Risk of Person-to-Person Transmission of Pneumonic Plague

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Plague has received much attention because it may be used as a weapon by terrorists. Intentionally released aerosols of *Yersinia pestis* would cause pneumonic plague. In order to prepare for such an event, it is important, particularly for medical personnel and first responders, to form a realistic idea of the risk of person-to-person spread of infection. Historical accounts and contemporary experience show that pneumonic plague is not as contagious as it is commonly believed to be. Persons with plague usually only transmit the infection when the disease is in the endstage, when infected persons cough copious amounts of bloody sputum, and only by means of close contact. Before antibiotics were available for postexposure prophylaxis for contacts, simple protective measures, such as wearing masks and avoiding close contact, were sufficient to interrupt transmission during pneumonic plague outbreaks. In this article, I review the historical literature and anecdotal evidence regarding the risk of transmission, and I discuss possible protective measures.

The plague depopulated towns, turned the country into desert, and made the habitations of men to become the haunts of wild beasts.

—Warnefried, on the Justinian plague epidemic, about 542–594 A.D. [1]

There is probably no infectious disease which is so easy to suppress as lung plague.

—Wu Lien-Teh, “Plague, a manual for medical and public health workers” [1]

Plague is a dangerous but cowardly disease.

—Sam Orochi-Orach, Uganda, 2003 (personal communication)

Plague has caused at least 3 pandemics: the Justinian plague, which caused almost 100 million deaths; the “Black Death” of the Middle Ages, which killed one-third of Europe’s population; and the pandemic of 1895–1930, which killed ~12 million people, mostly in India. Attention to plague has been renewed recently because it might be used as a biological weapon by terrorists [2].

Historical accounts still give this disease a mythical and fear-some connotation. In India in 1994, for instance, the media reported that pneumonic plague had broken-out in the city of Surat. Over 500,000 people, including thousands of physicians, fled the city. Products and travelers from India were quarantined throughout the world, and tourism to India slowed to a standstill, costing India’s economy billions of dollars. In hindsight, only a few tens of patients had had symptoms of pneumonia, and not a single case of plague was laboratory-confirmed. Some experts have even questioned whether there really was a pneumonic plague outbreak in Surat [3, 4].

In this article, I review the historical literature about and contemporary experience with person-to-person transmission of pneumonic plague. I intend to show that the risk of infection for contacts is quite low under normal circumstances, and that simple protective measures can lower this risk even further.
CLINICAL ASPECTS OF PNEUMONIC PLAGUE

Naturally occurring instances of bubonic plague usually result from the bite of an infected rodent flea. This form of plague is characterized by a tender swelling (bubo) of the regional lymph nodes that drain the affected skin. Bubonic plague never spreads directly from one person to another. The bacteria may reach the lungs of people through hematogenous spread; these people develop secondary pneumonic plague. Secondary pneumonic plague occurs in <5% of patients that are promptly treated, but that proportion was much higher in the preantibiotic era [5].

Pneumonic plague is the only form of plague that can be transmitted from human to human. The disease resulting from direct infection of the airways is usually called primary pneumonic plague. This form would also occur after an intentional release of aerosolized Yersinia pestis. It has an incubation period of 2–4 days (range, probably 1–6 days) and is characterized by the sudden onset of severe headache, chills, malaise, and increased respiratory and heart rates. Body temperature rises steadily during this initial stage. Generally, cough develops after 20–24 h, and it is dry at first but becomes progressively productive. Initially, the sputum contains no blood and very few plague bacilli, but over time it becomes increasingly blood-stained and/or purulent. In the final stage (one to several hours before death), the patient produces copious amounts of bright red sputum containing "enormous numbers of plague bacilli in almost pure culture" [6, 7, p. 183].

Before antibiotics were available, the mortality associated with pneumonic plague was virtually 100%, with most infected people succumbing 1–3 days after onset of the first symptoms. Antibiotics such as aminoglycosides and tetracyclines significantly reduce mortality if they are administered in a timely manner (i.e., within 20 h after the onset of disease) [8].

Radiology is helpful for the early detection of pneumonia [9]. Alveolar infiltrates, usually bilateral, are seen in the lower lobes. In some cases, these are preceded by nodular or patchy lesions. Hilar lymphadenopathy is sometimes seen [5, 8]. Alveolar infiltrates can also occur with ARDS (acute respiratory distress syndrome) and disseminated intravascular coagulation; therefore, even in a person with known nonpneumonic plague, chest radiograph abnormalities do not always indicate secondary pneumonia [5].

