COMMENTARY

Origin, transmission, and evolution of plague over 400 y in Europe

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Plague is a deadly zoonosis caused by the gram-negative bacteria *Yersinia pestis*, and the clinical aspect of the disease partially depends on the way of transmission. While primary bubonic and septicemic plagues chiefly result from an ectoparasite bite or contact with an animal's carcass, primary pneumonic plague is caused by the inhalation of infected droplets (1). Paleogenomics data indicate that plague has affected humans for at least 5,000 y in Eurasia (2), culminating in three historical deadly pandemics. The Justinianic Plague occurred from circa 541 to 750 CE, diffusing from the Mediterranean basin in successive waves; its human, social, and economic consequences remain contested (3). The second pandemic started in 1346 in the city of Caffa prior to ravaging Europe until the 19th century (4), responsible for the death of 30 to 50% of the population alone during the "Black Death" episode (1346 to1353) (5). In 1772, the third pandemic commenced in the Chinese province of Yunnan before reaching Hong Kong in 1994 and spreading to the whole world via steamboat and railroad (1). At the beginning of the third pandemic, the natural epidemiological cycle of plague seemed to have been fully resolved with the discovery of the role of rats (*Rattus rattus*) as reservoirs in 1894 (6) and their fleas (*Xenospylla cheopis*) as vectors in 1898 (Table 1) (7). However, analysis of ancient plague genomes combined or not with historical texts pointed out that the sources of transmission, dynamics, and origins of past epidemics have evolved considerably over millennia. For example, during the Bronze Age *Y. pestis* could not be transmitted to humans by flea bites because of the absence of the *ymt* gene that allows the bacteria to survive in the midgut of fleas (Table 1) (8). In the same way, during the massive outbreak of the second pandemic, sources, vectors, and origins of plague were extremely debated. In PNAS, Bramanti et al., by reviewing all arguments from scientific literature comprising paleogenomic, phylogenetic, ecological, and historical data, conclude that human ectoparasites would have been the vectors of plague which was regularly imported into Europe via Asian reservoirs and propose a hypothesis concerning the evolution of plague during the second pandemic (4).

The second plague pandemic has always been problematic for researchers, first of all because of its extremely high mortality, killing about 50% of the living population, whereas such high rates do not seem to be found during the first or the third pandemic. Because of this, plague was initially interpreted as hemorrhagic fever or to be caused by unknown pathogens (9). The first paleomicrobiological analyses performed in 1998 and the sequencing of the complete genome of the Black Death strain in 2011 resolved this long-standing debate on the etiology of plague, undoubtedly caused by *Y. pestis* (5, 9). In order to understand the cause of this massive mortality, Bramanti et al. focused their work on the vectors of plague, opposing the two main hypotheses currently proposed in the literature. Briefly, hypothesis 1 argues that rats and their fleas were the vectors of plague and that after a single introduction from Asia plague was established for 400 y in a currently extinct reservoir in Europe. In contrast, hypothesis 2 suggests multiple reintroductions of plague from Asia—via infected rats or goods—along the commercial routes such as the silk roads or the fur roads and a transmission of plague via human ectoparasites such as body lice (*Pediculus humanus humanus*) and the human flea (*Pulex irritans*) (4).

Hypothesis 1 is based on the epidemiological features observed during the third pandemic and applied to the second one. There have been numerous arguments in opposition to this hypothesis, such as the absence of rats' mortality from ancient plague-related texts (10), the low number of rodent remains found in the plague archeological context—except for the recent demonstration of a rat infected by *Y. pestis* in the port of Gdansk in the 15th–16th century (11)—and the absence of *X. cheopis* fossils in Europe. Moreover, the existence of massive plague epidemics in

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Table 1. Latest epidemiological and genomic data concerning dynamics of prehistoric plague and the three historical pandemics

	Prehistoric plague (2)	First pandemic (3)	Second pandemic (4)	Third (current) pandemic (1)
Dating	5,000–3,800 BP	541–750 CE	1346–19th century	1772–present
Confirmed pathogen	*Y. pestis*	*Y. pestis*	*Y. pestis*	*Y. pestis*
Geographical origin	Eurasian plains	Central Asia; East Africa?	Eastern Europe/Asia	China (Yunnan Region)
Relevant genomic observations	Absence of the *ymt* gene	Slight *pla* depletion and a 49-kb deletion in some strains	Slight *pla* depletion and a 49-kb deletion in some strains	
Main form	?	?	Bubonic	Bubonic
Principal sources/ vectors	? (Inability of fleas to transmit plague)	?	Human ectoparasites	Rats and fleas
Hypothesis for decay/control	Strains less transmissible and virulent	Loss of virulence	Loss of virulence; acquired immunity; quarantine and prevention	Monitoring of plague foci; rat control; insecticide; antibiotics; vaccines; serotherapy; better hygiene; prevention and quarantine

Northern Europe coincided with an attested absence of rats and fleas and the speed of dissemination of plague during the second pandemic (1.5 to 6 km/d), different from that observed during the third pandemic mediated by rats and fleas (1).

