This educational program is supported by the John and Nan Frymoyer Fund for Medical Education from the University of Vermont College of Medicine.

Category B and C Bioterrorism Agents

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INTRODUCTION

The Centers for Diseases Control and Prevention (CDC) and the National Institutes of Allergy and Infectious Diseases (NIAID) have grouped potential biological agents or toxins into three categories based on the level of concern that these microbes could be used as biological weapon. See Table 1.

Category A agents:

- Have already been developed as biological weapons.
- Can be easily disseminated or transmitted from person to person.
- Are stable in aerosol form and can be delivered in this form.
- Have the potential for large-scale dissemination.
- Have the potential to cause high mortality and morbidity.
- Would cause widespread public panic.
- Pose the greatest threat to national safety and security.
- E-mail modules discussing these agents can be accessed by going to the **FAHC HOME PAGE** (www.fahc.org). Click on healthcare provider education at the top of the page.

Category B agents:

- Are moderately easy to disseminate.
- Can cause moderate morbidity but generally lower mortality.
- Include food and water related pathogens

Category C agents:

- Are available.
- Can be produced and disseminated.
- Have potential for high mortality and morbidity.

Table 1: Categories of Pathogen Risk

Centers of Diseases Control and Prevention	National Institutes of Allergy and Infectious Diseases
Category A	
• *Bacillus anthracis* (anthrax) • *Clostridium botulinum* (botulism) • *Yersinia pestis* (Plague) • *Variola major* (smallpox) • *Francisella tularensis* (tularemia) • Viral hemorrhagic fevers[1]	• *Bacillus anthracis* (anthrax) • *Clostridium botulinum* (botulism) • *Yersinia pestis* (Plague) • *Variola major* (smallpox) • *Francisella tularensis* (tularemia) • Viral hemorrhagic fevers[2]
Category B	
• *Brucella species* (brucellosis) • *Clostridium perfringens* (epsilon toxin) • *Burkholderia mallei* (Glanders) • *Burkholderia pseudomallei* (Melioidosis) • *Chlamydia psittaci* (Psittacosis) • *Coxiella burnetii* (Q fever) • *Ricinus communis* (Ricin toxin) • Staphylococcus enterotoxin B • *Rickettsia prowazekii* (Typhus fever) • Viral encephalitis[3] • Water safety threats[4]	• *Brucella species* (brucellosis) • *Clostridium perfringens* (epsilon toxin) • *Burkholderia mallei* (Glanders) • *Burkholderia pseudomallei* (Melioidosis) • *Chlamydia psittaci* (Psittacosis) • *Coxiella burnetii* (Q fever) • *Ricinus communis* (Ricin toxin) • Staphylococcus enterotoxin B • *Rickettsia prowazekii* (Typhus fever) • Viral encephalitis[5] • Water safety threats[6]
Category C	
• Nipah virus • Hantavirus • Tick borne hemorrhagic fever • Tick borne encephalitis virus • Multi-drug resistant *Mycobacterium tuberculosis*	

[1] viral hemorrhagic fevers include Ebola, Marburg, Lassa, Rift Valley fever and New World Arenaviruses

[2] viral hemorrhagic fevers include Ebola, Marburg, Lassa, Rift Valley fever, Hanta viruses, Dengue, New World Arenaviruses and lymphocytic choriomeningitis virus

[3] Venezuelan, Eastern, and Western equine encephalitis virus

[4] *Vibrio cholerae*, *Cryptosporidium parvum, Shigella dysenteriae, and E. coli 0157:H7*

[5] Venezuelan, eastern, and western equine encephalitis virus, West Nile virus, LaCrosse virus, Japanese encephalitis virus, Kyasanur forest virus

[6] Escherichia coli, pathogenic vibrios, Shigella sp., Salmonella sp., Listeria monocytogenes, Campylobacter jejuni, Yersinia enterocolitica, Caliciviruses, hepatitis A virus, *Cryptosporidium parvum*, Cyclospora cayetanensis, Giardia lamblia, Entamoeba histolytica, and Microsporida

The NIAID convened an expert panel on Immunity and Bio-Defense that stressed the importance of research initiatives concerning the B and C agents. See further reading. Category A agents listed by the CDC and NIAID are similar with the exception that more agents that cause viral hemorrhagic fever (VHF) are included in the NIAID listing than CDC. The NIAID has suggested that other Rickettsial agents, *Coccidioides immitis*, hepatis E virus, additional toxins made by *Clostridium perfringens* and Congo Hemorrhagic fever be placed in Category B. The NIAID has stressed the importance of ongoing research initiatives on these lesser known pathogens.