The major clinical clues that should raise suspicion of primary pneumonic plague are the sudden onset, the very rapid progression, and, in the late stage of disease, hemoptysis. The diagnosis should be confirmed through microbiological examination of respiratory secretions or lung tissue [8, 9]. Rapid diagnostic tests based on the detection of the F1 antigen of Y. pestis have been developed and are currently being evaluated in a clinical trial.

EPIDEMIOLOGIC DATA ON TRANSMISSION OF PNEUMONIC PLAGUE

Manchurian epidemics. Much of what we know about human-to-human transmission of pneumonic plague is based on historical accounts, particularly accounts of the Manchurian pneumonic plague epidemics of 1910–11 and 1920–21. Both Manchurian epidemics started among seasonal marmot hunters, who were unfamiliar with plague and often careless when handling sick or dead animals. They traveled in crowded railway cars and stayed in overcrowded underground inns, where they were "packed like sardines" [10]. During winter, all the doors and windows of these inns were kept tightly closed to keep the occupants warm, thus reducing ventilation. In both epidemics, the pneumonic form of plague appeared in October; it spread directly from human to human and followed railway routes. The epidemic of 1910–11 lasted 5 months and left 60,000 people dead; the epidemic of 1920–21 killed ~9300 persons [1]. These epidemics were the last opportunity to study this disease on a large scale.

The physician in charge of the Chinese plague control efforts, Dr. Wu Lien-Teh, observed that patients in the early stage of primary pneumonic plague (i.e., patients without macroscopic blood in their sputum who did not cough significantly) were practically noninfective; very few or no plague bacteria were found in their sputum. Wu [1] describes many patients in the early stages of disease who had come in close contact with others without passing the infection to anyone. He speaks of a "noninfective period" of ~24 h. Wu states that infection seemed to transmit only from patients with late-stage disease, and that prolonged and close contact was necessary. Wu, Strong, and other plague physicians report an apparent low risk of infection in well-ventilated hospital wards. They observe that most infections occurred in badly ventilated houses and inns [6, 7]. Even within households, only some of the household members would usually become infected, and these persons tended to be the ones who were most intimately in contact with the patient. Simple precautions seemed to significantly reduce the risk of transmission. For example, one man did not get infected while sleeping in the same bed as his infected wife, apparently because he slept with his head turned away from her [6]. Wu gives many other examples of people staying in rooms adjacent to those of infected people—or in the same room but avoiding close contact—and being spared from the disease [6, 1].

Control measures included house-to-house searches for people with pneumonic plague, the quarantining of suspected affected households and contacts, and the disposal of bodies. People often tried to keep outbreaks that occurred in their household a secret by, for example, throwing sick or dead family members out on the street so that it could not be determined where the disease had originated. Both epidemics abated in the
spring. Some believed that control measures were responsible for the decline, but others argued that it may just have been the warmer weather that permitted better ventilation of houses and inns [11].

Protection of medical staff during the Manchurian epidemics. During the Manchurian epidemics, suspected patients were taken to improvised hospitals to die. Patients lay side-by-side on wooden platforms along the wall, and the “floors and walls of the wards were [splattered] with bloody sputum” [7, p. 133]. Health care workers protected themselves with masks made of cotton and gauze. The latest model, worn during the epidemic of 1920–21, was made of a half-inch thick cotton pad enclosed by 2 layers of gauze and tied around the head with 2 tails (figure 1). The mask was changed after each visit to the plague ward [6]. To further reduce risk, it was preferred that patients be examined outdoors. These measures were thought to be responsible for the low infection rate among physicians. Tables 1 and 2 show the incidence of plague and the mortality rate among medical staffs in 3 cities in Manchuria. Wu [6] reports that none of the Chinese medical staff in a fourth city became ill but does not give a denominator for the statistic. Considering that the medical staff was exposed for many months to thousands of pneumonic plague–infected people up to the final stage of illness, the infection rate among physicians was remarkably low.

Sanitary attendants (or “coolies”) showed a much higher infection rate. These attendants were the lowest ranking personnel in the hospitals, apparently employed for tasks such as caring for patients and disposing of bodies. Although they had a high degree of patient contact, Wu [6] and Strong [7] attribute their higher infection rate to their lack of training, their frequent improper use of masks, and the assumption that they often contracted the infection in their own houses. In Wu’s words: the heavy mortality among the auxiliary staff may partly be ascribed to the fact that it consisted largely of untrained men...Some [did not] grasp the importance of the prescribed measures, while others neglected them because they were alcoholics or were bent upon hoarding the effects of plague victims...Of considerable importance are those instances where [they] became infected...while in contact with their sick colleagues. Not rarely such infections were due to the noble desire of saving the lives of their comrades; in other instances, the true diagnosis was not established in time for the necessary precautions to be taken. In a third group, infection occurred among attendants who seem to have been poorly housed and where the infection was not detected early enough [to prevent spread within the living quarters] [6, pp. 390-1].

