Effects of the Black Death on Treatments, Medical Understandings, and the Human Immune System

Kelly Fai, Katelyn Kim, Elie Wang, Mindy Wang, Isabella Yu
Concordia International School Shanghai
Shanghai, China
Faculty Advisor: Mr. Todd Gordon

Introduction

The Black Death is largely and widely regarded as a devastating disease that not only wiped out populations and affected citizens' health, but also damaged various civilizations' economies. Nevertheless, the evolutionary innovations that arose from these times have undoubtedly and significantly improved global health, medicine, and understanding of diseases. This shows that despite the extreme detriments it brought, the Black Death was necessary to the development of the modern world and had long-term effects that were ultimately beneficial to human populations and civilizations.

Treatments and Medical Responses Before and During the Plague (Kelly Fai)

People knew little about the prevention or treatment when the Black Death first struck their land in the middle of the 14th century. Mostly they strictly followed the ancient records and theories, such as the works done by Hippocrates, a 4th century BCE physician, Aristotle, and Galen, a physician in the 2nd century BCE.

It was hard for the people to correctly explain what was happening during the plague because there was such a reluctance to change the model of physiology and disease, which was mostly explained by mythological reasons. Especially for Christians, who have little intention to do the practical investigations of human bodies. Traditionally, cremation and burial were commonly practiced. As mentioned in the Torah, "And [God] buried him (Moses) in the depression in the land of Moab, opposite Beth Peor. No man knows the place that he was buried, even to this day." (Deuteronomy 34:6) This direct excerpt from the Bible emphasizes the advocacy of the burial of the dead. In the light of the Christian dogma of the resurrection of the body, the burial of the mortal remains of the dead was also regarded as an act of religious import. Destroying a human body was prohibited. Consequently, the doctrine restrained their development of anatomy and medicines. The majority in Europe at the time believed the plague was sent for the punishment of sins from God. Some even believed the pain that one takes would

have spiritual benefits and that person would be rewarded afterlife. It was also assumed that those who could not be cured were evil. This belief system of divinity causing the Plague continued up until the 17th century.

Since Catholic education mainly emphasized philosophy and was only mildly practiced, the scholars and physicians relied more on Greek and Arabic medical works and treaties for most of the time. Compared to the Christian dogma, Muslims, on the other hand, were more advanced and eager at anatomy. Andalusian polymath Ibn Rushd (1198 AD), a scholar of Greek and Islamic philosophy, said that "whosoever becomes fully familiar with human anatomy and physiology, his faith in God will increase." Thus, Europeans adopted the Greek medical theories and their Arabic translations, for example, European physicians were reliant on Arabic translations of Galen's medical work [Galen: a physician, surgeon, and philosopher in the Roman Empire around 200-300AD]. One of the most famous Muslim physicians is *Ibn Sina*, his work of *The Canon of Medicine* was a summary of all medical and pharmaceutical knowledge up to his time and was widely accepted throughout Europe and the Middle East.

Despite their knowledge of treating sickness and diseases, the physicians in most of the European countries did have distinctions between themselves based on the level of training. In Aristotle's work, medical practitioners had mainly three divisions: master physicians, skilled craftsmen, or educated laymen. Master physicians who had university training were considered to be more proficient compared to surgeons who were educated by an apprentice system and carried out most of the surgical procedures. Barber-surgeons performed mainly minor surgeries. However, the groups all get trained bases upon the classical ideas expressed by Hippocrates and Galen. While during the early 14th century, in contrast, apothecaries, who would prepare various herbs, minerals, pills, and concoctions for doctors, were the better respected. For most of the cases, physicians were least competent of all the health care providers. Even though their education gave them high status, but all these learnings were theoretical and not practical. And the Black Death in the 14th century made a big shift in their position and the necessity of health care providers in a society.

<u>Treatments and Medical Responses During the Plague</u>

Black Death had put medieval medicine in the middle of a crossroad. Physicians were experiencing a "win or lose" situation during the 14th century Plague. They either gain credibility and reputation or fail miserably. It was a "surge in competition" with little or no train at all. Whether because professional physicians were not available, or these practitioners believed that they had cures that would be effective against the plague, or simply that the patients

were desperate for a possible cure. There was a rise in the activity of such unlicensed medicine.

