THE BUBONIC PLAGUE

BY SARAH BARLOW
HISTORY OF THE BUBONIC PLAGUE

Ring-a-round the rosie,
A pocket full of posies,
Ashes! Ashes!
We all fall down.

Since the 20th century, the rhyme has often been associated with the Great Plague which happened in England in 1665, or with earlier outbreaks of the Black Death in the mid 1300’s. Interpreters of the rhyme before World War II make no mention of this. Ring-a-round the rosies are the buboes on the sick’s skin, and “a pocket full of posies,” is in reference to people trying to ward off the ‘evil spirits’ or cover up the smell of the sick by carrying flowers in their pockets. The line Ashes, Ashes in colonial versions of the rhyme is claimed to refer variously to cremation of the bodies, the burning of victims’ houses, or blackening of their skin, and the theory has been adapted to be applied to other versions of the rhyme.
HISTORY OF THE BUBONIC PLAGUE

• In history, several pandemics of the plague occurred. A first pandemic, the Plague of Justinian (AD 541–542, 557, 570) might have contributed to the fall of the Roman Empire.

• In 1347, a second pandemic started. Originating from central Asia, it spread to the Middle East, northern Africa, and to Europe via trade ships infested with infected rats transmitted to the human host by fleas. Within a few years, it killed more than 30% of the European population, massively uprooting medieval societies. From 1347 on, the plague regularly re-emerged. Coinciding with the warmer months of the year when flea populations were at the highest.

• The plague disappeared from Europe in the 18th century. In the late 19th century, a third pandemic spread mainly in India and China. This led to intense research resulting in the discovery of the causative agent of plague and in the description of its mode of transmission.
Lucinda and John, both residents of New Mexico traveled to New York for vacation in the year 2002. Within a few days of their arrival, they started to feel very sick. The average incubation time of the Bubonic plague is 3 days, but can range from 2-8 days. They were exposed to the disease in their home of Santa Fe, New Mexico by an infected flea. At first they thought it was the flu, because of the burning fever, vomiting, chills, headache and weakness, but then they both developed painful swellings in their groins (red swollen infected lymph nodes ‘buboes’). After being transmitted via flea bite, the \textit{Y. pestis} bacteria becomes localized in an inflamed lymph node where they begin to colonize and reproduce. The couple continued to get sicker and sicker. Their hotel sent them to a travel doctor who was familiar with bizarre diseases and he diagnosed them immediately. Unsurprisingly, he had never seen a case of bubonic plague before – there hadn’t been one in New York City in more than 100 years.

They were sent straight to the hospital, and quarantined. Bubonic plague is a possible bio-terrorism disease, bio-terrorism is a form of terrorism where there is the intentional release of biological agents (bacteria, viruses, or other germs), so they were, until proven otherwise, suspected terrorists or victims of terrorism. They were immediately dosed with antibiotics, which worked on Lucinda almost at once. Vaccines have not been found to be very useful for plague prevention, but several antibiotics are effective for treatment including streptomycin, gentamicin, and doxycycline. Without treatment it results in the death of 30% to 90% of those infected. With treatment the risk of death is around 10%. Twenty-four hours later it was clear John was getting worse. His body did not respond to the antibiotic like Lucinda and the \textit{Y. pestis} virus infiltrated and infected his blood (septicemic plague). He had something called disseminated intravascular coagulation, which meant his blood was clotting and his organs shutting down. This was due to the massive bacterial growth in the blood called septicemic plague. His body and face swelled up, and his hands and feet developed gangrene (Acral gangrene (i.e., of the fingers, toes, lips and nose) which is another common symptom. The doctors put him into a drug-induced coma and pumped him full of liquids to rehydrate him. Eventually the doctors had to amputate his legs below the knees. He was in a coma for 2 and a half months and had to wait another month, after he awoke till he was stable enough to fly home and be admitted to a local hospital in Santa Fe.
ETIOLOGIC AGENTS:

- The cause of this disease is *Yersinia pestis* a tiny gram-negative rod-shaped, non-motile, non-spore-forming coccobacillus, and a member of the family *Enterobacteriaceae*. They produce an anti-phagocytic slime layer. It is a facultative anaerobic bacterium that can infect humans and animals.

  - *Y. pestis* displays unusual bipolar staining that makes it look like a safety pin.

  - The number of bacteria required to initiate a plague infection is small—perhaps only 3-50 cells.

VIRULENCE FACTORS:

- The plasminogen activator (Pla) protein of *Y. pestis* facilitates the adhesion and invasion of the bacterium to the extracellular matrix of host tissues. Pla induces the activation of plasminogen into plasmin, which causes proteolysis and damage to host tissues. In addition, Pla contributes to *Y. pestis*’s ability to invade epithelial cells.

- The anti-phagocytic antigens Factor 1 (F1) and V-antigen (LcrV) also contribute to the virulence of *Y. pestis*. The bacterium exports F1, and it is assembled into a capsule-like structure. This structure increases *Y. pestis* resistance to phagocytosis by macrophages. LcrV also increases resistance to phagocytosis as well as downregulation of the inflammatory response. LcrV works with the adhesion YadA and the Yop effectors to facilitate this response.