Strong wrote that “the high death rate among sanitary staff cannot be regarded as proof of the inefficiency of the masks” [11].

Recent experience with pneumonic plague. The last documented outbreak of pneumonic plague occurred in Madagascar in 1997. A man who traveled to a village where no plague had occurred for 50 years developed bubonic and secondary pneumonic plague. He was treated by a traditional healer who then became ill and passed the infection to his family and visitors. A total of 16 persons became infected with primary pneumonic plague. Ten days after the start of the outbreak, plague was first suspected as the cause, and all persons known to be infected were hospitalized. Control measures, including chemoprophylaxis of contacts, were implemented during the following days. Interestingly, all patients seemed to have ac-
Table 1. No. of deaths of medical and sanitary staff at Fuchia
tien during the first Manchurian plague epidemic, 1910–1911 [6].

<table>
<thead>
<tr>
<th>Occupation</th>
<th>No. of employees</th>
<th>No. of deaths</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
<td>20</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Sanitary attendant</td>
<td>550</td>
<td>102</td>
<td>19</td>
</tr>
<tr>
<td>Sanitary police</td>
<td>206</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Ambulance staff</td>
<td>150</td>
<td>69</td>
<td>46</td>
</tr>
</tbody>
</table>

NOTE. Physicians were thought to be more disciplined with respect to wearing masks and observing other precautions.

required their infection before plague was suspected [12], meaning that the awareness of the risk and subsequent avoidance of close contact with patients may have been at least as important for ending the outbreak as hospitalization of patients and chemoprophylaxis of contacts.

The Centers for Disease Control and Prevention (CDC) is currently doing clinical trials for plague diagnosis and treatment in Madagascar and Uganda, and I have discussed the question of the contagiousness of pneumonic plague with our collaborators in those countries. Dr. Jean Randriambelosoa, the medical director of the main plague hospital in Madagascar, estimates that he has treated or has been consulted regarding 2004 patients with plague, of whom 90% had suspected or confirmed pneumonic plague. In that same period, 3 of >130 exposed health care workers have been infected with primary pneumonic plague. Dr. Randriambelosoa reports that 2 of these 3 health care workers were not familiar with the proper protective measures against plague, and 1 did not take precautions because he did not realize that the patient had plague. Instead, health care workers try to avoid exposure by instructing the patient to turn his/her back to them and examining the patient from behind. The body temperature of exposed health care workers is monitored. In the past 10 years, 90 cases of pneumonic plague have been laboratory confirmed. In that same period, 3 of >130 exposed health care workers have been infected with primary pneumonic plague. Dr. Randriambelosoa reports that 2 of these 3 health care workers were not familiar with the proper protective measures against plague, and 1 did not take precautions because he did not realize that the patient had plague. All 3 survived (J. Randriambelosoa; written and verbal communications, October 2003 and June 2004).

Dr. Sam Orochi-Orach, the former medical director of the main plague hospital in Uganda, estimates that he has seen ∼2000 patients with plague, of whom ∼20–25% had suspected or confirmed pneumonic plague. Family members and other close contacts receive prophylaxis with cotrimoxazole. Health care workers generally do not receive chemoprophylaxis, and protective masks are not available for most of them. The wards are well-ventilated; health staff limit the time they spend in close proximity of pneumonic plague patients; and they ask the patient to turn his/her head away during examinations. Dr. Orochi-Orach is not aware of any instances of person-to-person transmission of pneumonic plague within Ugandan health care facilities in the 20 years that he worked on plague (Dr. Orochi-Orach; written and verbal communications, January 2003).

Pneumonic plague in the United States. In the United States, the only known instances of human-to-human transmission of plague occurred in 1919 and in 1924. The outbreak in 1919 in Oakland consisted of 1 confirmed case and 12 or 13 suspected cases, including suspected cases in 2 physicians and 2 nurses. The disease was initially misdiagnosed as influenza, and all infections occurred before the diagnosis of plague was suspected. The outbreak started with a case of secondary pneumonic plague in a squirrel hunter, who probably infected 5 or 6 visitors in his house. These exposed persons then passed the disease to 7 others. By that time, the diagnosis of plague finally was suspected. Six surviving patients were hospitalized in isolation, and no new cases occurred. Other control measures apparently were instituted several days later. The author of the article that describes the outbreak wrote, “ordinary measures of [prevention], which were easy of application, sufficed to check the progress of the infection” [13, p. 603]. The author gave no other details except that the medical staff observed “careful medical asepsis, which no doubt was more careful than would have usually been the case with [nonplague] pneumonia” [13, p. 604].

