Trends in Microbiology

CellPress

Review

Pneumonic Plague: The Darker Side of *Yersinia pestis*

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Inhalation of the bacterium *Yersinia pestis* results in primary pneumonic plague. Pneumonic plague is the most severe manifestation of plague, with mortality rates approaching 100% in the absence of treatment. Its rapid disease progression, lethality, and ability to be transmitted via aerosol have compounded fears of the intentional release of *Y. pestis* as a biological weapon. Importantly, recent epidemics of plague have highlighted a significant role for pneumonic plague during outbreaks of *Y. pestis* infections. In this review we describe the characteristics of pneumonic plague, focusing on its disease progression and pathogenesis. The rapid time-course, severity, and difficulty of treating pneumonic plague highlight how differences in the route of disease transmission can enhance the lethality of an already deadly pathogen.

Trends

The evolution of *Yersinia pestis* from *Yersinia pseudotuberculosis* resulted in a dramatic shift from a relatively mild enteric pathogen to one able to cause a rapidly progressing and ultimately lethal pneumonia.

Recent outbreaks of plague have included a significant pneumonic plague component.

The progression of pneumonic plague is biphasic, with an early preinflammatory phase followed by the rapid onset of severe proinflammatory responses.

The onset of general flu-like symptoms coupled with rapid and fatal disease progression complicate treatment of pneumonic plague and contribute to high mortality rates associated with disease.

Yersinia pestis Virulence

Y. pestis is a Gram-negative coccobacillus that is able to cause three forms of plague (bubonic, pneumonic, and septicemic). The genus *Yersinia* is a member of the family Enterobacteriaceae and consists of 11 species, including three that are pathogenic in humans: *Y. pestis*, *Y. pseudotuberculosis*, and *Y. enterocolitica*. While *Y. enterocolitica* and *Y. pseudotuberculosis* cause a self-limiting gastrointestinal illness, *Y. pestis* causes a severe, acute, and rapidly progressing febrile illness with significant mortality rates. *Y. pestis* strains carry three plasmids, each harboring important virulence mediators: pPCP1 (also called pPla), pMT1 (pFra), and pCD1 (pYV). Plasmid pCD1 encodes the low-calcium response (lcr) type III secretion system (T3SS), which is essential for virulence in all *Yersinia* species via all known routes of infection. The *Yersinia* T3SS is responsible for injecting the *Yersinia* outer proteins (Yops) into target host cells, where the Yops have antiphagocytic and/or anti-inflammatory effects.

It is generally thought that the high virulence of *Y. pestis* emerged from a clone of *Y. pseudotuberculosis* that acquired the ability to survive within the flea [1]. However, recent analysis of bacterial genomes from the teeth of Bronze Age humans suggests that fully virulent plague strains originated roughly 5000 years ago from *Y. pestis* strains lacking the *Yersinia* murine toxin necessary for growth in the flea. These ancestral strains did not have the ability to cause bubonic plague, but still harbored the virulence factors required for pneumonic and septicemic plague [2]. While parasitizing the flea, *Y. pestis* forms a biofilm that blocks access to the flea midgut and is ultimately regurgitated into the mammalian host upon feeding [3]. Reservoirs of *Y. pestis* in nature include a variety of small mammal species, particularly rodents. Humans become accidental hosts as a consequence of contact with infected animals or via a flea vector that has fed on an infected animal. Intradermal infection of humans via the flea results in bubonic plague, while primary septicemic plague arises from a deeper bite that inoculates bacteria directly into the bloodstream. Secondary pneumonic plague develops from dissemination of *Y. pestis* into the lungs during bubonic or septicemic plague. Individuals with secondary pneumonic plague can become the first step in person-to-person transmission of *Y. pestis*.

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Primary pneumonic plague is caused by aerosol exposure to *Y. pestis*, most likely resulting from the inhalation of expelled respiratory droplets. Symptoms of primary pneumonic plague typically begin between 2 and 4 days after inoculation and include a productive cough with bloody sputum, fever, headache, malaise, nausea, and vomiting [4,5]. If appropriate antibiotic therapy is not administered within 24 h after the onset of symptoms, mortality rates approach 100% [6]. Even with proper antibiotic treatment, mortality rates can reach 50% [7]. Though rare, multidrug-resistant strains of *Y. pestis* have been isolated, highlighting the need for research focused on identifying novel therapeutic targets [3,8–11].

In this review, we examine pulmonary infection with *Y. pestis*, focusing on its threat potential and those characteristics that contribute to disease pathogenesis in the lung. What emerges is a compelling picture of how a dangerous pathogen becomes even more deadly as a result of respiratory transmission.

Y. pestis and Pneumonic Plague: An Emerging Threat with a Proven History

The emergence of *Y. pestis* represents a striking evolutionary divergence from an organism that causes a mild enteric infection to one that causes a severe and highly lethal infection with pandemic potential. Historically, *Y. pestis* has been attributed to at least three major pandemics that were responsible for significant morbidity and mortality. The first major pandemic, 'the Justinian plague', originated in either Ethiopia or Central Asia in the 6th century AD and spread along trade routes around the Mediterranean Sea [1,12,13]. The plague swept across the Roman world and is thought to be responsible for population losses of between 50% and 60% in North Africa, Europe, and central and Southern Asia [3,8,13]. The second major pandemic, known as the 'Black Death', began in the early 1330s in China, making its way to Europe through shipping and trade routes. Made famous through its depiction in centuries of art and literature, the Black Death lasted for more than 130 years and had significant economic and cultural impact. Between 1346 and 1352 the Black Death caused the death of approximately one-third of the world's population [8,14] and continued to be a significant public health threat into the 18th century. The most recent major pandemic arose in China in 1855, eventually spreading throughout Asia, the Middle East, Africa, Europe, and parts of North and South America via transoceanic shipping routes [4,5,12,13]. The Chinese pandemic took the lives of more than 13 million people over a 50-year period, beginning after its arrival in Bombay, and is likely responsible for a number of current outbreaks [6,15]. The modern plague era, beginning at the turn of the 20th century, has seen outbreaks of plague on every continent except Antarctica. In the first decade of the 21st century, the Democratic Republic of the Congo became the number one reporting country, with over 10 500 cases of plague [7,16]. This is followed by Madagascar with just over 7000 cases, and then Zambia with roughly 1300 cases of human plague [16]. In total, it is estimated that *Y. pestis* has killed up to 200 million people throughout history [3]. Due to is appearance in several countries in the 1990s, plague has been categorized as a re-emerging disease in the modern world [17,18]. Importantly, pneumonic plague has played a prominent role in the re-emergence of plague during this time [8].

Due to its extreme lethality and ability to be transmitted via aerosol, *Y. pestis* is categorized by the Centers for Disease Control and Prevention (CDC) as a Tier 1 select agent, or one of the few agents most likely to be utilized as a biological weapon. Of great concern is the progression of pneumonic plague, which can be fatal within 72 h after exposure and begins with nondescript flu-like symptoms that might delay appropriate diagnosis and treatment. The recorded use of plague as a biological weapon dates back to the mid-1300s and includes the catapulting of corpses of plague victims at Genoese sailors by the Tatar army in the Crimean city of Caffa [13]. During World War II the Japanese employed plague as a biological weapon on several occasions, dispersing vessels containing infected fleas over parts of China and causing tens of thousands of deaths [19,20]. In 1972, the Biological and Toxin Weapons Convention (BWC)