At the beginning of the Plague, most of the European physicians held the old values and responded to the Black Death with the contents written by Galen and Hippocrates, etc. Here are a few techniques and theories that were applied:

- Theory of Humors
    - It was believed that the Earth is composed of four elements: earth, water, fire, and air. Each element is linked to a body fluid: fire is hot and dry and was associated with yellow bile; the air is hot and moist and was associated with blood; water, which was moist and cold, was an element of phlegm; the earth was thought to be cold and dry, and was the element of black bile. Each humor was also associated with a color, a taste, an age, a temperament, and a season of the year.
    - This theory was directly related to the methods of uroscopy and pulse-taking for diagnosis among the physicians. Uroscopy was a technique of analyzing the color, texture, order, and even taste of one's urine, in order to determine the sickness of that person. Physicians would often take the sample of the urine and compare it to other samples of urine either in the flask or in medical books. Excess bodily humors were expected to be apparent in the urine. Pulse-reading was, again, featured in Galen and Ibn Sina's manuscripts. Various rhythms of heartbeats could be classified, and each was thought to be able to show a certain state of diseases.

- Celestial causes and effects
    - Astronomy was commonly believed to be associated with medicine in Europe. Multiple philosophers and well-known physicians supported this idea. Galen was an advocate for utilizing astrology with medicine; Albert the Great had explained in "*On the Causes and Properties of Elements*" that "For a conjunction of two stars in particular, which are Jupiter and Mars, with others assisting in the sign of Gemini, which is a sign of an airy triplicity, cause pestilent winds and corrupt air, which suddenly kill a large number of men and animals." He pointed out that air can be corrupted from celestial bodies, for example, Jupiter is hot and moist, so it would lift wind and vapors; Mars is hot and dry, so it ignites the vapors elevated by Jupiter. These celestial movements and alignment were believed to have severe effects on Earth and causing the phenomenon of lightning corrupted air, which leads to plagues.
    - From the documents by the Medical Faculty of the University of Paris, *Compendium de Epidemia, Book 2, 1348* and *The Black Death,* Joseph P. Byrne,

Greenwood Guides to Historic Events of the Medieval World, people were suggested to keep dry and calm, "he who wants to protect himself from this epidemic," as recorded, "should choose air as clean and pure as possible; dry, with no mixtures of corrupting vapors." The Plague was understood as a force of nature.

- This system of explanations was more popular among the lower classes, and physicians tended to focus more on the humors and environment because these were easier to modify on preventive medicine.

As a combination of both explanations and short-term observation, the medical *consilia*, the formal communications in the form of explanations between physicians and patients, had made conclusions about the "evil vapors" filled with "evil humors".

<u>During the Plague</u>

Through observations, their recognition of the Plague came closer to the modern version. People started to realize that the Plague was contagious, which were not included in the ancient works. People wrote down new works of literature about the therapies, strategies, and precautions. One of the few was effective at preventing the Plague was the one mentioned by Dionysius Colle in the 16th century, which he recommended to "…throw a powder consisting of sulfur, and antimony into a fire." From modern medical knowledge, we understand that sulfur is indeed destructive to the bacteria, fleas, and rats, so it can prevent the Plague ineffectively.

Some physicians also pointed out that people should avoid things that would moisten or heat the body. Negative feelings, such as anger, sadness, jealousy, and weariness could affect the bodily balance, which should be avoided. From modern studies, we can see that these negative emotions could affect hormone production and lower the antibody level; in some senses, a hot and moistened atmosphere, a lovely habitat for bacteria, could indeed make it easier to get sick.

As for diet, physicians suggested moderation. John Lydgate, the English monk poet in the fifteenth century, has recommended some eating habits in his poem that "not to eat raw food", "drink wholesome wine and eat white bread", "warned of overeating and eating late at night". Even though the recommendations from various experts were contradictory, we can see that observations have increased people's common sense and knowledge about the Plague.