The outbreak in Los Angeles in 1924 started when a man and a woman from the same household developed bubonic and then secondary pneumonic plague. The diagnosis of plague was confirmed 3 days later, but by that time 32 persons already had developed the disease [14]. It is remarkable that no new cases occurred after the third day. Transmission must have stopped as soon as the population at risk became aware that this was a dangerous infectious disease, several days before any control measures were implemented, and even before the public was informed of the nature of the outbreak. Doctors and nurses protected themselves with masks made of celluloid and cotton and wore gowns and gloves. No nosocomial transmission occurred [15].

Since 1925, person-to-person transmission of pneumonic plague has not been documented in the United States. From

Table 2. Incidence of primary pneumonic plague infection among medical and sanitary personnel in Harbin Hospital and Dalainor during the Manchurian epidemic of 1920–1921 [6].

<table>
<thead>
<tr>
<th>Occupation</th>
<th>No. of employees</th>
<th>No. of infected employees</th>
<th>Incidence rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
<td>11</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Dresser</td>
<td>25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sanitary attendant</td>
<td>23</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>Sanitary police</td>
<td>50</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

NOTE. The high infection rate among sanitary attendants was explained by their poor adherence to prescribed protective measures, the transmission of plague among colleagues, and their poor housing.
Table 3. Results of agar plate experiments on transmission of Yersinia pestis done by Strong and Teague [7] during the Manchurian epidemic of pneumonic plague in 1910–11.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of plates, by finding</th>
<th>Y. pestis captured on plate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Y. pestis not captured on plate</th>
<th>Indeterminate&lt;sup&gt;b&lt;/sup&gt;</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient coughed during plate exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>15</td>
<td>16</td>
<td>6</td>
<td>37</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>1</td>
<td>40</td>
<td>3</td>
<td>44</td>
</tr>
<tr>
<td>Distance between plate and patient who coughed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–30 cm</td>
<td></td>
<td>6</td>
<td>13</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>70–85 cm</td>
<td></td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>1 m</td>
<td></td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2 m</td>
<td></td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

NOTE. Agar plates were exposed to hospitalized pneumonic plague patients at various distances from the mouth and for various periods of time. All patients had bloody sputum. Values in the table are based on a count made from the published line list of culture results, which differs slightly from a summary given by Strong and Teague [7].

<sup>a</sup> Confirmed by Gram staining and microscopy and/or inoculation in guinea pigs.

<sup>b</sup> The majority of plates with indeterminate results were overgrown with other bacteria.

1925 to 2003, there were 447 cases of plague reported to the CDC, and 48 developed into secondary pneumonic plague. Thirteen cases of primary pneumonic plague were reported in the same period; 5 of these were caused by cats with plague pneumonia, 1 was associated with caring for a sick dog, and 3 cases were laboratory-acquired. In 4 cases, the origin of the infection remained unknown (CDC; unpublished data) [16–20]. None of the contacts of these 61 patients with pneumonic plague seem to have developed the disease.

EXPERIMENTAL DATA

During the Manchurian epidemic of 1910–11, Strong and Teague did experiments to characterize the airborne spread of the bacteria [7]. Agar plates were exposed for different durations at distances varying from 5 cm to 2 m from patients’ mouths. All experiments were done with patients in the final stage of disease, who produced bloody sputum. Plates with visible drops of sputum were discarded. These experiments were done under extremely difficult conditions; their sensitivity to detect airborne bacteria is unknown. Only 1 of 39 plates held in front of noncoughing patients yielded positive results. The furthest observed distance of spread was 1 m (3.3 ft) (table 3). The only 2 plates that were exposed at 2 m were overgrown with other bacteria and could not be evaluated [7]. Other researchers have done similar experiments; the largest reported distance of spread varies from 50 cm to 1.12 m (3.7 ft) [6].

DISCUSSION

Pneumonic plague is perhaps the only disease for which we have to rely largely on information that is almost a century old. This information is often anecdotal, may have been subject to bias, and may not satisfy modern scientific standards. Nevertheless, I believe that the researchers of those days tried to be conscientious and professional, and that their assessments are still valuable. The historical accounts as well as the limited evidence from more recent outbreaks discussed in this article agree that pneumonic plague is not easily transmitted from one person to another. Most modern experts agree with this interpretation [9, 12], which was also strengthened by a mathematical model using data from published outbreaks that found an $R_0$ value (i.e., the average number of secondary cases per primary case) that was close to 1 [21].