A recent study by the CDC reviewed mandatory reporting requirements for 24 potential biological weapons in 54 jurisdictions in the United States. Of the Category A agents, anthrax, botulism and plague are reportable immediately (within 24 hours) in >90% of the jurisdictions while smallpox, tularemia and viral hemorrhagic fevers are immediately reportable in <50% of the jurisdictions. Of the Category B agents, infections with *Salmonella* and *Shigella* are required to be reported immediately in all jurisdiction. Brucellosis, cryptosporidium, *Escherichia coli,* psittacosis, Q fever and *Vibrio cholerae* have mandatory reporting requirements in the majority of jurisdictions. Some of the category B agents such as glanders, melioidosis, mycotoxins, ricin poisoning and staphylococcal enterotoxin B poisoning have mandatory reporting requirements in < 20% of surveyed jurisdictions. Limited or delayed reporting of these agents will impede the recognition of a bioweapons attack.

This e-mail module will briefly review the CDC classified B and C agents that are considered significant threats. Table 2 summarizes the clinical syndromes and table 3 summarizes the infection control measures needed.

USE AS BIOWEAPONS

The United States began offensive bioweapons research in 1943. Category B agents developed by the US included *Coxiella burnetii* (Q fever), Venezuelan equine encephalitis (VEE) virus, *Brucella suis* and Staphylococcal enterotoxin B (SEB). The former Soviet Union weaponized several category B agents including those that cause Q fever, brucellosis, glanders, ricin poisoning, SEB, VEE and typhus. Iraq conducted research into the use of *Clostridium perfringens***,** aflatoxins and ricin as biological weapons.

Brucella has been considered a strong candidate for use as a bioweapon. It is highly infectious as an aerosol. It can be freeze-dried and it is able survive in the environment for prolonged periods of time. Brucella species have been developed as bioweapons by the US, Britain and the former Soviet Union. These agents were field-tested in 1944 by the US and Britain using aerosolized *Brucella abortus* in open-air sea trials in the Caribbean Sea.

Interest in **Q fever** as a biological weapon is high since *C. burnetii* is very resistant to heat and desiccation and extremely contagious in aerosol form. A single inhaled organism may produce clinical illness. The US developed *C. burnetii* (Q fever) as a biological weapon. In the Camp Detrick research facilities in Maryland, 3.5 liters of *C. burnetii* was grown in embryonated chicken eggs. In 1955, it was transported to the Dugway Proving Ground in Utah were it was aerosolized over human volunteers. The Biopreparet of the former Soviet Union also weaponized Q fever.

Glanders has been used as a biological weapon during WWI to incapacitate Russian horses, the major means of transport on the Eastern Front. The Japanese used Glanders to attack the Chinese during WWII infecting horses, civilians and prisoners of war. The Soviet Union and US studied glanders and **melioidosis** as a potential biological weapon.

Ricin toxin has been used for assassination and is a prime candidate for use as a biological weapon. In 1978, Georgi Markov, a Bulgarian journalist in London, was assassinated when a small pellet of ricin toxin, loaded in an umbrella tip, was injected into his thigh. Ricin may have been used during the Iran-Iraq war in the 1980s. Ricin was recently found in caves in Afghanistan used by Al Qaeda. In January of 2003, seven persons were arrested in London, England after being found in possession of ricin.

The religious cult, Rajneeshee used ***Salmonella typhimurium*** to contaminate restaurant salad bars in Dalles, Oregon. 751 persons developed gastroenteritis, though no one died. Their hope was to disrupt regional elections in order to shift local power to their cult.

Staphylococcal enterotoxin B (SEB) was mass-produced and stockpiled at the Army's Directorate of Biological Operations at Pines Bluff Arsenal in Arkansas. It was explored by the US as a potential weapon in 1968 when monkeys, housed in the Eniwetok Atoll (in the Marshall Islands) were exposed to aerosolized SEB.