<table>
<thead>
<tr>
<th>Plague:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causative organism(s)</td>
</tr>
<tr>
<td>Most Common Modes of</td>
</tr>
<tr>
<td>Transmission</td>
</tr>
<tr>
<td>Virulence Factors</td>
</tr>
<tr>
<td>Culture/Diagnosis</td>
</tr>
<tr>
<td>Prevention</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Epidemiological features</td>
</tr>
</tbody>
</table>
D) PATHOPHYSIOLOGY

- Humans are infected through the bite of an infected flea or by inhalation of bacteria-infested droplets. The infection exists in three major plague forms: bubonic, septic, and pneumonic. The incubation period of the bubonic, septicemic, and pneumonic plague types ranges from 2-8 days. The bubonic plague is the most common form of infection and targets the victim’s lymphatic system. *Y. pestis* colonizes macrophages and the bacteria proliferate in the affected lymph nodes, causing inflammation and swelling to occur (buboes), and then proliferates extracellularly. Left untreated, *Y. pestis* is able to spread to the bloodstream leading to septicemic plague. The septic plague courses through the body via the bloodstream, disseminating from infected lymph nodes. Victims of septic plague are usually covered with black patches due to hemorrhages throughout the skin, leading to its “Black Death” nickname. Occasionally, *Y. pestis* causes infection of the lungs, resulting in the pneumonic plague. What distinguishes the plague from other invasive, systemic, and infectious diseases is that the bacteria replicate extracellularly in tissues following lysis of macrophages and hence, the microbial population in the affected host is enormous. Victims were not likely to survive plague without treatment.

- For *Yersinia pestis*, at the initial moment of infection, there is no damage to the host, and the host does not benefit from the bacteria’s presence. From this point, the damage response timeline can vary depending on the mode of transmission. If *Y. pestis* enters the lungs via aerosolized droplets, it incubates for 1 to 3 days. After the incubation period, pneumonic plague symptoms abruptly appear, corresponding to the sharp increase in the damage response. However, if *Y. pestis* enters through a flea bite, such as bubonic plague, the incubation period is 2 to 6 days. Again, during this time the damage response does not change. After the incubation period, the abrupt onset of initial symptoms, such as fever, headache, and chills, pushes the damage response sharply up. Within 24 hours of the appearance of symptoms, buboes develop, which pushes the damage response up further. At this point, the damage response can take several pathways, depending, primarily on treatment. If treatment is delayed for too long, *Y. pestis* can spread throughout the body as secondary septicemic plague, which can result in massive, systematic damage. *Y. pestis* can also spread to the lungs if treatment is delayed, resulting in secondary pneumonic plague. Again, this causes a massive increase in the damage response, frequently leading to death. If the bubonic plague is treated early enough with antibiotics, damage goes down in around 2 to 5 days, but the buboes could take weeks to completely heal.
MODES OF TRANSMISSION

- **Vector:** *Y. pestis* is most commonly transmitted to humans through the bites of infected fleas, resulting in either primary bubonic plague or septicemic plague.

- **Fluid/Tissue:** *Y. pestis* can be transmitted to humans through the handling of fluids or tissue from infected animals. Increased numbers of bacteria in the bloodstream promote the odds of human-human transmission. Contact with contaminated fluid or tissue typically results in bubonic plague or septicemic plague.

- **Infectious Droplets:** *Y. pestis* can be transmitted through the air via infectious droplets from coughing. Interaction by infectious droplets is the only method of spreading the *Y. pestis* from person to person without physical contact. Transmission of infectious droplets through coughing enables *Y. pestis* to colonize the lungs. This type of infection is called “pneumonic plague,” and it has a mortality rate close to 100 percent.

PREVENTION:

- Effective means of prevention are to diminish the possibility of rodent infestation around homes by clearing away cluttered debris and to apply flea control products for pets that roam freely in the open.

- The application of insect repellent for individuals in outdoor areas is an effective measure for protection against flea bites. Any contact with potentially infected animals should be limited, and the usage of gloves as a barrier against possible transmission should be utilized when necessary.

- Means of prevention can also be applied in hospital settings where the possibility of transmission can be high. Standardized procedures of handwashing and utilization of gowns, latex gloves, and protective devices should be followed to protect all body orifices from coming into contact with \textit{Yersinia pestis}.

- Restrictions of patients suspected with plague should be enacted to prevent the spread of disease to other individuals. This includes isolated treatment of infected patient as well as the inhibition of movement of the patient outside of the isolation room until the infection ceases to exist.

TREATMENT:

- Streptomycin is the antibiotic of choice for treating \textit{Yersinia pestis} infections.

- Other possible antibiotics include gentamicin, chloramphenicol, tetracyclines, and fluoroquinolones.

- Antibiotic dosages are typically administered for the full period of ten days or for three days after the fever has subsided.

- However, the selection of antibiotic therapy is crucial, as several classes of antibiotics have proven to be ineffective in treatment for the plague. These include penicillins, cephalosporins, and macrolides.