Various medical therapies were putting out for curing the Plague as well:

- Bloodletting was very popular during the 14th and 15th centuries. What they came to understand was that blood was the easiest humor to get to. Physicians combined the

knowledge of astronomy in consideration of the best time for phlebotomy. ["An encyclopedia from a monastery in Cambridgeshire warned practitioners not to perform bloodletting on days divisible by five."] Normally, the bloodletting resulted in no harm from doing so, and it may have been considered to be slightly beneficial because it encouraged people to rest more.

- Another popular therapy was to use surgical techniques to pierce up the buboes or draw blood from around them, which were thought to contain the Plague's poison.

Treatments and Medical Responses After the Black Death (Mindy Wang)

First, the Black Death led to a change in mindset about medicine. During the Black Death, old medical beliefs and texts largely failed. They were either extremely ineffective or completely unable to fight against the plague. As written in the Florentine Chronicle, "neither physicians nor medicines were effective." One reason for this was that most medical texts had little information on the plague or how to treat diseases of the kind. The flaws of medicine at the time were revealed when doctors were unable to give sound medical advice. The Black Death was unprecedented, inevitably leading to major changes in the medical field, including changes in mindset about medicine, as the old beliefs had been discredited. As a result, people started to lean towards experience based evidence that was gathered through experimentation while treating the plague.

There was also a change in mindset about the relationship between God and medicine. Many people believed at the time that the plague was sent as punishment by God and that people who were infected deserved to be sick, or that the pain would be beneficial spiritually. However, a change in perspective can be seen in the Report of the Paris Medical Faculty in October 1348. This document states that "We must not overlook the fact that any pestilence proceeds from the divine will…but this does not mean forsaking doctors. For the Most High created earthly medicine, and although God alone cures the sick, he does so through the medicine which in his generosity he provided." This statement shows a new point of view on God and medical treatment; instead of thinking of treatment as interference, it is seen as a way for God to help the sick through doctors. Although religion continued to play a major role in medicine and science, this shows a step in the right direction, as doctors were no longer held back by the church. Once doctors stopped being seen as going against divine will, many doors opened up for the development of medicine.

These changes led to changes in surgery and dissection. Dissection had previously been seen in a negative light by the church, as the tampering of bodies, both dead and alive, was strictly forbidden. Surgery and dissection were both banned in many universities and institutions.

They were not common practices for doctors or physicians. This severely limited anatomical knowledge, enforcing old beliefs that were inaccurate. It was hard for medical knowledge to advance, as human anatomy had never been fully studied. This changed however, in the 1300s, when French physician Guy de Chauliac was given permission by the Pope to perform a dissection in order to find the cause of the Black Death. This act removed the stigma surrounding dissection and surgery, as the Catholic church had now allowed and encouraged a dissection. At the same time, practical surgeons rose to prominence. As a result of the Black Death, people began to embrace new types of medicine after seeing the ineffectiveness of old medicine. One new type of medical professionals were surgeons. One example of a practical surgeon who gained prominence because of the Black Death is John of Arderne who served King Edward the Third of England.

One more change in medical treatments and responses was the rise of public health laws and increase in hygiene. As seen in the Ordinances For Sanitation in a Time Of Mortality in Pistoia, many laws regarding public health were put into place, especially regarding the burial of the dead and butchering of animals. These laws were strictly enforced in order to combat the spread of the plague. While the initial intentions of these procedures may have been flawed (including reasons such as keeping away “bad air”), this increase in sanitation and hygiene had a positive effect on overall health. Some of these public health laws continued to stay in place after the Black Death and set a precedent for future policies regarding public sanitation and hygiene. During the plague, some doctors and physicians also gave beneficial advice on how to best avoid the plague. Advice included avoiding consumption of raw meat and avoiding wet and humid areas. Properly cooking meat kills bacteria that could cause numerous illnesses and wet and humid areas are prone to bacterial growth. Both of these lifestyle changes increased the health and hygiene of people during and after the Black Death. While avoiding raw meat and humid living conditions seem like common sense to some people nowadays, their start during the Black Death era led to increases in personal hygiene that continue to influence us today.

