Black Death and how the 'pale rider' lost his force

The Black Death caused by Yersinia pestis took the lives of millions. Three major plague pandemics profoundly influenced historical developments and affected our immune system at the cost of a risk for autoimmune diseases.

The penultimate issue of the Science journal for the year 2022 (2564) proposed a winner and runners-up as the year's scientific achievements. For Science, the 'breakthrough of the year' is the launching of the James Webb Space Telescope and one of the 'runners-up' an investigation into the genetic code of survivors from the plague which started to haunt Europe, the Middle East, and Northern Africa in the year AD 1346 to 1350 (BE 1889 to 1893) (1, 2). The extended view into space by the Webb Telescope is of general academic interest. The immunological protection against one of the deadliest pandemics in history, caused by Yersinia pestis, is particularly interesting for medicine and public health. Those interested and engaged in public health should be familiar with the disasters this germ caused throughout history and should know that it is still with us and that it makes a highly potent weapon for bioterrorism.

A well-known historical bioterrorism event was conducted by the armies of the Tatar Khan Janibeg in 1347, who could not conquer the town of Kaffa (now Feodosia in Ukraine) and, as an act of revenge, catapulted corpses of those who died from the Black Death into the town. The town served as a Genoese trading post. The Genoese fled and were instrumental in spreading the plague further into the Mediterranean (3).

The disease

Textbook knowledge tells us that there are three types of plague, namely, the bubonic, septicemic, and pneumonic types, transmitted from rodents through fleas to humans or from humans to humans (4). Most of the pandemics started with the Bubonic plague attacking the lymph nodes. From there, the bacterium spreads, causing hemorrhaging and skin necrosis. Finally, the victim succumbs to septicemic chock. Person-to-person infection might attack the lungs, and fatal pneumonia occurs. Antibiotics became the 'miracle' treatment for infectious diseases at the end of the Second World War. Probably antibiotic treatment helped to end the last outbreak of the plague in Europe in 1945, the year the war ended for many European countries (5).

The Justinian Plague and the Black Death

Although the disease by now lost its dangerousness, the germ Y. pestis might have engraved the fear of infectious diseases into the subconsciousness of humankind. (It is believed, generally and wrongly, that non-communicable diseases are not that dangerous.) The plaque caused three major pandemics throughout history, namely the Justinian Plaque (541 to 544 C.E.), the Black Death (1347 to 1352), which was an on-and-off affair for several centuries, and the Third Plague Pandemic starting in China and spreading globally somehow fading out at the end of the 19th, beginning of the 20th century.

The Justinian Plaque might have killed 100 million in Asia, Africa, and Europe ending Roman rule and starting to shape the nations of medieval Europe. The infection continued to occur sporadically over the following 200 years and less frequently up to the 8th century (3). The disease came back as the Black Death, as it is now called, in the 14th century. It reduced the population in Europe significantly, with 25 million deaths, and Asia and Africa, with another 25 million (6).

The pandemic changed the societal structure of many parts of the world, which is best documented in the Western world. For instance, the massive loss of people resulted in a shortage of laborers, giving the lower classes more freedom to look for work in England. Authorities became aware of the disease's dynamic spread and tried to curb it. For instance, quarantine was established at that time. Throughout the following centuries, most countries in Europe enforced quarantine.

Since the underlying reason for the spread of death could not be known, at times, special population groups were blamed for having caused it, such as the Jews, who were attacked and murdered. Natural phenomena such as earthquakes, comets, and conjunctions of the planets were believed to be the reason as well. The 'flagellants' were a religious movement and, thinking that the sins of mankind triggered the revenge of God, processed from town to town by whipping themselves.

An outstanding event in the 17th century was the Great Plague of London from 1665 to 1666, when about 100.000 people died, making up a fifth of the London population (7). At the end of the 18th century, the plague vanished from Europe but not from other areas of the world. The plague continued to spread through 'the Ottoman imperium, and from Southeast Europe to the Persian Gulf, and from the Black Sea basin to Yemen during 1700 to 1850' (8, 9).

The third plague pandemic (5)

Throughout the third Plague pandemic, the history of the epidemiology and distribution of the plague was better understood and prompted improved ways and means to control it. The pandemic started in China at the end of the 19th century and spread throughout South- and Western Europe, North- and South America, Africa, and Asia. In Hong Kong, Alexander Yersin discovered the germ in 1894, and his compatriot from France, Paul-Louis Simond, a naval doctor, detected 1898 as one of the main vectors for the bacterium and the sewer rats as one animal host of the bacterium (10).

The plague reached Europe around 1899, with 1692 cases and 457 deaths reported until 1947. The main entry points for the disease were the harbor cities of southern Europe, but the plague made it also to England through London and Liverpool. At the same time as the plague attacked, also cholera threatened the population. One vehicle for the spread of these diseases was the newly developed steamships. It was found that besides rats, cats and dogs could transmit the disease through fleas, bugs, lice, and ticks. The vectors could even infect humans by handling clothes from persons who died and merchandise brought in by the ships.

