel be counseled on methods to avoid flea bites and autoinoculation when handling potentially infected live or dead animals.

BSL-3 and ABSL-3 practices, containment equipment, and facilities are recommended for all manipulations of suspect cultures, animal necropsies, and for experimental animal studies. BSL-3 practices, containment equipment, and facilities are appropriate for production operations. Characterized strains of reduced virulence such as *Y. pestis* strain A1122 can be manipulated at BSL-2. BSL-2 practices, containment equipment, and facilities are recommended for primary inoculation of cultures from potentially infectious clinical materials.

When performing fieldwork involving animals that may have fleas, gloves and appropriate clothing should be worn to prevent contact with skin, and insect

repellent can be used to reduce the risk of flea bites. Arthropod Containment Level 3 (ACL-3) facilities and practices are recommended for all laboratory work involving infected arthropods.[255] See Appendix G for additional information on Arthropod Containment Guidelines.

Special Issues

Be advised of possible misidentification using automated systems. For identification of samples suspected of containing *Y. pestis* using MALDI-TOF MS, it is recommended to use alternative tube extraction that kills viable organisms and not direct spotting of plates in the open laboratory.

Vaccines There are no licensed vaccines currently available in the United States.[259] New plague vaccines are in development but are not expected to be commercially available in the immediate future.[206]

Select Agent *Y. pestis* is a Select Agent requiring registration with CDC and/or USDA for possession, use, storage and/or transfer. See Appendix F for additional information.

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

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Section VIII-B: Fungal Agents

Blastomyces dermatitidis and *Blastomyces gilchristii*

Blastomyces dermatitidis is a dimorphic fungal pathogen existing in nature and in laboratory cultures at room temperature as a filamentous mold with asexual spores (conidia) that are the infectious particles; conidia convert to large budding yeasts under the appropriate culture conditions *in vitro* at 37°C and in the parasitic phase *in vivo* in warm-blooded animals. Infections with *B. dermatitidis* occur when conidia are inhaled or when yeast forms are injected. The sexual stage is an Ascomycete with infectious ascospores. *Blastomyces gilchristii* was recently recognized as a novel species found predominantly in northwestern Ontario, Wisconsin, and Minnesota.[1]

Occupational Infections

Three groups are at greatest risk of Laboratory-associated infection (LAI): microbiologists, veterinarians, and pathologists.[2] Laboratory-associated local infections have been reported following accidental parenteral inoculation with infected tissues or cultures containing yeast forms of *B. dermatitidis*.[3–9] Laboratory infections have also occurred following the presumed inhalation of conidia from mold-form cultures.[10,11] Infection with *B. dermatitidis* can be pulmonary, cutaneous, or disseminated. Disseminated blastomycosis usually begins with pulmonary infection. Transmission occurs rarely via animal bites, sexual means, or vertical transmission. Forestry workers and other workers with outdoor occupations have developed blastomycosis after exposure to contaminated soil or plant material, particularly moist soil with decaying vegetation.[12] At least 11 reported LAIs with two fatalities have occurred.[13,14]

Natural Modes of Infection

The fungus has been reported in multiple geographically separated countries, but it is best known as a fungus endemic to North America and in association with plant material in the environment. Infections are not communicable but require common exposure from a point source. Although presumed to dwell within the soil of endemic areas, *B. dermatitidis* is extremely difficult to isolate from soil. Outbreaks associated with the exposure of people to decaying wood have been reported. However, outdoor activities were not a risk factor in the largest outbreak reported through 2017; instead, the large Hmong population in the area of Wisconsin that was involved in the outbreak may have had an underlying genetic predisposition.[15] *B. dermatitidis* infections are most common in humans and dogs though other animals, such as cats and horses, may also develop blastomycosis. Human-to-human transmission occurs rarely via perinatal or sexual transmission.

Laboratory Safety and Containment Recommendations

Yeast forms may be present in the tissues of infected animals and in clinical specimens. Parenteral (subcutaneous) inoculation of these materials may cause local skin infection and granulomas. Mold-form cultures of *B. dermatitidis* containing infectious conidia and processing of soil or other environmental samples may pose a hazard of aerosol exposure.

BSL-3 practices, containment equipment, and facilities are recommended for handling sporulating mold-form cultures already identified as *B. dermatitidis* and soil or other environmental samples known or likely to contain infectious conidia.