Table 2: Category B agents clinical syndromes

Pathogen	Signs and Symptoms
Brucellosis	Nonspecific constitutional symptoms of fever, sweats, malaise, nausea, vomiting and abdominal pain. Chronic arthritis, osteomyelitis, endocarditis and meningitis
Q fever	Non-specific febrile illness. Patients often have atypical pneumonia and
Glanders	Acute cutaneous abscesses, pneumonia and bacteremia. Chronic cutaneous or visceral abscesses, osteomyelitis or septic arthritis
Melioidosis	Acute cutaneous abscesses, pneumonia and bacteremia. Chronic cutaneous or visceral abscesses, osteomyelitis or septic arthritis
Ricin Toxin	Severe gastroenteritis if ingested. Pulmonary edema with respiratory failure if inhaled.
Psittacosis	Atypical community acquired pneumonia, hepatitis, encephalitis
Food and water borne pathogens[1]	Gastroenteritis with nausea, vomiting, abdominal pains. Bacterial patho colitis with bloody diarrhea and fever.
Epidemic Typhus	Fever, headache, rash and confusion
Bacterial Toxins	Gastroenteritis or acute respiratory syndrome with fever, cough and shortness of breath, depending on the mode of distribution
Viral encephalitis	Encephalitis
Nipah virus	Encephalitis

[1] *Campylobacter jejuni*, non-typhoidal *Salmonella*, *Vibrio cholerae*, *Cryptosporidium parvum* and *Escherichia coli 0157:H7*

Table 3: Infection control

Pathogen	Direct person to person transmission	Infection control precautions
Brucellosis	Extremely rare[1]	Standard[2]
Q fever	NO	Standard[2]
Glanders	Extremely rare[3]	Standard[2]
Melioidosis	Extremely rare[3]	Standard[2]
Ricin Toxin	NO	Standard
Psittacosis	Rare[4]	Standard[2]
Food and water borne pathogens[4]	YES[5]	Standard
Epidemic Typhus	NO[6]	Standard
Bacterial Toxins	NO	Standard
Viral encephalitis	NO	Standard
Nipah virus	NO	Standard

[1] mother to infant in breast milk, sexual and contaminated tissue transplants. No reports of patient to health care provider.
[2] the microbiology laboratory should be notified since culturing of the pathogen may be very contagious to the technologist.
[3] sexual transmission has been hypothesized. No reports of patient to health care provider by inhalation or sexually.
[4] *Campylobacter jejuni*, non-typhoidal *Salmonella, Vibrio cholerae, Cryptosporidium parvum* and *Escherichia coli 0157:H7*
[5] fecal-oral transmission
[6] indirect person to person transmission by the human body louse.

SPECIFIC PATHOGENS

- **Brucellosis** (undulant, Malta or Mediterranean fever)

  Brucellosis is a group of zoonotic illnesses caused by small aerobic, non-spore forming intracellular gram negative coccobacilli. Four of the six brucella species are capable of causing human illness. Despite being a gram-negative rod (GNR), its cell wall lipopolysaccharide is much less potent toxin than other GNR such as *Escherichia coli.*

  B. melitensis can be transmitted from sheep, goats and camels, *B. abortus* from cattle, buffalo, yaks and camels, *B. suis* from pigs and *B. canis* from kennel raised dogs. In animals, brucellosis can cause life-long infection and is responsible for causing abortions in cattle.

  British army surgeons stationed on the island of Minorca (a Mediterranean island off the eastern coast of Spain) reported descriptions of a brucella-like infection in 1751. JA Marston, a British Army physician, described his own illness when

stationed in Malta during the Crimean War (1854-1856) when Franco-British forces were battling the troops of Tzar Nicholas I of Russia over control of holy shrines in Jerusalem and Nazareth. Sir David Bruce (1855–1931) isolated *B. melitensis* in 1886. The Maltese bacteriologist Zammit Themistocles, working for the Mediterranean Fever Commission in Malta, isolated *B. melitensis* from goat's milk in 1897 and recognized goats as the infectious reservoir for the human infection.

Human infection is transmitted primarily from goats, sheep, pigs, cattle, dogs, deer and elk under the circumstances of unsanitary animal husbandry. Humans most often become infected by ingestion of unpasteurized milk and cheese developing a wide array of acute and chronic infections. Direct cutaneous contact with infected meat has spread brucellosis to slaughterhouse workers, hunters and veterinarians. Less often, brucella may be inhaled by veterinarians and abattoir workers exposed to aerosols. Transmission of *B. canis* from domesticated dogs is extremely rare. Brucellosis is still a common infection worldwide. High-risk areas include Portugal, Spain, Southern France, Italy, Greece, Turkey, South and Central America, Eastern Europe, Africa, the Middle East and Asia. Brucellosis is uncommon in the US with only 136 cases reported in 2001. Most of these cases were seen in persons from Texas and California who ingested contaminated goat milk products imported from Mexico, in international travelers and in recent immigrants to the US.