- It is also important to hospitalize and quarantine any suspected or confirmed cases of \textit{Yersinia pestis} in order to provide effective treatment and prevent the spread of the disease if it develops into secondary pneumonic plague.
A diagnosis is often obtained based on patient symptoms, such as the development of a bubo, and patient history. Usually, blood from the patient and parts of the swollen lymph nodes are submitted to a Level A lab for testing. For a culture ID, blood is checked for a positive blood culture, with BACTEC Media and SEPTI-CHEK BHI. Next, it is cultured on TSA w/5% Sheep Blood/MacConkey II Agar, and incubated for 24 hours at 28°C. The colonies should be gray-white, translucent, little to no hemolysis, and be non-lactose fermentor. Afterwards, it should test positive for catalase, but negative for oxidase and Christensen’s Urea Slant. All suspected cases of *Yersinia pestis* are reported to local and state health departments, who forward the information to the CDC to confirm the diagnosis. In turn, the CDC reports all confirmed cases of *Yersinia pestis* to the WHO.
Between 1900 and 2012, 1006 confirmed or probable human plague cases occurred in the United States. Over 80% of United States plague cases have been the bubonic form. In recent decades, an average of seven human plague cases have been reported each year (range: 1–17 cases per year). Plague has occurred in people of all ages (infants up to age 96), though 50% of cases occur in people ages 12–45. It occurs in both men and women, though historically is slightly more common among men, probably because of increased outdoor activities that put them at higher risk. In 2015 there were 16 reported plague cases, the 16th being a teenage girl from Bend, Oregon. She was thought to be exposed to the disease from a flea bite while on a hunting trip. Plague is rare in Oregon, with only eight human cases diagnosed since 1995 and no deaths, according to the Oregon Health Authority. The plague usually occurs in rural and semi-rural areas of the western United States, most commonly in New Mexico, Arizona and Colorado.

Plague epidemics have occurred in Africa, Asia, and South America but most human cases since the 1990s have occurred in Africa. From 2000-2009, Africa: in Congo 10,581 people contracted plague, followed by Madagascar with 7,182 cases and Zambia with 1,309 cases. Almost all of the cases reported in the last 20 years have occurred among people living in small towns and villages or agricultural areas rather than in larger towns and cities. Between 1,000 and 2,000 cases each year are reported to the World Health Organization (WHO), though the true number is likely much higher. It is hard to assess the mortality rate of plague in developing countries, as relatively few cases are reliably diagnosed and reported to health authorities.
Bubonic plague is an important disease to study because too many people believe this disease has been completely eradicated. I, myself, used to be one of them. When one thinks of this disease they think of the middle ages when it killed millions of people in Europe and Asia, but the disease has not disappeared. While it is still rare in developed countries, like the U.S. and Europe, but it is still a problem in underdeveloped countries. However, since the 1990's, human plague has reappeared in countries where no cases had been reported for decades, and thus the plague is now categorized as a re-emerging disease. \textit{Y. pestis} possesses the potential threat as a bioterror weapon and was successfully used during World War II. The multi-drug resistance, rapid microevolution and resistance to phagocytosis observed in \textit{Y. pestis} paints a grim picture if a future epidemic of the disease were to occur.

\textbf{Pneumonic plague as a bioweapon}

\textit{Yersinia pestis} used in an aerosol attack could cause multiple cases of the pneumonic form of plague. One to six days after becoming infected with the bacteria, people would develop pneumonic plague. Once people have the disease, the bacteria can spread to others who have close contact with them. Because of the delay between being exposed to the bacteria and becoming sick, people could travel over a large area before becoming contagious and possibly infecting others. Controlling the disease would then be more difficult. A bioweapon carrying \textit{Y. pestis} is possible because the bacterium occurs in nature and could be isolated and grown in quantity in a laboratory. Even so, manufacturing an effective weapon using \textit{Y. pestis} would require advanced knowledge and technology.
REFERENCES

   ❖ This reference is a news article that gives statistics, history and knowledge of the plague including that it is still an issue in certain parts of the world.

   https://microbewiki.kenyon.edu/index.php/Yersinia_Pestis_(Pathogenesis)
   ❖ This source provided me with the pathophysiology, transmission and prevention/treatment information needed for this powerpoint.

   http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0034714
   ❖ This source provided me with details about the bacteria Y. pestis and important pathophysiological information.

   ❖ This source provided me with historical and Y. pestis bacteria information found in the introduction of the article.

   http://www.theguardian.com/lifeandstyle/2010/feb/06/experience-bubonic-plague
   ❖ This is the source I used for my specific case example of the bubonic plague.

   http://www.cdc.gov/plague/maps/
   ❖ This source gave me the information I needed for the United States and world plague statistics.

   http://www.nbcnews.com/health/health-news/oregon-girl-16th-u-s-plague-case-year-n454496
   ❖ This source provided me with the Oregon plague case information I needed.

   ❖ I used the disease table information on page 516 and I also used this sources signs and symptoms information.