BSL-2 and ABSL-2 practices, containment equipment, and facilities are recommended for activities with clinical materials, animal tissues, yeast-form cultures, and infected animals.

Special Issues

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Coccidioides immitis and *Coccidioides posadasii*

Coccidioides spp. are endemic to the Sonoran Desert of the western hemisphere including northern Mexico, southern Arizona, central and southern California, and western Texas. In recent decades, *C. immitis* has been divided into two species: *C. immitis* and *C. posadasii*.[16] These species are dimorphic fungal pathogens existing in nature and in laboratory cultures at room temperature as filamentous molds with asexual spores (single-cell arthroconidia three to five microns in size) that are the infectious particles. The arthroconidia convert to spherules under the appropriate culture conditions *in vitro* at 37°C and *in vivo* in warm-blooded animals. The verification code for this document is 481375

Occupational Infections

Laboratory-associated coccidioidomycosis is a documented hazard of working with sporulating cultures of *Coccidioides* spp.[17–19] Occupational exposure in archeologists and prison employees in endemic regions has been associated with high dust exposure.[20,21] Attack rates for laboratory and occupational exposures where a larger number of spores are inhaled are higher than for non-occupational environmental exposures. Smith reported that 28 of 31 (90%) Laboratory-associated infections in his institution resulted in clinical disease, but more than half of infections acquired in nature were asymptomatic.[22] Risk of respiratory infection from exposure to infected tissue or aerosols of infected secretions is very low. Accidental percutaneous inoculation has typically resulted in localized granuloma formation.[23]

Natural Modes of Infection

Single spores in environmental exposures can produce infections by the respiratory route. Peak exposures occur during arid seasons, and exposure can also occur during natural disasters such as earthquakes.[24] *Coccidioides* spp. grow in infected tissue as larger multicellular spherules up to 70 microns in diameter and pose little or no risk of infection from direct exposure.

Most infections from environmental exposure are subclinical and result in life-long protection from subsequent exposures. The incubation period is one to three weeks, and the disease manifests as community-acquired pneumonia with immunologically mediated fatigue, skin rashes, and joint pain. One of the synonyms for coccidioidomycosis is desert rheumatism. A small proportion of infections are complicated by hematogenous dissemination from the lungs to other organs, most frequently skin, the skeleton, and the meninges. Disseminated infection is much more likely in persons with cellular immunodeficiencies (e.g., AIDS, organ transplant recipient, lymphoma, receipt of tumor necrosis factor [TNF] inhibitors) and in pregnant women in the third trimester.

Laboratory Safety and Containment Recommendations

Because of their size, arthroconidia are conducive to ready dispersal in air and retention in the deep pulmonary spaces. The much larger size of the spherule considerably reduces the effectiveness of this form of the fungus as an airborne pathogen.

Spherules of the fungus may be present in clinical specimens and animal tissues, and infectious arthroconidia may be present in mold cultures and soil or other samples from natural sites. Inhalation of arthroconidia from either environmental samples or mold isolates is a serious laboratory hazard.[19] Most exposures occur due to personnel handling cultures of unknown infectious status on the bench, rather than in a BSC. Personnel should be aware that infected animal or human clinical specimens or tissues stored or shipped under temperature and nutrient conditions that could promote germination of arthroconidia pose a theoretical laboratory hazard. Slide cultures should never be prepared from unknown hyaline (colorless) isolates, as they could contain *Coccidioides* spp.

BSL-3 practices, containment equipment, and facilities are recommended for propagating and manipulating sporulating cultures already identified as *Coccidioides* spp. and for processing soil or other environmental materials known or suspected to contain infectious arthroconidia. Experimental animal studies should be done at BSL-3 when challenge is via the intranasal or pulmonary route.

BSL-2 practices, containment equipment, and facilities are recommended for handling and processing clinical specimens, identifying isolates, and processing animal tissues that may contain *Coccidioides* spp. ABSL-2 practices, containment

equipment, and facilities are appropriate for experimental animal studies when the route of challenge is parenteral.

Special Issues

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Histoplasma capsulatum

Histoplasma capsulatum is a dimorphic fungal pathogen existing in nature and in laboratory cultures at room temperature as a filamentous mold with asexual spores (macro-and/or microconidia); microconidia are the infectious particles that convert to small budding yeasts under the appropriate culture conditions in vitro at 37°C and in the parasitic phase in vivo. The sexual stage is an Ascomycete with infectious ascospores.