In 1983, 29 Mexican immigrants living in Houston, Texas were found to be ill with brucellosis. The great majority had eaten goat cheese made in Mexico. Nineteen of the 29 had positive blood cultures for *B. melitensis*. An outbreak of brucellosis occurred in 1992 in a pork processing plant in North Carolina involving 30 employees. Transmission was felt to have occurred through breaks in the workers skin, inhalation or conjunctival contact.

Brucellosis may present as an acute or indolent infection, a systemic infection or a localized process. After an incubation period of 2-4 weeks, patients develop fever, sweats, malaise, headaches and irritability. Other common but nonspecific symptoms include nausea, vomiting, abdominal pain and depression. Examination may reveal hepatosplenomegaly and lymphadenopathy. Chronic infection can lead to osteomyelitis and arthritis often involving the axial skeleton, the sacroiliac joints or the large joints of the extremities. Less often infection can cause orchitis, meningitis, endocarditis, iridocyclitis and pulmonary nodules. Complete blood counts may reveal anemia, leukopenia and thrombocytopenia. *B. melitensis* causes more severe disease while *B. suis* more often leads to chronic localized diseases. Mortality is generally < 2%, though patients may experience significant longterm morbidity.

Diagnosis can be made by isolation of the pathogen from blood, bone marrow and other biopsied tissues. When sending a specimen for culture, the laboratory should be informed that brucellosis is suspected so that special biosafety precautions can be taken and to be sure that the blood culture is held for at least two months. More often diagnosis is made serologically. Most patients with brucellosis have a serum agglutination test (SAT) titer of greater than 160.

The recommended treatment is a six week course of oral doxycycline and rifampin. Six weeks of oral doxycycline can also be combined with an initial three weeks of parenteral gentamicin. Live attenuated vaccines exist for animals. There are no safe human vaccines. Postexposure prophylaxis is not indicated. Transmission from patient to health care worker has not been demonstrated. Standard precautions can be used.

- **Q fever**

Q fever is a zoonotic febrile illness transmitted from animals to humans most commonly as an aerosol caused during the birthing process of sheep. The Q comes from "query", referring to a new illness known as "abattoir fever" that infected meatpackers in Queensland Australia in 1933-35. Dr. F. MacFarlane Burnet showed that Q fever was caused by a rickettsial organism. In 1936, Herald Rae Cox, PhD and Gordon Davis, PhD discovered a new rickettsial organism in Montana ticks that subsequently was shown to be the causative agent of Q fever. The pathogen was thus named *Coxiella burnetii,* a gram-negative coccobacillus of the Rickettsia family. It is able to form spores thus contributing to its ability to survive for prolonged periods in the environment. Unique to this is organism is its ability to shift from a Phase I to a Phase II antigenic pattern. This shift in antigen pattern is important for serological diagnosis. The cell wall lipopolysaccharide (LPS) is not virulent as it is in other gram-negative pathogens.

Cattle, sheep and goats are the natural reservoir for *C. burnetii*. Although these animals are usually asymptomatic, they excrete the pathogen in urine, feces and milk. There are particularly large concentrations in the amnionic fluid, placenta and fetal membranes. Human infection usually occurs from inhalation of the aerosolized organism by farm workers or veterinarians during parturition, for example during lambing season. Aerosols may also be generated from contaminated soils and hay causing illness.

Most often infection with *C. burnetii* is asymptomatic. Up to 60% of infected patients do not develop symptomatic illness. Symptomatic infection generally presents as a self-limited febrile illness associated with headache, myalgias and fatigue after an incubation period of 2-14 days. About 50% of patients develop an atypical pneumonia and 30% hepatitis. Rarely patients may develop endocarditis, encephalitis or osteomyelitis. About one third of patients demonstrate a leukocytosis. The differential diagnosis includes other atypical pneumonias due to *Mycoplasma pneumoniae, Legionella pneumophila, Chlamydia psittaci, C. pneumoniae, tularemia or plague.* Pneumonia and hepatitis should raise a concern for leptospirosis. Mortality is 1-2 %, most often attributable to endocarditis.

