Speaker 1 (00:05):

Welcome to part one of CDC's training on Plague Response for Healthcare Providers. Today, we will provide an overview of plague, including microbiologic characteristics, epidemiology, the most common clinical forms of plague and a summary of plague diagnostics. Each section will include special considerations in the event of an intentional release of *Yersinia pestis*, the causative agent of plague. First, we will review the microbiologic characteristics and epidemiology of plague. Plague is caused by *Yersinia pestis*, a gram-negative bacillus and facultative intracellular pathogen. *Y. pestis* has a safety pin appearance with bipolar staining on microscopy, shown here using a Wright-Giemsa stain. The bacteria initially infects macrophages. Then in later stages of infection fulminate extracellular growth can result in local spread of infection and bacteriemia. Plague is endemic in parts of Africa, South America, and Central Asia, as well as the Western United States. Scientists believe that plague evolved on the high plains of Eurasia.

It has since become endemic in many areas worldwide. The natural hosts in the United States are ground rodents, primarily prairie dogs, and certain squirrels. Fleas serve as the vector and transmit *Y. pestis* in an enzootic cycle among rodents in the wild. Other mammals, including humans, can become infected after being bitten by an infected flea or handling the carcasses of animals that died of plague. Domestic pets can be infected with *Y. pestis* either from infected fleas or direct contact with infected wildlife. While both dogs and cats can develop plague, cats tend to develop more severe illness. Both cats and dogs can transmit the infection to their owners indirectly through flea bites or directly by coughing, in cases where the pet has pneumonic plague. This map shows reported cases of plague in the United States by county of residence. Each dot represents a single case and is randomly placed within the county. Note that the dot in Illinois was in a laboratory worker and does not represent natural exposure.

In recent decades, there have been an average of seven human plague cases reported each year in the United States with a range of one to 17 cases per year. There are three primary ways that people become infected with *Y. pestis*. The first is from the bite of an infected flea, which is the most common method of transmission. Second, people become infected by directly handling the tissues or carcasses of infected animals. Finally, *Y. pestis* can be transmitted through direct inhalation of infectious droplets. This usually results in pneumonic plague. Direct inhalation of *Y. pestis* can occur when a person or animal with pneumonic plague, coughs and generates droplets that are then inhaled by another person. Aerosolizing procedures, such as necropsy, can also spread *Y. pestis* to people if adequate personal protective equipment is not worn. *Yersinia pestis* has bioterrorism potential and is classified as a tier one select agent, the highest risk category, because it can be transmitted from person-to-person, has a high case fatality rate if untreated and can be aerosolized.

Plague was used as a bioterrorism agent during World War II when the Japanese Army dropped plague infected fleas over cities in China. Additionally, both the United States and the Soviet Union had active bioweapons programs during the Cold War. More recently, domestic extremists and people with links to terrorist organizations have considered the use of plague bioweapons in terrorist attacks. The three most common clinical forms of plague are bubonic, septicemic, and pneumonic. Bubonic plague accounts for approximately 75% of plague cases. It most commonly occurs after the bite of an infected flea. The incubation period is two to eight days. The case fatality rate is approximately 66% for patients who do not receive treatment and 13% for patients who are treated with antimicrobials. As with other forms of plague, illness begins with a fever, headache, chills, myalgias, arthralgias, and weakness. Patients with plague typically have white blood cell counts of 12,000-25,000 cells per cubic milliliter with a predominance of immature polymorph nuclear leukocytes. Leukemoid reactions with white blood cell counts as high as 50,000 cells per cubic milliliter or more can occur, especially in children.

The characteristic bubo forms in a lymph node near the inoculation site. Patients typically have tenderness and pain in one or more regional lymph nodes. Femoral and inguinal lymph nodes are most commonly involved, followed by the axillary and cervical nodes. The surrounding tissue of the infected nodes may become edematous and the overlying skin may be erythematous. Buboes are exquisitely tender, and often remained enlarged and painful for a week or more after treatment has begun. Buboes can occasionally become fluctuant. In about 5-10% of cases, inspection of the skin surrounding or distal to the bubo reveals the site of a flea bite marked by a small papule, pustule, scab or ulcer, which in some instances may be confused with lesions caused by tularemia or anthrax.