Specific hazards/risks associated with *Histoplasma* include:

1. Immunocompromised individuals are at increased risk of infection and experience more severe infections and higher mortality;
2. Dissemination throughout body has resulted in death but usually results in chronic infection;
3. Previously controlled infections can be re-activated when cellular immunity is impaired;
4. The adrenal gland can be destroyed by visceral infection; and
5. 5–20% of cases involve the central nervous system and appear as chronic meningitis or focal brain lesions.

Occupational Infections

Laboratory-associated histoplasmosis is a documented hazard in facilities conducting diagnostic or investigative work.[9,25–27] Pulmonary infections have resulted from handling mold form cultures.[28,29] Local infection has resulted from skin puncture during autopsy of an infected human,[30] from accidental needle inoculation of a viable culture,[31] from accidental inoculation with a lymph node biopsy sample from an infected patient,[32] and from spray into the eye.[33] Collecting and processing soil samples from endemic areas has caused pulmonary infections in laboratory workers,[34] and one death was reported in 1962.[35] Conidia are resistant to drying and may remain viable for long periods of time. The small size of the infective conidia (less than five microns) is conducive to airborne dispersal and intrapulmonary retention. Work with experimental animals suggests that hyphal fragments are also capable of serving as viable inocula.[25]

Natural Modes of Infection

The fungus is distributed worldwide in the environment and is associated with bird and bat feces. It has been isolated from soil, often in river valleys, between latitudes 45°N and 45°S. Histoplasmosis is naturally acquired by the inhalation of infectious microconidia, which can survive in excess of ten years in soil.[25] Infections are not transmissible from person-to-person but require common exposure to a point source. Large outbreaks have been reported from exposure to soil or plant material contaminated with bird or bat feces[36,37] and from exposure to soil during construction projects.[38]

Laboratory Safety and Containment Recommendations

The infective stage of this dimorphic fungus (microconidia) is present in sporulating mold form cultures and in soil from endemic areas. The yeast form is present in tissues or fluids from infected animals and may produce local infection following parenteral inoculation or splash onto mucous membranes.

BSL-3 practices, containment equipment, and facilities are recommended for propagating sporulating cultures of *H. capsulatum* in the mold form, as well as for processing soil or other environmental materials known or likely to contain infectious conidia.

BSL-2 and ABSL-2 practices, containment equipment, and facilities are recommended for handling and processing clinical specimens; identifying isolates, animal tissues, and mold cultures; identifying cultures that may contain *Histoplasma* in routine diagnostic laboratories; and for inoculating experimental animals, regardless of route. Any culture identifying dimorphic fungi should be handled in a Class II BSC. Protective eyewear should be worn when splash(es) to mucous membranes may occur.

Special Issues

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Sporothrix schenckii species complex

The *Sporothrix schenckii* species complex is composed of at least six species (*Sporothrix brasiliensis*, *Sporothrix mexicana*, *Sporothrix globosa*, *S. schenckii sensu stricto, Sporothrix luriei*, and *Sporothrix albicans*) of dimorphic fungal pathogens existing in nature and in laboratory cultures at room temperature as filamentous mold with asexual spores (conidia); the conidia are the infectious particles that convert to small budding yeasts in the parasitic phase in vivo.[39] The sexual stage is unknown.

Occupational Infections

Most cases of sporotrichosis are reported sporadically following accidental inoculation with contaminated material. Large outbreaks have been documented in persons occupationally or recreationally exposed to soil or plant material containing the fungus. However, members of the *S. schenckii* species complex have caused a substantial number of local skin or eye infections in laboratory personnel.[40] Most occupational cases have been associated with accidents and have involved splashing culture material into the eye,[41,42] scratching,[43] injecting infected material into the skin,[44] or being bitten by an experimentally infected animal.[45,46] Skin infections without any apparent trauma to the skin have also resulted from handling cultures[47–49] and from the necropsy of animals.[50]

Laboratory Safety and Containment Recommendations

Although localized skin and eye infections have occurred in an occupational setting, no pulmonary infections have been reported as a result of laboratory exposure. It should be noted that serious disseminated infections have been reported in immunocompromised persons.[51]

BSL-2 and ABSL-2 practices, containment equipment, and facilities are recommended for laboratory handling of clinical specimens suspected of containing infectious particles, soil and vegetation suspected to contain *S. schenckii*, and experimental animal activities with *S. schenckii*. Any culture identifying dimorphic fungi should be handled in a Class II BSC. Protective eyewear should be worn when splash(es) to mucous membranes may occur.

