

Melioidosis

*Pseudoglanders,
Whitmore Disease*

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IOWA STATE UNIVERSITY®

College of Veterinary Medicine
Iowa State University
Ames, Iowa 50011
Phone: 515.294.7189
Fax: 515.294.8259
cfsph@iastate.edu
www.cfsph.iastate.edu



INSTITUTE FOR
INTERNATIONAL
COOPERATION IN
ANIMAL BIOLOGICS

an OIE Collaborating Center

Iowa State University
College of Veterinary Medicine
www.cfsph.iastate.edu/IIAB/



Importance

Melioidosis is a bacterial disease that affects humans and many species of animals. While some infections are subclinical, others result in localized acute or chronic disease, or fatal septicemia. Because it can affect almost any organ, melioidosis can mimic many other diseases; it is sometimes called “the great imitator.” A misdiagnosis may be fatal; the causative organism, *Burkholderia pseudomallei*, is susceptible to a limited number of antibiotics. In endemic areas, melioidosis is an important cause of illness and death in humans and animals. It is also a serious concern in imported animals. In 1975, a panda apparently introduced melioidosis to the Paris Zoo, where it caused a severe outbreak. The epidemic spread to other zoos in Paris and Mulhouse, and to equestrian clubs throughout France. It decimated some zoo populations and caused at least two human deaths. In addition, there are fears that *B. pseudomallei* might be used as a biological weapon.

Etiology

Melioidosis results from infection by *Burkholderia pseudomallei*, a Gram negative bacillus in the family Burkholderiaceae. This organism was formerly known as *Pseudomonas pseudomallei*. It is closely related to *Burkholderia mallei*, the agent of glanders, as well as to *B. thailandensis* and *B. oklahomensis*.

Geographic Distribution

Melioidosis is endemic in Southeast Asia, China, the Indian subcontinent and parts of Australia. It has also been reported from the Caribbean, the Middle East, South America, Singapore and Taiwan. The situation in Africa is uncertain. Although isolated cases were reported from some African countries in the past, melioidosis is not a commonly reported disease in Africa. However, laboratory support is absent or weak in some countries, and this disease may be underdiagnosed.

Only non-indigenous cases of melioidosis have been reported in the U.S. Cases formerly thought to be *B. pseudomallei* were reported from Oklahoma after a farming accident and in Georgia after a car accident; these organisms have been reclassified as *Burkholderia oklahomensis* sp. nov.

Transmission

Animals and humans usually acquire melioidosis from organisms in the environment. *B. pseudomallei* is a saprophytic bacterium that is widespread in soil and muddy water in endemic areas. It is particularly common in moist clay soils.

Infections can occur by ingestion, by inhalation, or through wounds and abrasions. All three routes are thought to occur in animals. Infected animals can shed the organism in wound exudates and, depending on the site of the infection, from other sources including nasal secretions, milk, feces and urine. Transplacental transmission has been reported in goats, a pig and a spider monkey. Nosocomial transmission was reported in four cats at a veterinary hospital, possibly via contamination of a multidose injectable solution. Vector-borne transmission by mosquitoes (*Aedes aegypti*) and rat fleas (*Xenopsylla cheopsis*) has been reported, but the role of insect bites remains uncertain.

There have been a few reports of zoonotic transmission, often after contamination of skin lesions by exposure to infected animals, tissues including meat, or milk. However, most people become infected directly from the environment. Inoculation through skin wounds is thought to be the major route of transmission to humans. Inhalation, which usually leads to the pneumonic form of the disease, may be particularly important during periods of heavy rainfall and strong winds. The importance of ingestion is controversial. Person-to-person transmission has been described rarely, generally to family members in close contact (e.g. family members who nursed patients). Sexual transmission has also been suggested in some cases. Vertical transmission has rarely been proven, but a few cases have been described in newborns. One infant may have been infected by nursing culture-positive breast milk.

In non-endemic areas, contamination of the environment from infected animals or humans is a concern. Shed organisms can survive for months or years in soil and

water. In one report, *B. pseudomallei* remained viable in triple distilled water for more than three years. This experiment is ongoing, and unpublished reports suggest that the organism is still present fourteen years later. Other laboratories have reported that *B. pseudomallei* can survive in room temperature water for as long as eight weeks, in muddy water for up to seven months, and in soil for up to 30 months. This organism can also survive in some antiseptic and detergent solutions, and resists pH 4.5 for up to 70 days. One outbreak was associated with a contaminated container of commercial hand-washing detergent. *B. pseudomallei* is also relatively resistant to desiccation in soil, and can survive soil water content of less than 10% for up to 70 days. In addition, it can enter the cells of protozoa (*Acanthamoeba* or the dinoflagellate *Alexandrium minutum*) or the mycorrhizal fungus *Gigaspora decipiens*. This characteristic may help it survive environmental stresses.