As Q fever only became reportable in the US in the late 1990s, recent reporting is incomplete. In addition many illnesses are mild or not recognized and therefore not reported. In 2001, only 21 cases were reported. In 1985, an outbreak of Q fever hepatitis occurred in five sheep slaughterhouse workers in California. An additional seven cases were discovered during the epidemiologic investigation. Patients had fever, malaise, headaches and abdominal pain. All recovered after about a week. In 1988, a group of poker players developed Q fever pneumonia from a parturient cat that had given birth in the gaming room. In 1996, 35 persons living in a rural town in Germany became ill with Q fever. Most presented with fever and fatigue. Another 14 were found to have asymptomatic infection. Four patients were admitted with pneumonia. Infection was felt to have been spread by aerosolized dust contaminated from birthing sheep in a nearby farm. Recent cases in the US have been documented from California, Georgia, Pennsylvania and Tennessee.

Diagnosis of the organism is challenging. *C. burnetii* is very difficult to culture in the laboratory and is a serious health risk to the laboratory staff. Confirmation of the

diagnosis is therefore done serologically using indirect fluorescent antibody (IFA), enzyme linked immunosorbent assay (ELISA) or complement fixation. Acute Q fever is characterized by high IgG antibody titers to Phase II antigens and low titers to phase I antigens. The reverse is true of chronic illness. Acute Q fever may also be diagnosed by elevated IgM and IgA antibodies. Tissues can be tested for the presence of *C. burnetii* using immunohistochemical techniques.

The treatment of choice for acute Q fever is doxycycline 100 mg orally twice daily for 14-21days. Ciprofloxacin also has good invitro activity. Chronic Q fever generally involves prolonged courses of doxycycline and ciprofloxacin or doxycycline and hydroxychloroquine.

Since Q fever is not transmitted from person to person, standard precautions are adequate for patient care. Postexposure prophylaxis with doxycycline can be effective. A vaccine is not commercially available in the US, but an inactivated whole cell product is under investigation at USAMRIID.

- **Glanders**

Glanders is a zoonotic infection caused by *Burkholderia mallei*, a gram-negative aerobic bacillus. Human infection is contracted from infected horses, mules or donkeys by direct cutaneous or mucous membrane contact with the bacterium. During the American Civil War, a large epizootic occurred in 1863 in the Confederacy stables of Robert E Lee's Army in Lynchburg, Virginia. Three thousand horses and mules died of the "baneful scourge" or "farcy". Humans also contracted the illness from the horses during that time. Generally human infection is rare and has not been seen in the US since 1945. It is endemic in Africa, Asia, the Middle East and Central and South America. Interest in use of glanders as a biological weapon arose because of its highly infectious nature in an aerosol form.

Human infection can be acute or chronic in nature. The incubation period is 1-14 days. Acutely, patients develop fever, myalgia, headache and diarrhea. There may be cervical lymphadenopathy, splenomegaly, mucositis and a pustular rash. Pneumonia and bacteremia often lead to multiorgan abscesses and death if untreated. Chronically, cutaneous, muscular and multiorgan abscesses can form.

Diagnosis is based in culturing the organism from sputum, blood or tissues. It can grow readily on routine microbiology agar used in the clinical laboratory. The laboratory should be notified that *B. pseudomallei* is suspected so the technologists can take appropriate precautions and to be sure not to misidentify the pathogen. In 2000, a microbiologist working with *B. pseudomallei* at USAMRIID developed axillary lymphadenopathy and fever. Automated bacterial identification suggested that the pathogen was *Pseudomonas fluorescens* or *P. putida*. Later gas-liquid chromatography and 16S-ribosome RNA sequencing revealed the infection was due to *B. pseudomallei,* the first such case in the US since 1949. Complement fixation tests are available to measure antibody response. Titers > 1:20 are considered diagnostic.

Use of antibiotics (until sensitivities are available) may include oral amoxicillin/clavulanate, oral or parenteral trimethoprim-sulfamethoxazole or ceftazidime. Cutaneous diseases should be treated for 60-150 days. Systemic illness should be treated for six months.

Vaccines are not available. Postexposure prophylaxis with trimethoprim-sulfamethoxazole may be considered. Human to human transmission has occurred but is very rare. Standard precautions are adequate for hospitalized patients.