Special Issues

Transfer of Agent Importation of this agent requires CDC and/or USDA importation permits. Domestic transport of this agent may require a permit from USDA APHIS VS. A DoC permit may be required for the export of this agent to another country. See Appendix C for additional information.

Miscellaneous Yeast and mold organisms causing human infection

The majority of mold organisms in Table 1 cause infection in compromised hosts. Risk factors may include neutropenia, previous exposure to antibiotics, treatment for cancer, especially leukemia and lymphoma, organ or stem cell transplant, severe burns, HIV infection with low CD4 cell counts, and placement of central lines or other monitoring devices.

The majority of these organisms are found in the environment and are transmitted through exposure to air, water, or dust. Mold conidia can be inhaled or injected subcutaneously through trauma or other accidental inoculation. Dermatophytes can be transmitted through the person-to-person route, the animal-to-person route, and the environment-to-person route.

Candida yeasts are found as part of the normal human respiratory or gastrointestinal flora and may cause infection after exposure to antibiotics, abdominal surgery, or other causes. Yeast outbreaks in hospitals can occur through exposure to contaminated hospital equipment, foods, or medications. Some yeast species, most notably *Candida auris*,[52] cause concern because they display resistance to multiple antifungal drugs. *Cryptococcus* basidiospores are found in the environment largely associated with bird droppings or certain trees. They cause infection in compromised hosts after inhaling fungal spores.

BSL-2 and ABSL-2 practices, containment equipment, and facilities are recommended for propagating and manipulating cultures known to contain these agents. All unknown mold cultures should be handled in a Class II BSC.

Table 1. Miscellaneous Yeast and Mold

Agent	Occupational Infection	Natural Mode of Infection	Biosafety Level
Candida species	Not common	From point source in environment; from gastrointestinal tract into bloodstream	BSL-2
Cryptococcus neoformans and *C. gattii*	Occasional inoculation into skin when working with laboratory animals	Inhalation from point source in environment. No person-to-person transmission reported.	BSL-2 (handle in BSC to prevent laboratory contamination)
Dermatophyte molds: *Trichophyton, Microsporum, Epidermophyton* species	Occasional direct inoculation from handling isolates or contaminated materials	Person-to-person; common exposure to a point source; handling infected animals	BSL-2
Hyaline Molds: *Aspergillus* spp., *Fusarium* spp.	Not common	Presumed inhalation; subcutaneous inoculation from environmental source	BSL-2 (handle in BSC to prevent laboratory contamination)
Talaromyces (Penicillium) marneffei	Occasional direct inoculation when working with laboratory animals; rare inhalation in immunocompromised individual	Mostly inhalation (in immunocompromised hosts)	BSL-2 (handle in BSC to prevent laboratory contamination)

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Agent	Occupational Infection	Natural Mode of Infection	Biosafety Level
Dematiaceous Molds: *Bipolaris* spp.; *Cladophialophora bantiana; Exophiala* spp*; Exserohilum rostratum; Fonsecaea* spp.*; Pseudallescheria* spp.*; Rhinocladiella* spp.*; Scedosporium* spp.*; Verruconis (Ochroconis) gallopava*	Not reported, but inhalation or subcutaneous inoculation are possible routes of exposure	Presumed inhalation; subcutaneous inoculation from environmental source. *C. bantiana, E. dermatitidis, V. gallopava*, and *R. mackenziei* are neurotropic. *C. bantiana* can cause disseminated infection in otherwise healthy hosts.	BSL-2 (handle in BSC to prevent laboratory contamination)
Mucormycete molds: *Mucor* spp.; *Rhizopus* spp.; *Rhizomucor* spp.; *Lichtheimia (Absidia)* spp.	Not reported	Presumed inhalation; subcutaneous inoculation from environmental source; ingestion	BSL-2 (handle in BSC to prevent laboratory contamination)

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