In general, plague buboes are distinguishable for most other causes of lymph adenitis by their rapid onset, extreme tenderness, accompanying signs of toxemia, an absence of obvious ascending lymphangitis. Differential diagnosis for bubonic plague includes streptococcal or staphylococcal adenitis, tularemia, cat scratch disease, mycobacterial infection, strangulated inguinal hernia, and Chancroid or other sexually transmitted diseases that cause regional lymph adenitis. Septicemic plague accounts for approximately 15% of plague cases. Septicemic plague most commonly develops after progressing from other clinical forms. Typically, bubonic.

The incubation period for septicemic plague is poorly defined, but likely occurs within days of exposure. The case fatality rate is 90% if untreated. And even with prompt treatment can still be as high as 30-40%. Septicemic plague is characterized by dissemination of infection and a rapidly progressive overwhelming endotoxemia. Presenting symptoms include acute fever, chills and prostration, often accompanied by gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and abdominal pain. The course of illness is fulminate. Patients develop disseminated intravascular coagulation, or DIC, with petechiae and ecchymosis, refractory hypotension, renal failure, obtundation, and other signs of shock. Acute respiratory distress syndrome, or ARDS, can occur in septicemic plague and may be refractory to treatment. Localizing signs are often absent and it can be difficult to distinguish septicemic plague from other types of sepsis. Differential diagnosis for septicemic plague includes any other overwhelming systemic infection, such as meningococcemia, gram-negative sepsis with other pathogens and bacterial endocarditis. As abdominal pain is a common feature, both appendicitis and diverticulitis could also be confused with septicemic plague.

Pneumonic plague is the third most common form of plague, accounting for approximately 10% of cases. It has a shorter incubation period of just one to three days. Pneumonic plague is notable because it is the only form that can be transmitted from person-to-person. Pneumonic plague is almost always fatal without treatment. Even with prompt treatment, the case fatality rate is high at nearly 30%. Patients with pneumonic plague are likely to have a prolonged hospitalization and slow recovery. Pneumonic plague is divided into primary and secondary disease. Primary pneumonic plague is caused by direct inhalation of infected respiratory droplets. The onset is often sudden with fever, chills, headache, myalgias, weakness, dizziness, and chest discomfort. Primary pneumonic plague is principally an alveolar process. And the sputum is most often watery or mucoid, blood tinged and frothy. Sputum may become frankly bloody in untreated patients. As illness progresses, cough, sputum production, chest pain, and tachypnea typically predominate.

These may be accompanied by hemoptysis, increasing respiratory distress and circulatory collapse. Secondary pneumonic plague is caused by hematogenous spread of infection to the lungs from another anatomic site. Initially, secondary pneumonic plague manifests as an interstitial pneumonitis in which sputum production is often scant. However, left untreated, it will also progress to a severe bronchopneumonia with bloody sputum. Radiographic findings in patients with pneumonic plague are variable and include unilateral or bilateral alveola infiltrates, plural effusions, and mediastinal or Hilar lymphadenopathy. Untreated patients show rapidly progressive bronchopneumonia, parenchymal

necrosis and hemorrhage. Occasionally, patients develop pneumonic abscesses and result in cavities. Management of patients with pneumonic plague requires intensive medical and nursing support. Death can occur quickly in patients who do not receive prompt treatment with effective antimicrobials. Bloody sputum, as found in patients in advanced stages of illness, contains large numbers of plague bacilli. A coughing patient can spread infection to people in close contact, defined as within six feet, through respiratory droplets.

Respiratory droplet precaution should be used with any suspect case due to the risk of person-to-person transmission. Patients with suspected pneumonic plague should wear surgical masks for evaluation and transport. Healthcare providers should wear a surgical mask when caring for these patients. Additionally, there is a theoretical risk of transmission during aerosol generating procedures. Consider wearing an N95 respirator during these procedures for additional protection. The differential diagnosis of pneumonic plague includes other bacterial pneumonias, such as pneumococcal pneumonia, tularemia, mycoplasma, Legionnaires' disease, and Q fever. Severe viral pneumonia, including influenza, Hantavirus pulmonary syndrome, COVID-19, and other coronavirus infection such as Middle East Respiratory Syndrome, could also be confused with plague.