B. pseudomallei seems to be capable of existing in a viable but non-cultivable state in the environment; although these organisms cannot be cultured, they can still cause disease. This phenomenon occurs in acid pH, as well as under other conditions. *B. pseudomallei* has an optimal pH range of 5-8. Below pH 4.5, there is a rapid reduction in the number of cells able to produce colonies, but a parallel increase in viable but non-cultivable organisms, which appear as Gram-positive, coccoid organisms. These organisms revert to conventional Gram-negative-bacilli if the acidic medium is replaced with fresh medium with a neutral pH.

Disinfection

B. pseudomallei is stated to be susceptible to numerous disinfectants including 1% sodium hypochlorite, 70% ethanol, glutaraldehyde and formaldehyde. However, unpublished experiments suggest that it can remain viable for some time in 0.3% chlorhexidine. Disinfectants may not completely eliminate this organism from drinking water, particularly when it is protected within protozoa or found in biofilms. Chlorination reduces the number of *B. pseudomallei* in water, but small numbers of bacteria have been isolated from water containing up to 1000 ppm. free chlorine.

There is little information on the susceptibility of this organism to sunlight or other sources of UV irradiation. Although one report suggested that *B. pseudomallei* is more resistant to UV light than most bacteria, several authors feel that its resistance is probably similar to other soil bacteria. Moist heat of 121°C (249°F) for at least 15 min or dry heat of 160-170°C (320-338°F) for at least one hour can also kill this organism.

Infections in Humans

Incubation Period

In naturally acquired infections, the incubation period varies from less than a day (after very high exposure) to several months or years. Incubation periods of more than two months are common. A few cases have remained subclinical for up to 29 years, and one infection apparently became symptomatic after 62 years. Infections from aerosolized forms in biological weapons are expected to have an incubation period of 10 to 14 days.

Clinical Signs

B. pseudomallei can cause a wide spectrum of clinical diseases. For this reason, melioidosis is sometimes called “the great imitator.” While some infections are inapparent, others result in acute pulmonary disease, septicemia, or localized acute or chronic suppurative infections. The frequency of the various syndromes can vary with the region; for example, parotid abscesses are common among children in Thailand, but rare in Australia. One syndrome can develop into another if the organisms spread to other sites.

Acute localized infections sometimes occur at the site of inoculation. In the skin, these infections appear as gray or white, firm nodules and ulcers. The nodules may caseate, and are often surrounded by inflammation. Regional lymphadenopathy and lymphangitis may also be seen. Other forms of acute localized disease include suppurative parotitis/ parotid abscesses, destructive corneal ulcers seen after corneal trauma, and cellulitis. Some infections may resemble necrotizing fasciitis. Genitourinary infections often manifest as prostatic abscesses. Localized infections can disseminate, but systemic infections are not always preceded by localized signs. Skin and subcutaneous infections can also result from the hematogenous spread of the organisms from other sites.

Pulmonary disease is the most common form of melioidosis. It can occur as either the primary syndrome or as a component of septicemia. The symptoms usually include fever, coughing, pleuritic chest pain and, in some cases, hemoptysis. Ulcerative lesions and nodules are sometimes found in the nose, and the septum may perforate. Severe weight loss may be seen. Pulmonary signs can develop suddenly, or may occur gradually after a prodromal syndrome characterized by headache, anorexia and generalized myalgia. Complications include pneumothorax, empyema and pericarditis. Untreated cases often progress to septicemia.

Septicemia is the most serious form of melioidosis. It is most common in people with pre-existing diseases such as diabetes, cancer and kidney failure. The onset is usually acute, with fever, rigors and other typical signs of sepsis. However, in some patients septicemia may develop more gradually, with a fluctuating fever often

associated with severe weight loss. Common symptoms of septicemic melioidosis include fever, severe headache, disorientation, pharyngitis, upper abdominal pain, diarrhea, jaundice and notable muscle tenderness. Pulmonary signs including dyspnea are common, and arthritis or meningitis may be seen. Some patients have a disseminated pustular rash with regional lymphadenopathy, cellulitis or lymphangitis. Septic shock is common, and it is usually fatal once it develops.