- **Melioidosis** (Whitmore's Disease)

Melioidosis is caused by *Burkholderia pseudomallei,* a gram-negative rod that is closely related to *B. mallei.* While melioidosis is a glanders-like illness, the natural reservoirs and human transmission are different for *B. pseudomallei* than for *B mallei*. It is not a zoonotic infection, although it can cause illness in sheep, cattle, goats, pigs, birds, cats, dogs and reptiles in addition to humans. The pathogen, originally named *Pseudomonas pseudomallei,* was discovered by Captain A. Whitmore in 1911 while working in Burma (now Myanmar). *B. pseudomallei* exists in soil and muddy waters in Southeast Asia and Northern Australia and to a lesser extent in the South Pacific islands, India, Africa, and the Middle East. Melioidosis is most common in Thailand where it be one of the more common causes of community-acquired pneumonia and bacteremia. Humans become infected most often from direct cutaneous contact with *B. pseudomallei* in muddy waters such as rice paddies during the rainy season. Illness can also be acquired by ingestion of contaminated water or inhalation of contaminated dust. Less commonly it can be transmitted sexually or by injection drug use. In endemic areas the great majority of the population becomes infected though severe illness is seen most often in those with underlying illnesses such as diabetes mellitus, renal failure, thalassemia, alcoholism and those with compromised immune systems.

Like glanders, patients with melioidosis may present acutely with localized cutaneous abscesses, pneumonia or bacteremia. The latter sepsis-like syndrome is seen in debilitated or immune compromised patients. Chronic suppurative infections may present as visceral abscesses, osteomyelitis or septic arthritis. Relapse after years of quiescence can be seen.

Diagnosis is based on the isolation of *B. pseudomallei* from the blood, sputum or abscesses. The laboratory should be notified that *B. pseudomallei* is suspected so the technologists can take appropriate precautions and to be sure not to misidentify the pathogen. A four-fold rise in complement fixing antibodies is considered diagnostic. Serological diagnosis of persons from endemic areas may be challenging because of the high background rate of positive titers.

Imipenem-cilastatin, meropenem or ceftazidime should be used for severe acute infections during the first two weeks of therapy. The remainder of the 20-week course can be completed with amoxicillin-clavulanate. Other agents with invitro activity include ceftriaxone, aztreonam, and ticarcillin-sulbactam. There is no vaccine. Nosocomial transmission can be avoided by the use of standard precautions.

- **Ricin Toxin**

Ricin is a glycopeptide toxin derived from beans or seeds of the castor plant, *Ricinus communis.* It is a byproduct of castor oil production. The poison is removed from the oil but remains in the waste "mash". Since castor beans are ubiquitous worldwide and the waste material contains 5% ricin toxin, illicit weapon production is possible. As little as 500 micrograms is lethal when injected. Accidental poisonings have occurred by chewing and swallowing as few as 2-20 seeds. Simply swallowing, but not chewing, the seed usually does not cause illness since the shell is very resistant to breakdown and release of the toxin. More

than 750 cases of accidental or deliberate ricin poisoning have been reported. The toxin acts by inhibiting protein synthesis.

Ricin can be used as a biological weapon in several different forms. If delivered as an aerosol, patients would become ill after about 8 hours with fever, cough and shortness of breath. Respiratory failure from non-cardiogenic pulmonary edema and shock with death ensuing would occur with 36-48 hours. Ingestion of ricin would cause fever, abdominal pain, nausea, vomiting and diarrhea. Gastrointestinal bleeding would follow with death occurring after several days from hemodynamic collapse.

Diagnosis in a single patient would be challenging. Large numbers of persons with similar symptoms may alert the clinician to ricin poisoning. Patients with inhalational poisoning would have bilateral infiltrates and a leukocytosis. Differential diagnosis would include other causes of severe community acquired pneumonia or gastroenteritis. Phosgene poisoning may cause similar pulmonary symptoms but would progress more rapidly. Ricin toxin assay from sputum, pharyngeal or blood samples can be attempted.

Treatment is supportive. There is no antidote, vaccine or postexposure prophylaxis available. There is no person to person transmission. Standard infection control precautions should be used.

- **Psittacosis** (parrot fever or ornithosis)

Psittacosis (from the Greek for parrot) is a pneumonic illness caused by *Chlamydia psittaci,* a gram-negative coccobacillary intracellular organism. Human infection is most often contracted by the inhalation of dried bird droppings or dust from psittacine birds such as parrots, macaws, cockatiels and parakeets. Turkeys, doves, pigeons and birds of prey may also transmit the illness as can, on rare occasions, mammals. Human illness has been described since the late 1800s. The organism was isolated in the 1930s. During the 10-year period of 1988-1998, 813 cases were reported to the CDC. Most of these infections were contracted from pet birds. This relatively low number of cases most likely represents an underestimation due the difficulty of diagnosing the illness.

Patients present after an incubation period of 5-14 days. Onset may be acute or insidious. Patients may have a nonspecific “flu-like” febrile illness or an atypical pneumonia with dry cough, shortness of breath, headache and myalgias. Physical examination may reveal a pulse-temperature deficit and hepatosplenomegaly. A blotchy erythematous rash (Horder’s spots) may be present. Infiltrates are seen on chest x-ray. Hepatitis, encephalitis, glomerulonephritis and a Coombs (+) hemolytic anemia may occasionally be present. Late and uncommon sequelae include endocarditis.