Although medicine after the Black Death was far from perfect, many revolutionary changes led to significant results that have paved the way for modern medicine. From public health to religious influence, medicine and treatments changed drastically as a result of the plague. The most important change, however, was a change in mindset about the way we view medicine; the changes caused by the Black Death set up the stage for further scientific discoveries based on empirical evidence. The Black Death was able to act as a catalyst, speeding up our path of medical achievements. Without it, medicine may have never been able to reach its heights today.

Evolution of Disease and Medical Understanding (Elie Wang)

As treatments and responses to diseases developed due to the Black Death, people's perceptions and medical understandings of illnesses began to change as well. Because the plague was such a tremendous loss to many European societies, the faith that people and medical thinkers had in traditional medicine began to waver, eventually shifting to theories based upon more empirical evidence and analysis. In order to fully understand the evolution of disease and medicine – specifically from the time of the Black Death until now – comparisons must be drawn to differentiate various norms, practices, and mindsets.

Misconceptions of Treatments and Disease

While the Black Death was still ongoing, European doctors had many misconceptions of disease. One particular misconception about diseases and treatments that was especially prominent and widespread was the use of scent and odor oriented methods to combat the plague. Medical thinkers in the Middle Ages largely based their theories upon traditional beliefs, and theories of olfactory elements in regards to disease had been a long-lasting continuity across various cultures and time periods throughout history. This was due to the fact that these thinkers existed in a time where means of research were limited, and a comprehensive understanding of microorganisms and viruses did not exist. Thus, it was inherently assumed that all of nature's substances could be detected by at least one of the human senses, which explains why doctors so often directly attributed diseases with smells.

The plague was said to have a "characteristic stink", and people were advised by medical officials to "eschew every cause of putrefaction and stinking" (Knutsson, p.176). In order to prevent the spread of these odors – which, supposedly, would prevent the spread of the disease as well – medical thinkers determined that pleasant odors could contrast and combat the unpleasant ones; for example, John of Burgundy suggested that people carry ambergris or "other suitable aromatic".

Although scents and odors are still useful in the medical field today, the difference lies in that medieval thinkers perceived "offensive odors" not as indications of disease or a lethal agent, but as the literal disease or lethal agent itself. The result of this reasoning was the emergence of many theoretical causes – such as celestial events, irregular weather, stagnant and even earthquakes (Rosa, p.1) – that all revolved around the common concept of "corrupted air".

Nevertheless, although perceptions of the relationship between odor and disease was skewed and inaccurate, that is not to say that the scent-oriented treatments were not beneficial – rather, because people were more aware and conscious of the presence of foul smells, measures were taken to prevent them from even originating in the first place, which resulted in cleaner facilities

and public spaces in general. Thus, even though the people of the Middle Ages did not fully grasp the concept of germs and microorganisms, the fact that odors were indeed indicative of disease enabled them to gain some understanding of what healthy/sanitary conditions were; this consequently led to the implementation of improved sanitation measures and the development of public health.

Evolution of Quarantines

During the Middle Ages, the concept of quarantines was also further developed and established by European public health boards. Comparisons can also be drawn between quarantines in the Middle Ages and quarantines in the modern world, as seen most recently with governmental responses to COVID-19.

Although the first quarantine was enforced long before the time of the Black Death, the Middle Ages was when the concept of structured and societal preventative quarantine emerged. In 1348, as a response to a major outbreak of the plague, the Republic of Venice – now known as Italy – established a quarantine system that gave a three person council the power and responsibility to detain individuals and ships entering the Venetian lagoon for 40 days. The state of Ragusa is another prime example of the government enforcing quarantines to protect citizens; the Rector of Ragusa established strict laws for travelers coming to Ragusa and created segregated isolation areas for people in quarantine. The chief physician of Ragusa, Jacob of Padua, also suggested building a site far away from the town to provide healthcare for suspected or definitely sick people. (Conti, p.1)

The general concept of quarantining as a response to a disease outbreak has remained relatively the same throughout history; quarantines were effective back then and they still are today, which is why so many countries affected by COVID-19 have opted to set laws and regulations on quarantines. During the Middle Ages, due to the lack and absence of vaccines or drugs, quarantining was one of the only effective measures that could be taken. Nowadays, now that scientific research has greatly improved, people now have access to vaccines and drugs that can prevent diseases or illnesses – the flu shot is just one of many examples. Nevertheless, in some instances – like when an unknown pandemic like COVID-19 occurs – quarantining is still necessary and becomes the best possible option, showing that even with the advanced evolution and innovation of medicine, the effectiveness of quarantines remains a continuity throughout history.