Chronic melioidosis is characterized by abscesses and suppurative lesions, which can occur in a variety of organs. Although the liver, spleen, skeletal muscle and prostate gland are affected most often, lesions can occur in any organ including the skin, lung, myocardium, bone, joints, lymph nodes and testes. Mycotic aneurysms are also seen. Rarely, melioidosis can result in brain abscesses, encephalomyelitis (often accompanied by flaccid paralysis) or meningitis. Fever may or may not be present in chronic melioidosis.

Some infected patients remain asymptomatic for years. These chronic carriers may eventually develop clinical disease, typically when they become immunosuppressed from another condition.

Communicability

In general, *B. pseudomallei* is not spread by casual contact. However, rare cases of person-to-person transmission have been described, usually between family members in close contact. Depending on the site of the infection, bacteria may be found in exudates from abscesses, urine, feces, nasal secretions and milk. Although vertical transmission has rarely been proven, a few cases of melioidosis have been described in newborns. Another infant was thought to be infected by nursing contaminated milk. Sexual transmission has been suggested in some cases, but it has not been proven. Transmission from humans to animals is theoretically possible.

Diagnostic Tests

Melioidosis can be diagnosed by recovering *B. pseudomallei* from blood, sputum, throat swabs, tissues or wound exudates. In the septicemic form, blood cultures may be negative until just before death. The soil and/or water may also be sampled during outbreaks. *B. pseudomallei* grows on most media including blood agar. Selective media such as Ashdown's selective medium are also used frequently. Mature colonies often have a wrinkled form; these colonies may be mixed with smooth colonies. A few strains, which are usually isolated from human sputum samples, form mucoid colonies. *B. pseudomallei* colonies have a characteristic putrid, earthy odor. (Due to the risk of infection, directly sniffing the plates is dangerous and not recommended.) On microscopic examination, the organisms are motile, short Gram negative bacilli, with bipolar or irregular staining in young cultures. *B. pseudomallei* can be identified by

biochemistry, or with latex agglutination tests to detect antigens. There are conflicting reports on the reliability of automated identification systems; however, some systems might misidentify *B. pseudomallei* as another organism. This is a particular concern in non-endemic areas where the isolation of *B. pseudomallei* is unexpected.

B. pseudomallei antigens can be identified directly in tissues, wound exudates or body fluids by direct immunofluorescence or latex agglutination. Antigen tests including enzyme-linked immunosorbent assays (ELISAs) have also been developed for the exotoxin and other bacterial components. PCR assays have been reported, and may be able to differentiate *B. mallei* DNA from *B. pseudomallei*. Other genetic techniques used to distinguish these two organisms include PCR–restriction fragment length polymorphism, pulse-field gel electrophoresis, 16S rRNA sequencing, variable number tandem repeat polymorphism, and multilocus sequence typing (MLST). These specialized genetic techniques may be mainly available in research laboratories.

Serologic tests may be helpful in some circumstances, particularly when paired sera are available. In some endemic areas, most of the population is seropositive, which limits the value of single tests. However, a high single titer in the presence of clinical signs may be suggestive. Serologic tests include agglutination, indirect hemagglutination, immunofluorescence, ELISAs, dot immunoassay, immunoblotting (Western blotting) and the immunochromatographic test (ICT). Complement fixation is uncommonly used. Cross-reactions can occur in serologic tests with closely related organisms including *Burkholderia mallei*, the causative agent of glanders, and *Burkholderia cepacia*. False positives have also been reported from other Gram negative bacteria including *Legionella* spp.

Treatment

B. pseudomallei is variably susceptible to antibiotics; this organism is intrinsically resistant to many drugs. Long-term treatment may be necessary. Multiple drugs were generally used in the past, but some newer single antibiotics are equally effective. Pulmonary resection or drainage of abscesses is sometimes necessary. Relapses can occur after apparently successful treatment, and lifelong monitoring is often recommended.