Diagnosis is suspected in persons with community acquired pneumonia who had been exposed to psittacine birds. Gram stain of sputum shows polymorphonuclear white cells but no pathogens. *C. psittaci* can be grown on tissue culture but not on routine laboratory agar. Diagnosis is usually confirmed by detection of antibodies by complement fixation.

The treatment of choice is oral or parenteral doxycycline for 21 days. Erythromycin may also be used but is felt to be less effective.

Person to person transmission is very rare but has been reported due to severe coughing paroxysms. Sexual transmission has also been reported. Standard infection control measures are adequate. There is no vaccine.

- **Food and water safety threats**

  Gastrointestinal infections caused by bacteria such as with *Campylobacter jejuni*, non-typhoidal *Salmonella*, *Vibrio cholerae* and *Escherichia coli 0157:H7* and parasites such as *Cryptosporidium parvum* are agents that could be used as bioweapons. Most of these agents would be used to contaminate food. Because of dilution of the pathogen(s) and chlorination of the water supply, contaminating reservoirs and drinking water sources are a less of a threat.

  C. jejuni, *Salmonella* and *Escherichia coli 0157:H7* are common causes of moderate to severe gastroenteritis worldwide. Patients may be incapacitated with colitis characterized by bloody diarrhea, abdominal pain and fever. Cholera is endemic in the Middle East, India, Africa, parts of Asia and Central and South America. It can cause a life threatening dehydrating diarrheal illness though without the symptoms of inflammatory colitis.

  Cryptosporidiosis is an acute watery diarrheal illness. It is most often self-limited except in immune compromised hosts who may continue to have chronic symptoms. A 1993 outbreak in Milwaukee from contaminated water supply caused an estimated 400,000 illnesses.

- **Epidemic Typhus** (Louse-borne, Jail fever, Brill-Zinsser disease)

  Epidemic or louse-borne typhus fever is caused by *Rickettsia prowazekii*, an obligate intracellular gram-negative coccobacillus that invades endothelial cells. It is found worldwide. Nathan Edwin Brill, an American internist, described a milder recurrent form of typhus. Hans Zinsser, an American microbiologist, recognized Brill's diseases as due to epidemic typhus.

  Acute epidemic typhus is transmitted from person to person by the human body louse (*Pediculus humanus corporis*) usually in the setting of overcrowding and poor sanitary conditions. It is therefore common during war and famine. After WWI an estimated 30 million cases occurred in the Soviet Union and Eastern Europe with 3 million deaths.

  During WWII epidemic typhus caused large number of infection in the concentration camps of the German Third Reich, making the German overseers fearful of this pathogen. Two Polish physicians, Drs. Eugeiusz Lazowski and Stanislav Matulewicz, took advantage of this fear and the fact that *R. prowazekii* cross reacts with certain *Proteus* species to create a pseudo-epidemic of typhus in war-torn Poland. These physicians "vaccinated" the non-Jewish members (Jewish persons found to have epidemic typhus were shot) of 12 villages with inactivated *Proteus* species (Proteus OX19) to cause false positive Weil-Felix reactions, an older test used to diagnose epidemic typhus. When the Nazis analyzed blood samples from these townspeople, it appeared that the villages had epidemic typhus. The towns were thus quarantined sparing up to 8,000 persons (Jewish and non-Jewish residents alike) from being transported to their deaths in concentration camps.

  The last US epidemic occurred among Irish immigrants coming to New York City in 1847. In the Eastern US, the flying squirrel was found to be a reservoir for *R. prowazekii*. Infected squirrel fleas are hypothesized as the vector to humans. From 1976 – 1983, 30 zoonotic cases were reported from US states including Georgia, Virginia, North Carolina, Tennessee, Indiana, Illinois, Ohio, Pennsylvania, Maryland, Massachusetts, New York and California. Symptoms included fever, headache, maculopapular rash, confusion and myalgias. There were no deaths.

Epidemic typhus begins acutely after an incubation period of 10-14 days. Most patients have fever, headache, myalgia, nausea and vomiting. Cough and confusion are common. A maculopapular rash begins on about day five of the illness and spreads centrifugally. Thrombocytopenia and elevated hepatic transaminases can be seen in patients with severe illness. Untreated patients have a 10%-30 % mortality rate.