Development of Medical Ethics

After the peak of the Black Death, many leading medical theoreticians perished, which opened

up the medical world to new ideas and concepts. This also gave way to the rise and development of medical ethics, professional medicine, and the prestige of doctors and hospitals.

Ethical codes were set and determined by associations of medical practitioners (Legan, p.56), and the professional image of doctors was curated and eventually became the norm. For instance, in Arderne's *Treatises of Fistula in Ano*, he advocated that doctors should have high standards of dress and appearance in order to maintain professional courtesy.

Professional medicine was not just limited to Europe; even though the Black Death did not impact medical responses in the Middle East as much as it did in Europe, it still contributed to advancing the professionalism of medicine – particularly in the Ottoman Empire by the 16th century – as well as public health and hygiene.

Additionally, as a whole, the general public also gained more access to medical texts, which demystified many theories and further catalyzed the advancement of the medical field.

Thus, due to the development of public health measures, evolution of medical ethics, and emphasis on empirical evidence to support the use of medical treatments, the world's understanding of medicine and disease today is better than ever.

Ultimately, all of this shows that the Black Death greatly contributed to the evolution of medical understanding, which has brought significant benefits and progress to society and will only continue to improve.

Human Immune System Before the Bubonic Plague (Isabella Yu)

It seemed that the spread of a disease called bubonic plague gradually ceased as humans won the war against the plague in the 14th century. However, the war has not still ended; even today, isolated plague outbreak cases continue to be observed. Experts and researchers, as a result, have strived hard to know the in-depth reason behind the plague. They have asked the important question of "how does the plague actually attack and infect humans?" But in order to answer that question, the researchers knew that they first needed to grasp how the plague infected humans when the disease first emerged in the early 14th century.

After the outbreak of the bubonic plague, in response to the spread of the deadly disease and its dire effects on society, the experts and researchers concerned in investigating the plague worked continuously to indicate the cause of the destructive disease. After conducting extensive research as well as rigorous analysis, the experts examining the plague finally discovered that the

cause of the plague was a pathogen - a microorganism that causes diseases and is found everywhere in life - called *Yersinia Pestis*, or *Y. Pestis*. More specifically, *Y. Pestis* was found to be a nonmotile gram-negative bacterium which is derived mainly from sylvatic rodents. The bacterium is transferred from one rodent to another or to humans by infected ectoparasites such as fleas.

Like other organisms, *Y. Pestis* also goes through the process of evolution, and one of the numerous adaptations accompanying its evolution within the last 20,000 years was that it became possible for the bacteria to be transmitted by insect vectors. Moreover, because of evolution, certain traits of *Y. Pestis* were favorably selected, one of which is the ability to breach issue barriers and become highly disseminated in targeted organisms' bloodstreams. Whenever the infected organisms died because of *Y. Pestis* infection, infecting fleas looked for more hosts to infect.

When infected with *Y. Pestis,* organisms first go through an incubation period which lasts about 2 to 6 days- in case of humans, during this period, they typically show symptoms of infection. For instance, they experience sudden headache, fever, malaise, and in some cases their lymph nodes swell prominently. Without proper and immediate treatment, sepsis, disseminated intravascular coagulopathy, and organ failures can follow the early symptoms. When bubonic and septicemic infections together result in secondary pneumonic infections, the infections can spread among humans using respiratory droplets that are detrimental. After comprehensive research, the researchers concluded that the F1 protein contained in the gel-like capsule produced by *Y. Pestis* is the accountable explanation for the dissemination of the bacteria.

The researchers speculated that the exceptional speed of the plague's spread strongly implies that human susceptibility to the plague is majorly caused by humans' inadequate innate immune response. Usually, humans' immune systems protect humans from harmful bacteria and deleterious infections by phagocytosis; however, when the researchers broke down pneumonic plague victims, there was rarely a hint of phagocytosis of the infectious bacteria.

