Yersinia pestis

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Plague, or more specifically, bubonic/septicemic/pneumonic plague is caused by the *Yersinia pestis* bacterium\(^1\). Discovered independently by both Alexandre Yersin and Shibasaburo Kitasato during the 3rd pandemic in June of 1894\(^2\), *Y. pestis* is a pleomorphic, gram-negative, nonsporulating, nonmotile, zoonotic, coccobacillus. Giemsa or methylene blue stained specimens exhibit bipolar staining (closed safety pin appearance) that may not be visible on a gram stain\(^3\). Additionally, *Y. pestis* is capsulated but nonacid-fast and is facultatively anaerobic, with an optimum growth temperature of 28°C and a growth range of 2-35°C. Along with being catalase positive, oxidase and urease negative, and non hemolytic, *Y. pestis* is not a lactose fermenting bacterium\(^4\).

When attempting to identify *Y. pestis* in a lab setting the samples should be inoculated on a sheep blood agar plate and MacConkey (MAC) agar plate incubated at 37°C with a comparison plate incubated at 28°C to look for increased growth typical of *Y. pestis*. If the sample is *Y. pestis* then after 24 hrs the SBA plate will have pinpoint grey-white translucent colonies that will have a "fried egg" or "hammered copper" appearance after 48 hours\(^5\). The MAC culture will have clear or white colonies. Any samples cultured in a broth will have flocculent clumps on the sides of an undisturbed tube at 24 hrs\(^5\). A Giemsa stain should be performed to check the bacteria for bipolar staining if not evident in the initial gram stain. Biochemical tests for *Y. pestis* will find it to be oxidase, urea, and indole negative; catalase positive, and TSI K/A with no gas or H\(_2\)S\(^6\). Once the above tests have confirmed a preliminary identification of the bacterium as *Y. pestis* a direct fluorescent antibody(DFA) stain can be performed to detect the F1 envelope antigen from a sample taken from an infected subject and cultured at above 37°C\(^3\). A positive DFA stain is a presumptive identification and does not constitute 100% confirmation that the sample is *Y. pestis*. Confirmation that a cultured sample is indeed *Y. pestis* can be achieved through bacteriophage lysis tests at 25°C and 37°C, an F1 antigen-capture ELISA test, and PCR assays which can ID signature genes of *Y. pestis* very quickly\(^3\).

Humans are not the primary hosts of *Y. pestis*, which uses rodents as its primary reservoir with transmission to the human host occurring through rat/rodent flea bites or inhalation of droplets from infected humans. After the fleas living on infected rodents ingest the bacterium living in the host's blood, *Y. pestis* multiply in the flea's stomach and eventually block entry into the stomach of the flea. This causes the flea to overcome starvation by sucking as much blood as possible from the host, re-depositing the bacterium in the victim's skin when the attempts to swallow more blood cause the flea to vomit the bacteria blocking its stomach into the wound\(^6\). After the host rat dies the infected fleas seek out other sources of blood which is when humans are normally infected through the infected flea bite. This route of infection causes bubonic plague in the majority of incidences with occasional septicemic plague resulting. Inhalation of
droplets from an infected person or animal causes pneumonic plague which is the most virulent and normally fatal if not treated within 24 hrs of infection. If *Y. pestis* is deposited directly into the bloodstream and does not cause buboes then septicemic plague can result. Septicemic plague normally follows bubonic or pneumonic plague.

Key signs and symptoms of *Y. pestis* infection vary depending on the portal of entry and thus the type of plague contracted. Bubonic plague is characterized by an incubation period of 1-7 days and the sudden onset of fever, chills, aches and weakness. Shortly after infection the subject will present one or many swollen lymph nodes in the form of buboes of 1-10 cm in the groin, under the armpits or cervical region. The buboes will be very tender and uniform in shape. Additionally the subject may experience vomiting and complications including secondary septicemic plague (occurs in majority of subjects), secondary pneumonic plague, meningitis and secondary infections may arise. Death occurs in approximately 50% of untreated cases and 15% of those that receive antibiotic therapy.

Septicemic plague is a normal secondary result of untreated bubonic plague and may present as the primary plague type if *Y. pestis* does not form buboes and directly infects the bloodstream. Fever, chills, nausea/vomiting, aches, gastrointestinal symptoms, low blood pressure, septic shock, and gangrene of the extremities caused by small arterial thrombosis are common symptoms. Septicemic plague can quickly produce sepsis, disseminated intravascular coagulation, and multisystem infection and failure if left untreated. As with bubonic plague, development of secondary pneumonic plague is possible. Death occurs in approximately 40% of treated individuals with untreated death rates approaching 100%.