As rickettsias are challenging and dangerous to isolate in the clinical laboratory routine culturing is not performed. The diagnosis is confirmed serologically with indirect fluorescence, complement fixation or enzyme immunoassay. Tissue samples can be stained by immunohistochemistry. Polymerase chain reaction may be used to attempt to identify the organism in blood. The Weil-Felix test is no longer used.

The treatment of choice is doxycycline 100 mg orally or intravenously twice per day to be continued for 2-3 days after defervescence. A single 100-mg dose of doxycycline may be curative. An inactivated vaccine has been made but is not wildly available. Health care workers can contract lice from infested patients. In the event of a biological attack with *R. prowazekii*, nosocomial transmission directly from person to person would not occur.

- **Bacterial Toxins**

Staphylococcal enterotoxin B (SEB) is an exotoxin produced by *Staphylococcus aureus*. It is one of the toxins responsible for food poisoning. As a weapon, it could be delivered as an aerosol or in food or water. After an incubation period of 3-12 hours, patients would develop fever, myalgias and headache. If ingested, additional symptoms would include nausea, vomiting and diarrhea. If inhaled, there may be cough, chest pain and shortness of breath. Estimated mortality after inhalation approaches 50-80%. Diagnosis would be challenging. The toxin can be detected in blood, sputum, urine and respiratory secretions early after the exposure by ELISA.

The *Epsilon toxin* is one of twelve toxins produced by *Clostridium perfringens*, an anaerobic gram-positive rod. *C. perfringens* is a well recognized cause of food poisoning and wound infections. Epsilon toxin is a neurotoxin capable of causing a hemorrhagic enteritis in goats and sheep. If used as a weapon, it would most likely be as an aerosol.

These toxins are not transmissible from person to person. Therapy is supportive. There is no vaccine or postexposure prophylaxis.

- **Viral encephalitis**

Arthropod transmitted encephalitis are well-established viral infections throughout the world. Their use as a biological weapon would most likely be in an aerosolized form. Infections endemic in North America include Eastern Equine Encephalitis (EEE), Western Equine Encephalitis (WEE), California Equine Encephalitis, LaCrosse virus and West Nile Virus (WNV). South America has Venezuelan Equine Encephalitis (VEE) and WEE. Asia has Japanese Encephalitis (JE). These viruses are transmitted by the bite of mosquitoes, ticks or sandflies depending on the viral species. WNV is endemic in Africa, West Asia and the Middle East. Since 1999, it has been a rapidly emerging epidemic in the US. In 2002, there were 4156 cases reported from 44 states and 284 deaths. In Vermont there was one human infection and no deaths, though 125 birds and 5 horses were found to be infected. Almost all counties in Vermont were found to harbor WNV infected birds with the largest numbers in Chittenden and Addison counties.

Most arboviral infections are asymptomatic. If clinical illness develops, patients become ill 3-21 days after the vector bite with fever, headache and altered mental status. Lumbar puncture reveals a lymphocytic pleocytosis. Therapy is supportive. There are no vaccines.

- **Nipah virus**

  Nipah virus is a zoonotic infection first recognized in 1997 in a farm worker in Sungai Nipah New Village in Malaysia who was hospitalized with encephalitis. Nipah virus, a paramyxovirus, is transmitted from pigs to human by close contact with respiratory secretion or urine. The Malaysian outbreak included 265 cases with 105 deaths. Control of the epidemic required the slaughter of a million pigs, devastating the regional economy and leading to billions in lost revenue. The pig culling was carried out by 1474 military personnel, six of whom seroconverted to the Nipah virus. Two of these soldiers developed encephalitis. As with other viral encephalitides, the illness may be asymptomatic, present as a "flu-like" illness or as progressive encephalitis ending in death. Use as a bioweapon would most likely be as an aerosol.

  Diagnosis would most commonly be serologic. The virus can be detected by PCR and grown in culture in specialty laboratories. Human to human transmission has not been reported. Therapy is supportive. There is no vaccine or postexposure prophylaxis available.

- **Other agents** suggested by the NIAID that have the potential to be used as biological weapons include Hanta virus, Crimea Congo hemorrhagic fever, Yellow Fever virus, Rabies virus, Influenza virus, other Rickettsia and multi-drug resistant tuberculosis.

FURTHER READING

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"The presenter does not have any financial arrangements or affiliations with a commercial entity that would impact the presentation. The presenter will be discussing the unlabeled use of drugs to treat category B and C agents"