Currently, researchers believe that the ability of *Y. Pestis* to avoid the eyes of phagocytes because of type III secretion system, which is temperature-regulated and plasmid-encoded. The type III secretion system makes injectisomes - a needle-like projection of protein which serves as a sensory probe - that help *Y. Pestis* move Yersinia outer proteins from the bacilli into the host organisms' cells. Then those Yersinia outer proteins, such as guanosine triphosphatase-activating protein, target neutrophils, macrophages and dendritic cells of the targeted humans and also disturb the process of phagocytosis and oxidative burst. Yet another protein called LcrV helps not only effectively deliver the Yersinia outer proteins from the bacilli into the host humans but also suppress other factors that could possibly interfere with Yersinia outer protein relocation.

In addition, *Y. Pestis* make use of macrophages for protection purposes while replicating. Some microscopic studies such as "pneumonic plague in monkeys" by Am J Pathol or the research conducted by Davis KJ, Fritz DL, and several others could serve as evidence pieces that suggest *Y. Pestis* were seen within the cells in certain primates. Y. enterocolitica, which is the enteropathogenic relative of *Y. Pestis*, does not have a ripA gene that suppresses antimicrobial nitric oxide production and helps the bacteria thrive within macrophages. Other genes such as PhoP-regulated genes also promote *Y. Pestis*'s survival within the macrophages. These data as well as several more studies conducted by experts in this field all together imply the fact that *Y. Pestis* surviving and even thriving within phagocytes of host organisms is significant in relation to plague and the bacterial infection on hosts, though more in vivo evidence and analyses are needed. Moreover, monocyte or macrophage cells may also help the *Y. Pestis* infect hosts, since those cells may serve as a protected niche that buys time for bacteria to adapt to the surrounding environment.

After research, the researchers have also noticed that the genetic differences among homologous Yersiniae virulence factors affect their activities; for instance, in some cases, the *Y. Pestis* LcrV activates Toll-like receptor 2-mediated production of anti-inflammatory IL-10 less effectively than do other Yersiniae. Observations and data gathered from them highly imply that the different natures of different strains of *Y. Pestis* (some try establishing localized infections while others try destroying the defense system and causing deadly disease) could account for the difference. In addition, the researchers also discovered that the wildtype *Y. Pestis* avoids the innate immune system's eyes partly by TLR-mediated activation of innate immunity.

Subsequently, Straley and colleagues found out yet another truth regarding *Y. Pestis* mechanism- *Y. Pestis* also targets non-phagocytic cells. The researchers have observed that YopM, which promotes *Y. Pestis* virulence, attacks and depletes Natural Killer cells in a mouse model of plague. However, further studies would be needed to establish a strong causal relationship between the two factors.

In sum, the data and observations the researchers have gained highly suggests the validity of the statement that *Y. Pestis*'s capability to avoid and attack the innate immune defenses.

Human Immune System After the Bubonic Plague (Katelyn Kim)

The Black Death that rampaged through Europe and Asia with immense magnitude resulted in a catastrophic disaster that wiped out more than fifty percent of the European population. Though this calamity destroyed millions of people, culture, and daily lives, it also

provided future generations with fitter immune systems that are still significant and beneficial to our population today.

The evolution of our immune system is fundamentally influenced by the forces of natural selection. Natural Selection, a process in which organisms with better adapted traits to an environment tend to have a higher survival and reproduction rates, is the basic mechanism of evolution. Likewise, during the 1300s, those who had stronger immune systems against the plague had better chances of survival than those who did not have strong immune systems. This meant that those who exhibited immune responses to the Black death were favored over those that did not exhibit immunity, thus leaving behind more offspring that inherited their useful genes containing immunity against the plague. Overtime, the advantageous traits accumulated in generations, which increased the allele frequency of the favored trait.