Prevention

B. pseudomallei is widely distributed in soil and standing water in endemic regions. People with diabetes or other predisposing conditions should take special precautions to avoid skin contact with these sources. In addition, gloves and rubber boots are recommended for anyone doing agricultural work. Skin wounds including abrasions or burns should be promptly and thoroughly cleansed. A few outbreaks have been linked to

contaminated drinking water supplies. Although small numbers of organisms may survive, chlorination of the water supply decreases the risk of infection. Because *B. pseudomallei* can be found in milk from infected ruminants, only pasteurized dairy products should be consumed. Veterinarians should take precautions to avoid exposure, including the use of gloves and protective clothing, when working with infected animals or collecting diagnostic samples. People who process meat should also wear gloves and disinfect knives regularly. In endemic areas, infected carcasses intended for human consumption are condemned and destroyed.

Laboratory workers may be exposed in clinical samples from patients, even where melioidosis is not endemic. Practices such as sniffing opened culture plates should be discouraged. Postexposure prophylaxis may be given after laboratory exposure to aerosols or contact with skin wounds, or to people with risk factors for septicemia.

In hospitals, ordinary precautions to prevent transmission in blood and body fluids should be taken. No vaccine is available.

Morbidity and Mortality

Melioidosis can occur as sporadic cases or outbreaks. A few outbreaks have been linked to contaminated drinking water supplies. In one outbreak, the source was a container of contaminated handwashing detergent. Increased numbers of cases are seen after heavy rainfall or flooding. In Australia, the risk for septicemia peaks two weeks after the beginning of the summer rains. Melioidosis is an underdiagnosed disease, because it mimics other diseases and because diagnostic facilities may be limited in some endemic areas. In some countries, cases are usually reported only from foreign travelers or in autopsy studies. Approximately 0-5 cases are seen annually in the U.S. These infections typically occur in immigrants and travelers, but clinical disease can also be seen in people who were exposed months or years earlier.

More than 70% of all cases of melioidosis occur in people who have other illnesses. This disease is particularly common in people with diabetes. Other chronic conditions including thalassemia, kidney disease, chronic lung disease, cancer and alcoholism, as well as the use of steroids, also increase the risk of disease. However, some clinical infections occur in previously healthy people, including laboratory workers who are occupationally exposed. The severity of the disease and the clinical signs are influenced by the strain of the organism, the host's immunity, the form of the disease and the dose of organisms. For example, acute suppurative parotiditis is common in children in Thailand, and usually has a good prognosis. However, even when treatment is optimal, the case fatality rate for acute severe melioidosis is 30% to 47%. The case fatality rate is greater than 90% in untreated septicemia, and 40-75% when it is treated. Once septic shock develops, the case

fatality rate is approximately 95%. Although the mortality rate is influenced by the availability of health care, melioidosis is a significant disease even when treatment is optimal. In Australia, the mortality rate for all patients with melioidosis is close to 20%.

Infections in Animals

Species Affected

Many terrestrial and aquatic mammals, as well as birds and fish, can be affected by melioidosis. In Australia, goats, sheep and pigs are infected most often; sheep and goats seem to be particularly susceptible to this disease. Cases of melioidosis have also been reported in dogs, cats, cattle, buffalo, camels, alpacas, horses, mules, zebra, deer, tree kangaroos, wallabies, koalas, various nonhuman primates, captive marine mammals, crocodiles, snakes, tropical fish and some species of birds including parrots. Rodents and rabbits can be infected in the laboratory.

Incubation Period

The incubation period ranges from days to months or years. Some abscesses are carried asymptotically.

Clinical Signs

Subclinical infections are common in animals, and asymptomatic abscesses may be found at slaughter. Symptomatic melioidosis may be acute, subacute or chronic, and mild or severe. The lungs, spleen, liver and associated lymph nodes are often involved in animals, but any organ can be affected. The effects vary with the site. Acute melioidosis, which is most often seen in young animals, often occurs as septicemia. Localized respiratory signs, gastrointestinal symptoms, septic arthritis with lameness, osteomyelitis, mastitis, orchitis, aortic aneurysms and other syndromes may be also seen. Neurological signs have been reported in many species including cows, goats and horses. Septicemia or extensive involvement of the vital organs can be fatal.

Forms of melioidosis reported in mammals and birds

Pulmonary melioidosis is common in sheep; typical symptoms are fever, severe coughing, respiratory distress and profuse mucopurulent yellow nasal and ocular discharge. Some sheep become arthritic and lame. In others, the only symptoms may be fever and generalized weakness. Neurological signs including circling, incoordination, blindness, hyperesthesia, nystagmus and spasms have also been reported. Orchitis with testicular nodules can occur in rams. In goats, respiratory disease is less severe than in sheep, and coughing is not a prominent sign. Progressive emaciation, lameness or hindleg paresis, and abortions have also been reported in goats. Mastitis and aortic aneurysms may be particularly common in this species.