Although rare, two other presentations of plague deserve mention. Plague pharyngitis and meningitis. Plague pharyngitis may develop after respiratory droplet exposure or from the ingestion of infectious undercooked meat. Plague pharyngitis is an uncommon condition and presents with fever, sore throat and cervical lymph adenitis. In its early stages, it may be clinically indistinguishable for more common causes of pharyngitis. Cervical or submandibular buboes usually develop secondary to the pharyngeal involvement. Meningitis is another uncommon, but serious manifestation of plague. Meningitis may be part of the initial presentation of plague. However, its onset is often delayed and may result from insufficient antimicrobial treatment of the primary illness. Plague meningitis presents as a typical bacterial meningitis with fever, headache, meningismus, altered mental status and polymorphonuclear leukocytosis in the cerebral spinal fluid.

In situations where you suspect plague, do not wait for diagnostic test results. Begin treatment with antimicrobials immediately. Plague can be rapidly fatal if not treated promptly. As with many diseases, a high index of clinical suspicion and a careful history and physical examination are required to make a timely diagnosis of plague. A delayed or misdiagnosis of plague is associated with a high case fatality rate. Travelers who become infected in an endemic area and seek care after returning home are especially at risk. Laboratory tests for plague are highly reliable when conducted by people experienced in working with *Y. pestis*, but such expertise is usually limited to specialized reference laboratories. Contact your local public health laboratory for assistance with diagnostic testing and coordination with CDC. Guidelines for *Y. pestis* laboratory testing from the American Society for Microbiology can be found at the link here.

If plague is suspected, laboratory personnel should be notified when clinical specimens are sent so they can take appropriate bio safety precautions. Laboratory specimens should be obtained promptly. Appropriate diagnostic specimens include blood, lymph node aspirates from patients with suspected buboes, sputum samples or tracheal-bronchial aspirates in patients with suspected pneumonic plague and cerebral spinal fluid in those with meningeal signs. Bacterial culture of blood, CSF, sputum, or bubo aspirates, and nucleic acid amplification tests, such as PCR, are the most accurate tests. The specific tests performed can vary by specimen type. Blood cultures should be collected from all patients with suspected plague. Keep in mind that blood cultures may be negative in the early stages of primary bubonic and pneumonic plague. If a lymph node aspirate is obtained for culture, a small amount of sterile saline can be injected into the bubo prior to aspiration. In culture, *Y. pestis* grows at 28-35 degrees Celsius.

The organism can be grown on a variety of different media, including blood auger. Small colonies develop after 48 hours. Laboratory confirmation of plague is based on one, a positive *Y. pestis* phage lysis assay on a clinical isolate. Or two, a fourfold or greater change in serum antibodies to *Y. pestis* F1 antigen in acute and convalescent paired sera. Here, you can see an image of phage lysis testing. The top band and three lowest bands are positive indicating the presence of *Y. pestis*. While the second band from the top is the negative control. A presumptive laboratory diagnosis of plague can be made when *Y. pestis* is detected by PCR from a clinical specimen, or if there's a positive F1 antigen antibody titer from a single serum specimen. Note, that plague may be initially misidentified by automated laboratory systems, particularly MALDI-TOF, resulting in a delay in accurate diagnosis and appropriate treatment.

It's important to note that antimicrobial resistance has never been observed in a naturally acquired *Y. pestis* infection in the United States. However, if a bioterrorism event is suspected, antimicrobial susceptibility testing should be performed as strains in these events may be modified to confer antimicrobial resistance. Because of recent concerns with bioterrorism, the Laboratory Response Network, or LRN, a system of participating laboratories across the United States has been developed. The LRN can conduct laboratory testing for specific pathogens when requested by a state or jurisdictional public health laboratory. In an emergency, the CDC Emergency Operations Center can be reached 24 hours a day, seven days a week at (800) 232-4636. Thank you for watching part one in this series. Part two will review treatment and prophylaxis of plague.