In Europe, the plague ended in 1954 with 30 cases and 15 deaths. However, the Third Pandemic left plague reservoirs in the USA, in the South American countries Peru, Bolivia, and Brazil, as well as in Africa within the Congo, Tanzania, Uganda, and Madagascar (3, 5). The disease is still present, and over 80.000 cases with over 6500 death were reported from 1954 to 1997 (11), and more recently, from the year 2010 up to the year 2015, with altogether 3248 cases with 584 death (12).

'Plague historians in lab coats'

It is thought that the relatively low number of cases and death in Europe was due to the awareness of the authorities and their counteractions, the introduction of insecticides and the overall improvement of hygiene, and finally, the availability of antibiotic treatment. An additional aspect could have kept mortality caused by Y. pestis at a much lower level than in the past due to improved immunity against the bacterium.

Thinking along this line, and having sophisticated methodology on hand, caused uproar in the sciences of history and archeology, because to formerly established methodology, advancements in molecular sciences were added. This anabled investigation of the genome down to the DNA level and increased incredibly the opportunity to look into the past. The newly established field of paleogenetics allowed to investigate homo species at times even before Homo sapiens made an inroad into history (13, 14). It has been suggested that because of the advancements in science and by avoiding the Eurocentric viewpoint on the history of the plague, the entire discipline needs to be profoundly revised (9). Whether Y. pestis has been the only germ causing the disease or a virus might have been involved, causing some sort of hemorrhagic fever, could be decided in the 'favor' of the bacterium (15-19).

'Black Death and the evolution of immune genes' - pros and cons

A step forward in revising history is assessing the evolution of immune genes in association with the Black Death (2). Since it is now generally agreed upon that Y. pestis readily killed millions of people throughout history, a remaining question could be tried to answer, namely, what saved those who survived and those who were not affected? What was considered by 'Science' as a breakthrough for the year 2022 was published in 'Nature', the competitor scientific magazine from England. Klunk et al. (2022) 'identified the loci …from ancient DNA extracts … before, during and after the Black Death'… that …' are strongly enriched for highly differential site relative to a set of non-immune loci, suggesting positive' (for those being immune) (20). Among the variants investigated, there was even one that increased the chances of surviving the plague by 40% (quote from Hendrick Poinar, co-lead author of the study, as reported in (2)).

For the investigation, the authors used samples from a London cemetery where the plague victim was buried in mass graves from 1348 to 1349. Later, on top, survivors of the plague died in the year 1350 and later were buried there as well after the disease vanished from London. To the samples from London, similar samples were added from Denmark. It is assumed that, to a great extent, only the human DNA from the bones was investigated from those dying and those surviving free from the influence of other infectious diseases.

Altogether, 318 samples from London and 198 samples from Denmark were studied. The method used is mentioned in the publication as a modified polymerase chain reaction (PCR) assay for the single copy nuclear c-myc gene (21, 22). From the Londoner samples, 245 gene variants, and 4 from the Denmark samples 'rose or fell in frequency before and after the Black Death'. The gene of primary interest encoded the enzyme 'endoplasmic reticulum aminopeptidase 2' (ERAP2). The protein is known to stimulate immune cells to recognize and work against viruses. ERAP2 consists of two alleles, differing only in one letter in the genetic code, which made the difference in response to the plague. 'Individuals homozygous for the protective allele (rs2549794) were about 40% more likely to survive the Black Death than those homozygous for the deleterious variant'.

Using cell cultures from present-day British individuals, the protective ERAP2 variants resulted in a high outcome of cytokines when exposed to Y. pestis. The immune response of ERAP2 variants is not limited to Y. pestis but to other infectious diseases as well (23, 24).

The bad news is that the variant also is a risk factor for Crohn's disease (25). An additional, promising locus to help in fighting Y. pestis was found near CTLA4 with rs11571319. While the allele is supposed to be beneficial in fighting off Y. pestis, the locus was expressed close to the cytotoxic T lymphocyte antigen 4 (CTLA4). The role of CTLA4 within the immune system seems ambiguous and needs further investigation (26). Unfortunately, the allele at this locus is linked to an increased risk for rheumatoid arthritis and systemic lupus erythematosus (27).

Conclusion

Yersinia pestis was probably a deadly germ even since the stone age and has been known to shape history since Roman times. People living through the Justinian Plague must have thought the world had ended. During the medieval period, the catastrophe was met with superstition. The delirious effects of the infectious disease were understood as punishment from God for our sins. Fortunately, authorities started to realize that the infection was spreading from man to man but thought wrongly that transmission happened through the air. The misunderstanding is known as the miasma theory. The theory only was put aside at the end of the 19th century. During the Third Pandemic, rational reactions of the authorities and a more scientific approach finally diminished the mortality of the plague, at least in the Western world. However, history still has to illuminate what happened in the rest of the world while facing the Black Death. It seems that one factor, if not even the most important one, to end the plaque finally is our immune system. The immune system is very delicate, and evolution plays in favor and against us humans. The risk of acquiring the infection is reduced; instead, we are more prone to autoimmune diseases.