Perhaps the most convincing evidence of the low risk of transmission is the absence of any documented human-to-human transmission of plague in the United States since 1925, long before effective antibiotics were available as prophylaxis for contacts. Antibiotic prophylaxis has been available since 1948. However, the diagnosis of plague often is delayed for several days, such as in the case of a patient in 1980 who was only diagnosed with plague 4 days after her death and after 180 persons had been in contact with her [22]. It is unlikely that postexposure prophylaxis could have been responsible for prevention of all infections, if plague would be easily transmitted from person to person. The conclusion is that improved living conditions, better hygiene, better understanding of the disease, and a low underlying risk of infection must have been important factors for the absence of transmission.

The historical accounts I have cited show large differences in infection rates. These can probably be explained by differences in living conditions, hygiene, and observance of protective
measures. There are no indications that differences in virulence or host factors could have played a role.

Transmission apparently occurs through direct contact or through inhalation of airborne droplets expelled by coughing persons. The very close contact required for transmission in clinical settings and the limited distance of spread demonstrated by experiments are indications that droplet nuclei do not play a significant role [23].

Patients in the early stage of pneumonic plague (approximately the first 20–24 h) apparently pose little risk [9]. This is likely because of the low counts of bacteria in their respiratory secretions and the general absence of coughing. Patients in the final stages of disease who cough sputum with much visible blood and/or pus pose the highest risk of infection.

Antibiotic medication rapidly clears the sputum of plague bacilli, so that a patient generally is not infective within hours after initiation of effective antibiotic treatment [8]. This means that in modern times many patients may not reach a stage where they pose a significant risk to others.

Simple protective measures can further reduce the risk of infection. This is evidenced by the numerous outbreaks that stopped as soon as the population at risk realized that they were dealing with a contagious disease and before public health authorities took measures to control it. The main factors preventing transmission must have included avoidance of direct contact with patients, maintenance of a greater physical distance between caretakers and ill persons, reduction of the time caretakers spent with each patient, and perhaps implementation of better hygienic practices, such as hand washing. In the Manchurian epidemics, a mask made of several layers of gauze seems to have protected almost all physicians who used it.

What precautions should health care workers take while caring for suspected pneumonic plague patients? In the case of a bioterrorist event involving plague, the health care system of a region will be easily overwhelmed, especially if strict isolation is instituted indiscriminately for many patients. Strict isolation by itself can reduce a patient’s chance of recovery [24]. Therefore, it is important to carefully triage patients according to which patients should be nursed with precautions, and it is important to reevaluate precautions for patients who may no longer pose a risk. Protective measures, prophylaxis, and treatment of the patient should be commenced as soon as there is suspicion of pneumonic plague. However, the diagnosis of pneumonic plague should be confirmed by microbiological examination of respiratory secretions. If a bioterrorist event is suspected, it is also important to obtain an isolate to determine its antibiotic susceptibility, because the bacteria may have been engineered for resistance.

Recommendations have been published by the Advisory Committee on Immunization Practices [25], the Working Group on Civilian Biodefense [2], and the Association for Professionals in Infection Control and Epidemiology, and CDC’s Hospital Infections Program [26]. All of these guidelines agree on an approach that balances the risk of person-to-person transmission with limited health care resources, and they include the following recommendations:

- Implement droplet precautions for patients with suspected cases of pneumonic plague until they have received effective antibiotic treatment for 48 h (72 h of treatment is recommended in [26]).
- Wear disposable surgical masks to help reduce the risk from large respiratory droplets. Because droplet nuclei are not thought to be a factor in the airborne spread of plague [2, 23], use of fitted N95 masks, full face pieces with N-/R-/P-100 filters, or powered air-purifying respirators with high-efficiency filters is not recommended.
- Use standard precautions for nonpneumonic plague patients.
- Monitor the body temperature of potentially exposed persons.
- Consider postexposure chemoprophylaxis for persons who have been in unprotected close contact (defined as coming within 2 m by [2] and [25] and within 1 m by [26]) with a person with pneumonic plague who has not received antibiotic treatment for at least 48 h. Doxycycline, ciprofloxacin, chloramphenicol, and cotrimoxazole can be used for prophylaxis. If possible, the choice of drug should be guided by the antimicrobial resistance profile of the isolated strain.
- Isolation of asymptomatic close contacts is not recommended.

Acknowledgments

I would like to thank Kenneth Gage and Russell Enscore for helping to locate many of the historical publications, and Dr. Erin Staples, for reviewing the historical plague surveillance data at the CDC.

Potential conflicts of interest. J.L.K.: no conflicts.

References