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Plague: History and contemporary analysis

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Summary Plague has caused ravaging outbreaks, including the Justinian plague and the "black death" in the Middle Ages. The causative agents of these outbreaks have been confirmed using modern molecular tests. The vector of plague during pandemics remains the subject of controversy. Nowadays, plague must be suspected in all areas where plague is endemic in rodents when patients present with adenitis or with pneumonia with a bloody expectorate. Diagnosis is more difficult in the situation of the reemergence of plague, as in Algeria for example, told by the first physician involved in that outbreak (NM). When in doubt, it is preferable to prescribe treatment with doxycycline while waiting for the test results because of the risk of fatality in individuals with plague. The typical bubo is a type of adenitis that is painful, red and nonfluctuating. The diagnosis is simple when microbiological analysis is conducted. Plague is a likely diagnosis when one sees gram-negative bacilli in lymph node aspirate or biopsy samples. *Yersinia pestis* grows very easily in blood cultures and is easy to identify by biochemical tests and MALDI-TOF mass spectrometry. Pneumonic plague and septicemic plague without adenitis are difficult to diagnose, and these diagnoses are often made by chance or retrospectively when cases are not part of an epidemic or related to another specific epidemiologic context. The treatment of plague must be based on gentamicin or doxycycline. Treatment with one of these antibiotics must be started as soon as plague is suspected. Analysis of past plague epidemics by using modern laboratory tools illustrated the value of epidemic buboes for the clinical diagnosis of plague; and brought new concepts regarding its transmission by human ectoparasites.

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Introduction

Plague is primarily a murine zoonosis. Humans are incidental hosts that do not contribute to the natural cycle of the disease outside of epidemics. The *Yersinia pestis* bacterium is the causative agent of plague and can be transmitted by fleas, bites, scratches, aerosols, or contaminated food.[1] Plague is one of the most important diseases shaping the history of humanity because few microbes have killed as many as a third of the whole population during a pandemic or have changed the course of history.[1] The transmission of *Y. pestis* during a pandemic is not completely understood. *Y. pestis* is primarily transmitted between wild animals by ectoparasites, fleas in particular. Sporadic cases in humans can be the result of various modes of transmission, but it is difficult to explain historical plague pandemics by transmission solely by rat fleas. The mode of plague transmission during pandemics has been the subject of a very heated debate.

It should be noted that the description of the buboes associated with an epidemic provided a clue leading to plague. A precise historical description by Procopus indicated that the Justinian plague was caused by *Y. pestis*. The second pandemic plague, which started in the 14th century (the "Black Death"), was well described by Guy de Chauliac as an epidemic associated with adenitis (bubo) and high mortality.[2] Currently, we do not know of any other epidemic diseases of this nature, and it is clear that this disease was also plague.

History

The analysis of plague corpses in Marseilles was instrumental in developing the field of paleomicrobiology. In these studies, modern diagnostic tools were used to analyze the dental pulp of people thought to have died of plague.[3–6] This analysis allowed the role of *Y. pestis* to be confirmed and the genotype of the causative agent to be identified.

The origin of the first historical epidemics of plague is unclear, as the name "plague" refers to nonspecific diseases. In contrast, the word "bubo" (defined as adenitis in the groin) is specific to plague. The plague in Athens does not seem to be related to *Y. pestis* but instead to *Salmonella typhi*.[5] The plague that prevailed at the beginning of the Roman Empire under the Antonine emperors has not been explained. The Justinian plague (starting in 541) is the first confirmed plague pandemic. This pandemic stopped the re-conquest of the Roman Empire and has been formally identified retrospectively as being caused by *Y. pestis* based on the analysis of the teeth of people buried at that time.[6] The medieval plague (starting in 1347) is the second pandemic. This pandemic devastated Europe and may have killed 30% of the population. This pandemic was also formally determined to be caused by *Y. pestis* in Northern and Southern Europe.[7] The last pandemic, which started in the 19th century (1894), has had a lesser effect on the demography of the human population but is ongoing in Africa and America.[8]

The telluric reservoir of *Y. pestis* has been the subject of many debates. It has been demonstrated that *Y. pestis* can remain alive in a dormant form in soil for a period of several months or years.[9] This finding was recently confirmed in laboratory experiments[10] and in the field following a small epidemic in the USA.[11]

Epidemiology

Overall, the epidemiology of plague must be seen in a much less diagrammatic manner than in the past. However, outbreaks of either bubonic or pneumonic plague, some causing dozens of deaths, have recently been reported in northeastern Democratic Republic of Congo. Many rodents are susceptible to plague, as many other animals are.[1,12] Sporadic cases of this zoonosis in humans can be due to transmission by rodent fleas or to the consumption of infected food, to wounds or to exposure to aerosolized bacteria. The consumption of infected camels is considered a source of *Y. pestis* infection[1] (Fig. 1).

In all cases, the ability of *Y. pestis* to survive in the soil makes it possible to explain the persistence of this bacterium in environments in which it has been established, even when no cases are observed among animals (Fig. 1).

Transmission during pandemics is difficult to explain based only on rat fleas, which are responsible for multiple sporadic cases. The inability of fleas to explain plague transmission is particularly clear during the winter, when flea activities are low. During the winter, inter-human transmission appears to be prevalent. Transmission via aerosols can cause plague pneumonia. However, it was recently shown that this mode of transmission was far from effective during an epidemic in Uganda, where only the premortem forms presented a direct risk of inter-human transmission by cough, and only with very close contacts.[13] Therefore, direct transmission by aerosols may not explain pandemics. Regarding inter-human transmission, at the beginning of 20th century, Balthazard hypothesized that the human body louse can be a vector of *Y. pestis* during pandemics, a hypothesis that we confirmed. *Y. pestis* can be found in lice during epidemics.[14] In experimental models, it is possible to transmit plague to rabbits via lice.[15] Indeed, louse-transmitted diseases have caused the worst pandemics (typhus, trench fever, louse borne relapsing fever). The recent discovery of concomitant outbreaks of *Bartonella quintana* and *Y. pestis* using human remains supports this hypothesis.[16,17] Finally, the role of the "human" flea *Pulex irritans* may have been important (Figs. 2 and 3).

Geographical distribution

In recent years, 90% of reported cases of plague occurred Africa, specifically eastern Africa, central Africa and Madagascar, with small outbreaks occurring in North Africa. Currently, only the *Orientalis* biovar is distributed worldwide and is thus the only pandemic biovar. From 1958 to 2008, 17,000 cases were reported in Madagascar, 9000 in Tanzania, 13,000 in Congo, 4800 in India, 3,500 in Vietnam, 5500 in Myanmar, 3693 in Brazil, 4091 in Peru and 438 in the United States (Fig. 4). Recently, cases were discovered in North Africa in countries including Algeria and Libya