Melioidosis

Pigs may be relatively resistant to melioidosis when husbandry and nutrition are good. Adult pigs tend to develop chronic infections with few symptoms; however, enlarged lymph nodes (particularly the submandibular nodes) may be palpable. Progressive emaciation, neurological signs, incoordination, multiple skin ulcers and diarrhea have also been reported. Young pigs can develop acute septicemia with fever, anorexia, coughing and nasal and ocular discharge. Occasional abortions or stillbirths have been seen in sows, and orchitis can occur in boars. In endemic regions, asymptomatic splenic abscesses are often found in pigs at slaughter.

Various forms of melioidosis have been reported in horses. Generally, the disease lasts approximately three weeks to three months. The symptoms may include weakness, emaciation, edema and lymphangitis of the limbs, mild colic, diarrhea, and signs of pneumonia including coughing and nasal discharge. Skin infections can initially resemble fungal eczema, but later become papular. Hyperacute septicemia with high fever, limb edema, diarrhea and rapid death has also been reported. Acute meningoencephalitis can be seen in rare cases.

Melioidosis is rarely reported in cattle. Most cases in adult cattle have been chronic. Fever, dyspnea, continuous profuse salivation and neurologic signs were reported in one animal. In two other cases, abscessation or acute, localized arthritis was seen after wound contamination. Acute melioidosis has been reported in a calf.

Camels may develop chronic respiratory disease with a hacking cough, purulent nasal discharge and dyspnea. Hindleg ataxia and a wasting disease with severe emaciation have also been reported. Acute septicemia has been seen in both camels and alpacas.

Acute, subacute or chronic melioidosis can occur in dogs. Acute cases are characterized by septicemia with fever, severe diarrhea and fulminant pneumonia. Subacute disease can begin as a skin lesion with lymphangitis and lymphadenitis; untreated cases may progress to septicemia over a week to several months. Respiratory disease can also be the initial syndrome. In addition, chronic disease can occur in any organ; it may be accompanied by anorexia, myalgia, edema of the limbs and skin abscesses. Abscesses have also been reported in various organs in cats. In two recently described cases, the symptoms were not strongly suggestive of an infectious disease. One cat presented with jaundice and anemia, and died soon after it was seen. Fatal neurological disease was reported in the second cat, possibly after dissemination from an infected foot wound.

Most cases in captive marine mammals have been characterized by acute septicemia with fever, inappetence, anorexia and listlessness followed by death. Unlike other species, respiratory distress was not reported. Enteric disease with diarrhea and liver abscesses has been seen in some dolphins.

Although birds may be relatively resistant to melioidosis, fatal cases with lethargy, anorexia and diarrhea have been reported in various avian species in Australia. Experimentally infected chickens remained asymptomatic.

Communicability

Most cases of melioidosis are acquired from the environment, and direct animal-to-animal transmission is uncommon. However, infected animals can shed *B. pseudomallei* in wound exudates, urine, feces and nasal secretions. This organism has been found in mastitic milk from goats and cattle. Subclinically infected animals can shed *B. pseudomallei*.

Rare cases of zoonotic transmission have been reported. Humans can be infected by ingesting contaminated milk, or by touching contaminated tissues and secretions with broken skin.

Post Mortem Lesions [Click to view images](#)

At necropsy, the major findings are multiple abscesses containing thick, caseous greenish-yellow or off-white material. These abscesses are generally not calcified. The regional lymph nodes, lungs, spleen, liver and subcutaneous tissues are most often involved, but abscesses can occur in most organs. In animals with respiratory disease, exudative bronchopneumonia, consolidation and/or abscesses may be found in the lungs. Suppurative lesions including nodules and ulcers may also be found on the nasal mucosa and septum, as well as on the turbinate bones. These nodules may coalesce to form irregular plaques. Meningoencephalitis, severe enteritis, suppurative polyarthritis and other syndromes have also been reported. Aortic aneurysms and mastitis are common in goats. Splenic abscesses are often found in asymptomatic pigs at slaughter.