References:

1. Clery D. Golden Eye. Science. 2022;378(6625):2.
2. Gibbons A. Black Death’s legacy detected in the genes of Europeans. Science 2022;378(6625):1.
3. Frith J. The history of plague - part 1. The three great pandemics. Journal of Military and Veterans’ Health. 2021;20(No. 2).

4. Overview. Plague Cleaveland Clinic2022 [Available from: https://my.clevelandclinic.org/health/diseases/17782-plague.
5. Bramanti B, Dean KR, Walloe L, Chr Stenseth N. The Third Plague Pandemic in Europe. Proc Biol Sci. 2019;286(1901):20182429.
6. Tikhomirov E. Epidemiology and distribution of plaque. Geneva: WHO; 1999.
7. Ziegler P. The Black Death. Strout, UK: The History Press LTD; 2010. 296 p.
8. Panzac D. La Peste dans l'Empire Ottoman. Biraban JN, editor1985.
9. Varlik N. New science and old sources: Why the Ottoman experience of plaque matters. The Medieval Globe [Internet]. 2014; 1(1/9). Available from: https://scholarworks.wmich.edu/tmg/vol1/iss1/9/?utm_source=scholarworks.wmich.edu%2Ftmg%2Fvol1%2Fiss1%2F9&utm_medium=PDF&utm_campaign=PDFCoverPages.
10. Butler T. Plague history: Yersin's discovery of the causative bacterium in 1894 enabled, in the subsequent century, scientific progress in understanding the disease and the development of treatments and vaccines. Clin Microbiol Infect. 2014;20(3):202-9.
11. Koirala J. Plague: disease, management, and recognition of act of terrorism. Infect Dis Clin North Am. 2006;20(2):273-87, viii.
12. Bertherat E. Plaque araound the world 2010-2015. Wkly Epidemiol Rec. 2016;91:5.
13. Callaway E. The battle for common ground. Nature. 2018;555:4.
14. Horsburgh KA. Moleciular anthropology: the judicial use of genetic data in archaeology. Journal of Archaeological Science. 2015;56:5.
15. Bos KI, Schuenemann VJ, Golding GB, Burbano HA, Waglechner N, Coombes BK, et al. A draft genome of Yersinia pestis from victims of the Black Death. Nature. 2011;478(7370):506-10.
16. Butler T. Plague into the 21st century. Clin Infect Dis. 2009;49(5):736-42.
17. Haensch S, Bianucci R, Signoli M, Rajerison M, Schultz M, Kacki S, et al. Distinct clones of Yersinia pestis caused the black death. PLoS Pathog. 2010;6(10):e1001134.
18. Little LK. Plague historians in lab coats. Past Present. 2011;213(1):267-90.
19. Tran TN, Signoli M, Fozzati L, Aboudharam G, Raoult D, Drancourt M. High throughput, multiplexed pathogen detection authenticates plague waves in medieval Venice, Italy. PLoS One. 2011;6(3):e16735.
20. Klunk J, Vilgalys TP, Demeure CE, Cheng X, Shiratori M, Madej J, et al. Evolution of immune genes is associated with the Black Death. Nature. 2022;611(7935):312-9.
21. Klunk J, Duggan AT, Redfern R, Gamble J, Boldsen JL, Golding GB, et al. Genetic resiliency and the Black Death: No apparent loss of mitogenomic diversity due to the Black Death in medieval London and Denmark. Am J Phys Anthropol. 2019;169(2):240-52.
22. Morin PA, Chambers KE, Boesch C, Vigilant L. Quantitative polymerase chain reaction analysis of DNA from noninvasive samples for accurate microsatellite genotyping of wild chimpanzees (Pan troglodytes verus). Mol Ecol. 2001;10(7):1835-44.
23. Saulle I, Vicentini C, Clerici M, Biasin M. An Overview on ERAP Roles in Infectious Diseases. Cells. 2020;9(3).
24. Yao Y, Liu N, Zhou Z, Shi L. Influence of ERAP1 and ERAP2 gene polymorphisms on disease susceptibility in different populations. Hum Immunol. 2019;80(5):325-34.
25. Di Narzo AF, Peters LA, Argmann C, Stojmirovic A, Perrigoue J, Li K, et al. Blood and Intestine eQTLs from an Anti-TNF-Resistant Crohn's Disease Cohort Inform IBD Genetic Association Loci. Clin Transl Gastroenterol. 2016;7(6):e177.

26. Walker LS, Sansom DM. The emerging role of CTLA4 as a cell-extrinsic regulator of T cell responses. Nat Rev Immunol. 2011;11(12):852-63.
27. Wang YF, Zhang Y, Lin Z, Zhang H, Wang TY, Cao Y, et al. Identification of 38 novel loci for systemic lupus erythematosus and genetic heterogeneity between ancestral groups. Nat Commun. 2021;12(1):772.

Frank P. Schelp is responsible for the content of the manuscript, and points of view expressed might not reflect the stance and policy of the Faculty of Public Health, Khon Kaen University, Thailand

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