Researchers Jaume Bertranpetit and Mihai G. Netea conducted an experiment based on the genetic differences of Romanian Europeans and people who lived in the same area of Romania but were of Roma ancestry. During the 5th and 11th centuries, the Roma migrated from northwest India to Romania. By comparing the SNPs (single nucleotide polymorphisms) of European Romanians, Romanies, and northwest Indians, results showed that the Europeans and the Romanies share a gene cluster called the TLR2, which contains the genes TLR1, TLR6, and TLR10. However, despite the Roma and northwest Indians originating from the same routes, they did not share the TLR genes. The results concluded that although the Europeans and the Romanies are from different origins, they share similarities of advantageous TLR genes code for receptors that is responsible for recognizing pathogens and triggering immune responses. "*We show that there are some immune receptors that are clearly influenced by evolution in Europe and not in northwest India"* said Netea, the leader of the study. Due to the corresponding environmental pressures during the bubonic plague, the European Romanians and the Romanies evolved similarly, showing evidence of convergent evolution of their immune system after the black death.

Moreover, according to Christopher Ducan of the University of Liverpool, UK, some of those who lived during the age of Black Death possessed a mutation on the CCR5 protein. This mutated CCR5 protein, specifically named CCR5- is a receptor of leukocytes that prevents the plague from entering the white blood cells of the host, therefore increasing one's survival rate. This mutation is found primarily in the Eurasia region where the Black Death occurred, which again provides further evidence that the immune system of those who experienced the Black Death has altered. The CCR5- not only increased the survival rate during the age of the Black Death, but also provides resistance to HIV by preventing the virus from entering the white blood cells and disturbing the immune system.

Correspondingly, an absence or a mutation on the FPR1 gene, which also codes for a receptor on human immune cells, can increase protection and survivability against the *Y. pestis,* the agent that caused the bubonic plague. An experiment on mice provided proof that while FPR1 deficient mice had increased survival rates and showed immune responses that triggered protection against the plague, FPR1 existent mice, or non-mutated mice did not show any sign of resistance to the plague.

As provided in the two examples of the mutated CCR5 gene and the FPR1 gene, it is understood that the mutation on these genes provided selective advantages that triggered immune responses against the plague and increased survivability rate. Since these specific mutations were advantageous at that time period, the frequency of the mutated proteins gradually increased, which accounts for the existence of the trait in some people even in the modern days.

In addition to the bubonic plague, other pandemics such as the 1918 influenza, also known as the Spanish flu, caused alterations in the human immune system. The 1918 influenza, which infected estimated 500 million people all over the globe, killed approximately 20 million to 50 million humans. Evolved from a strain that commonly infected birds, the 1918 flu mutated which allowed it to spread into and infect the upper respiratory system. As a result, this induced the flu to be easily transmitted through the air by the means of coughing and sneezing.

Several institutions including Vanderbilt University conducted a study that determined that the people who survived during the 1918 flu had immune responses which displayed neutralizing activity against the virus. James E. Crow, director of the Vanderbilt Program concluded that the B cells of the immune system were capable of retaining their activity for as long as ninety years until the 1918 virus invaded their bodies again. This meant that after exposure to the 1918 influenza, the acquired immune system, also known as the third line of defense, was immensely developed such that the system, which relies primarily on B lymphocytes and T lymphocytes, was able to retain memory of the 1918 antigen, therefore exhibiting specific immune responses to the flu even after decades.

Ultimately, by following back the traces of previous pandemics in history such as the bubonic plague and the 1918 influenza has left us with, we can conclude that as the human race experiences fatal pandemics, the immune system adapts to the specific environment by the pressure of natural selection, and alters the immune system that may bring positive impacts and future immunities against the viruses. As study researcher Sharon DeWitte, a biological anthropologist at the University of South Carolina stated, "*Diseases like the Black Death have the ability to powerfully shape human demography and human biology.*".

Conclusion

Thus, from the research that has been conducted, it can be concluded that over time, the Black Death has greatly impacted our global society, providing an opportunity for humans to significantly improve upon several important aspects of life. Moreover, the outbreak of the plague and its dire impacts on our human society has resulted in a greater understanding of science and health as well as the natural world. Therefore, although the black death was devastating and damaging, other benefits such as the evolutionary innovations and improved immune systems have arisen over time, ultimately proving beneficial to human populations and civilizations.

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