On the other hand, hypothesis 2 relies on household clusters identified by historians (12) during ancient plague outbreaks combined with fossil records of body lice and human fleas discovered by the hundreds in every latitude of Europe during the medieval period. The infestation of populations by these ectoparasites is documented in historical texts as well as their effectiveness in transmitting *Y. pestis* by bite or via their infected feces (1). Based on these ectoparasite transmission rates, a study claimed that only human ectoparasites could be responsible for massive outbreaks of the second pandemic in comparison to rodent fleas or aerosols (13). This mathematical study was recently completed by the description of Glasgow's plague outbreak in 1900 without any involvement of rat and their fleas (14). Furthermore, the authors noticed that plague travels at the same speed as humans, probably because populations harbor human ectoparasites in their clothing (4), allowing them to survive the extreme temperatures of winter or the Northern European climate. In light of these findings, study of ancient plague-related texts is of particular interest because clothes, goods, or textiles are considered the principal vectors of plague.

Once the question of the vectors is settled, the question of the origins and dynamics of plague in Europe for 400 y naturally arises. Are there any reservoirs in Europe during the second pandemic from which plague would have ravaged Europe in successive waves? For Bramanti et al. (4), the existence of reservoir of plague in Europe is inseparable from a transmission by rats and fleas (hypothesis 1), while the second hypothesis (hypothesis 2) of a reintroduction of plague by successive waves in Europe via foci/reservoirs in Eastern Europe or Asia is intertwined with an interhuman transmission mediated by human ectoparasites.

Hypothesis 1 is mainly based on phylogenetic analyses of ancient plague genomes which confirmed the almost clonal nature of the Black Death strains (which is in favor of a single plague introduction) combined with a plague strains cluster in Germany and Switzerland following the Black Death suggesting an endemic circulation of plague in the region of the Alps, implying the existence of resistant rodent reservoirs such as marmots (15). However, Bramanti et al. (4) suggest that the Western plague reservoir could stem from an overrepresentation of Western genomes compared to Eastern ones. Moreover, a recent study demonstrated that the alpine cluster was occasioned by troops' movements during the Thirty Years' War (1618 to 1648) (16). In addition, as shown in the updated phylogeny reported by Bramanti et al., a large part of plague outbreaks occurring in harbors are caused unambiguously by infected goods, clothes, or rats coming by ship from Eastern plague reservoirs (4). Furthermore, there is now evidence to affirm that the primary reservoir of plague is the soil and that the existence of a group of resistant rodents might not be sufficient to maintain an active reservoir for several centuries (1), which reinforces hypothesis 2 defended by the authors. Indeed, all historical plague foci/reservoirs were and still are located in regions formerly crossed by commercial terrestrial routes such as Mongolia, China, Iran, or the south of Russia during the second pandemic.

The study of Bramanti et al. illuminates the dynamics of the deadliest pandemic in human history. The data gathered here sketch the end of the paradigmatic vision of rats and fleas as vectors of the second pandemic plague prevailing since the third pandemic by highlighting human ectoparasite transmission as the main part of a complex epidemiological cycle.

Consistent with Bramanti et al. (4), hypothesis 2 is the most parsimonious (Table 1), whereby rats and their ectoparasites are not excluded from the epidemiological cycle, but instead of being the main vectors they are the initiators. As explained by the authors, rats infected with *Y. pestis* could probably disembark from ships from the Orient in European ports and initiate human outbreaks that were then entirely sustained by human ectoparasites. The two hypotheses presented in this work might also not be mutually exclusive, and the epidemiology of the plague could be more complex during the second pandemic with the presence of secondary temporary plague reservoirs sustained by continuous plague reintroduction from the East.

Finally, one of the most interesting points of this study is the question of the evolution of plague during the second pandemic. It turns out that in some strains belonging to the last lineages of epidemics scientist noticed a chromosomal deletion of 49 kb with unknown effect on plague transmission/pathogenicity, both at the end of the first and the second pandemic. One step further, the depletion of the plasmidic *pla* virulence gene has been

observed in an 18th-century genome (17). In vivo experiments demonstrated that the *pla* gene allows *Y. pestis* to cause bubonic and pneumonic forms (18). These two convergent mutations could explain the decay of plague during the first and the second pandemic (4).

Interestingly, by analyzing all the ancient genomes available Bramanti et al. (4) found this depletion also at the beginning of the second pandemic, which could suggest a *pla* evolution dependent on plague forms (bubonic, septicemic, or pulmonic). Indeed, contrary to the bubonic and pulmonary forms, the deadly septicemic forms of plague (100% lethality without treatment) do not require the *pla* gene. However, in accord with medieval and modern physicians, the majority of reported plague cases were bubonic (19). Moreover, further studies might address whether the *pla*-depleted strain found at the beginning of a European epidemic could result from a late Eastern epidemic.

In PNAS Bramanti et al. (4) propose that slightly *pla*-depleted strains are not linked to plague decay but rather to an evolutionary adaptation of *Y. pestis* to reduce its virulence in order to gain better survival inside new hosts, namely humans and their ectoparasites (4). These data suggest the existence of probable attenuated forms of plague that may be similar to the contested *Pestis minor* form reported by physicians during the third pandemic (20).

The study of Bramanti et al. (4) illuminates the dynamics of the deadliest pandemic in human history. The data gathered here sketch the end of the paradigmatic vision of rats and fleas as vectors of the second pandemic plague prevailing since the third pandemic by highlighting human ectoparasite transmission as the main part of a complex epidemiological cycle (rats, rodent fleas, body lice, human fleas, goods, clothing, etc.). In addition, this study focuses on the roles and existence of more- or less-virulent host-adapted plague variants, providing a key element in the puzzle of plague evolution.

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