Pneumonic plague is the most deadly type of *Y. pestis* infection and is extremely contagious through exhaled droplets. Typically the pneumonic form results from advanced bubonic plague but can be the primary from if droplets are inhaled from an infected person. Common symptoms include fever, chest pain, infiltrate in lungs, hemeptysis, nausea, vomiting, abdominal pain, diarrhea, cyanosis, sepsis syndrome and meningitis. Close to 100% of cases end in death if antibiotics are not administrated within 24 hours of the onset of symptoms. This is not a hard line however and recovery is possible if the 24 hr windows is missed.

The plague that *Y. pestis* is responsible for is also known as the "Black Death" during the medieval ages and is responsible for the deaths of approximately 60% of the total European population during the second pandemic or "Great Plague" during the 14th century. The Black Death as it was called then wiped out entire towns and killed so many people that European social structures were permanently changed. So great was the impact of this pandemic that the symptoms of the bubonic plague were immortalized in the original iteration of the nursery rhyme "Ring Around the Rosy." This second pandemic originated in China and is the most commonly thought of example of the plague, but there was one pandemic that occurred earlier around 541 AD called the Justinian Plague. This earlier pandemic lasted approximately 200 years and killed over 25 million people. A third plague appeared in china in the 1860s and over the course of
twenty years spread to every major continent using the shipping lines. This third plague claimed over 10 million lives, but it was during this plague that a bacterium (\textit{Y. pestis}) was determined to be the cause and rat fleas were the primary form of transmission. This discovery greatly aided the control of the plague but \textit{Y. pestis} found other hosts that allowed it to become endemic to many rural areas.

\textit{Y. pestis} possesses many virulence factors that allows it to easily infect a human host and evade its host's immune response. The heat labile capsule that surrounds the coccobacilli protects it from phagocytosis as do the F1,V, and W antigens that appears on its surface. Once inside the host's body \textit{Y. pestis} produces a protease called plasminogen activator (Pla) that degrades fibrin and other extracellular proteins to aid the spread of the bacterium from the infection site. Pla expression during primary pneumonic plague is crucial for the rapid replication of \textit{Y. pestis} in the host's airways. Additionally pla protease degrades the C3b and C5a components of complement, preventing the opsonization of the bacterium and allowing it to evade phagocytes to an even greater extent. Multiple toxins are produced but the two associated with virulence are a lipopolysaccharide endotoxin ("plague toxin") and \textit{Yersinia} murine toxin (Ymt). Plague toxin produces classic endotoxic shock symptoms mostly though interactions with the lipid A element of the toxin. Ymt plays a crucial role for maintaining \textit{Y. pestis} populations in infected fleas, and is highly toxic to rats but does not affect humans infected with the bacterium.

Once a human has been infected with \textit{Y pestis} early diagnosis is imperative to the well being of the patient. After a \textit{Y pestis} infection has been confirmed the patient should be isolated from others and be immediately started on antibiotics. Isolation is especially important if the patient has pneumonic plague as it is extremely east to transmit this variant. It has been shown that \textit{Y pestis} is vulnerable to sulfadiazine, streptomycin, tetracycline, chloramphenicol, and recently levofloxacin if properly administered in conjunction with supportive therapy including respiratory support when needed. In addition to treating the \textit{Y pestis} it is important to treat those who have been exposed to the infected person to neutralize the risk of an epidemic occurring with a pneumonic plague patient. If multiple cases of \textit{Y pestis} infection occur in a localized area then control of the bacterium can be achieved through the reduction of the local rodent and flea populations and removal of possible habitats in the area. While rodents are the primary reservoir of \textit{Y pestis} effective control can be maintained by taking precautions against flea bites. If \textit{Y pestis} is known to be endemic to a particular region efforts should be taken to monitor its presence in local rodent populations to predict and prevent outbreaks.

Efforts to develop a vaccine for plague have been underway for almost a century and while a vaccine was developed it was generally ineffective any only protected those vaccinated for 6 months against the bubonic form of the plague. The only vaccine developed is no longer being produced and is not currently available to the public, with only laboratory workers and those involved in crisis situations receiving it. The vaccine itself, containing formulin-inactivated whole cell \textit{Y pestis}, was developed in 1890 and was commercially available in the United States until 1999 when it was discontinued. There are efforts currently underway to
produce an effective vaccine to *Y. pestis* with most candidates focusing on the F1 capsular antigen and the V antigen.

*Y. pestis* mostly resides in the African countries (95% of reported cases) with the three most endemic countries being Madagascar, the Democratic Republic of Congo, and Peru. Worldwide in 2013 there were 783 reported cases with 126 deaths. In the United States *Y. pestis* is found in the rural western areas but there have been no epidemics in the United States in the 20th or 21st centuries and only 999 confirmed or probable cases between 1900 and 2010.

**Bibliography**

3. Center for Infectious Disease Research and Policy, Academic Health Center, University of Minnesota, Minneapolis, MN; "Plague"; February 27, 2013; visited 12/7/2014; http://www.cidrap.umn.edu/infectious-disease-topics/plague#overview&1-9