Diagnostic Tests

Melioidosis is diagnosed by isolating *B. pseudomallei* from infected animals. This organism can be found in abscesses and wound exudates, in the milk of animals with mastitis, and in the feces of animals with diarrhea. Throat swabs, sputum, blood and urine are also expected to contain bacteria in some cases. Because the number of bacteria in the latter samples is usually small, particular care should be taken to preserve them during sample shipment to the laboratory. Environmental samples may be taken from soil and/ or water during outbreaks.

B. pseudomallei grows on most media including blood agar. Selective media such as Ashdown's selective medium are also used often. Mature colonies often have a wrinkled form; these colonies may be mixed with smooth colonies. A few strains form mucoid colonies. *B. pseudomallei* colonies have a characteristic putrid, earthy odor. (Due to the risk of infection, directly sniffing the plates is dangerous and not recommended.) On microscopic examination, the organisms are motile, short Gram negative bacilli, with bipolar or irregular staining in

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Serology is used in some species including horses, goats and dairy cattle. Animals in endemic areas often have pre-existing titers. Available serologic tests include indirect hemagglutination, immunofluorescence, complement fixation and other assays. Cross-reactions can occur in serologic tests with closely related organisms including *Burkholderia mallei*, the causative agent of glanders, and *Burkholderia cepacia*. False positives have also been reported from other Gram negative bacteria including *Legionella* spp.

Treatment

B. pseudomallei is susceptible to some antibiotics; however, this organism is intrinsically resistant to many drugs. Relapses can occur when treatment is stopped.

In non-endemic regions, infected animals are euthanized rather than treated. Livestock may also be culled in endemic areas, as treatment can be expensive and protracted, and it is often unsuccessful; however, pets are sometimes treated. To minimize the risk of relapses, lifelong monitoring may be advisable.

Prevention

Melioidosis is usually acquired from the environment, particularly after contact with soil or water. To minimize contact with dirt, animals can be raised on wooden slats, concrete or paved floors. Providing safe drinking water is important in endemic areas. *B. pseudomallei* is particularly common in muddy water, and it is less likely to be found in fresh or clear water. Although small numbers of bacteria may survive treatment, chlorination of the water supply decreases the risk of infection. Carnivores and omnivores should not be allowed to eat contaminated carcasses. Licensed vaccines are not available.

Euthanasia of infected animals is often recommended even in endemic areas, because melioidosis is difficult to treat and can be zoonotic. After culling infected animals, the premises should be disinfected. If infected animals are not euthanized, precautions should be taken to protect people and other animals. Strict hygiene is necessary to prevent transmission from infected horses in stables. The feces from infected horses should be removed several times a day, and the premises should be disinfected regularly with potassium hypochlorite and cresol solutions. The hooves and lower legs of the animals should also be disinfected. Food and water should be provided as aseptically as possible. Standing water should be allowed only in limited quantities or disinfected immediately.

In non-endemic areas, infected animals are usually euthanized to prevent the introduction of disease, and the premises are disinfected.

Morbidity and Mortality

The susceptibility to clinical disease may vary between species. Pigs generally seem to be more resistant to symptomatic melioidosis than sheep and goats, and infections in cattle are very rare. Immunosuppression may predispose cats and dogs to clinical disease. Approximately 19% of a group of military dogs that served in the Vietnam War was seropositive but asymptomatic. One outbreak occurred in marine mammals at a Hong Kong oceanarium after heavy summer rains washed soil into the animals' water. However, melioidosis does not appear to be a problem in marine mammals in the wild.

The mortality rate varies with the site of the lesions, but can be high in sheep. Extensive abscesses and involvement of the vital organs can be fatal. Septicemia has a high case fatality rate, but it seems to be less common in animals than humans. Most cases of septicemia are seen in young animals.

Internet Resources

Centers for Disease Control and Prevention (CDC)

http://www.cdc.gov/ncidod/dbmd/diseaseinfo/melioidosis_g.htm

eMedicine. Glanders and Melioidosis

<http://www.emedicine.com/emerg/topic884.htm>

Food and Agriculture Organization of the United Nations (FAO). Manual for the Recognition of Exotic Diseases of Livestock

<http://www.spc.int/rahs/>

FAO. Manual on Meat Inspection for Developing Countries

<http://www.fao.org/docrep/003/t0756e/t0756e00.htm>

Public Health Agency of Canada. Material Safety Data Sheets

<http://www.phac-aspc.gc.ca/msds-ftss/index.html>

The Merck Manual
<http://www.merck.com/pubs/mmanual/>
The Merck Veterinary Manual
<http://www.merckvetmanual.com/mvm/index.jsp>

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