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Microbiology

A bacterium with the power of changing the course of Human history

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ABSTRACT

Around 5,000 years ago, different Neolithic populations in Europe started to reduce in size and even disappear. The reasons of this decay are still largely discussed, but the process is known as the Neolithic Decline. We found evidences suggesting that infectious diseases, and precisely plague, may have played a role on this process

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Our work started when we discovered that Neolithic farmers from Sweden from 4,900 years ago were infected with *Yersinia pestis*, the bacterium that causes plague, one of the most devastating infectious diseases of all times. This finding could potentially explain, why there was an unexpectedly high number of bodies (71) in the passage grave were these individuals were found.

But most surprising was to find plague in this place and time. So far, the oldest cases of plague infections had been found in individuals living in the Eurasian Steppe 4,700 years ago, and wasn't found in Europe until at least 500 years later. The previously proposed model indicated that massive human migration from the Steppe into Europe (well-documented migrations), which started around 4,800 years ago, could have been a major driver of the spread of the disease, specifically from the Steppe into Europe. Our finding changed this picture, as we found that plague was already in Europe before these migrations.

We collected all the available modern and ancient genomes of *Y. pestis*, including those from Bronze Age, and performed different genomic, phylogenetic and molecular clock analyses to get a clear picture of the historical and evolutionary relationships between plague strains.

The first thing we found was that the 4,900-year-old strain from Sweden was not only the oldest, but also the most basal, i.e., the closest to the original *Y. pestis* strain that first infected humans. The genomic

analyses revealed that the strain in Sweden belonged to a different *Y. pestis* lineage than the remaining seven strains found in Neolithic and Bronze Age individuals, which were all part of the same lineage. The molecular clock analyses showed that the Swedish lineage, the Bronze Age lineage and two of the most basal lineages of modern *Y. pestis* (including the ancestral to all strains involved in the first, second and third pandemics) diverged all within a rather short period of time, between 5,700 and 5,100 years ago. Next question was, what was going on during that period of time that could explain such a large expansion?

To answer this, we had to check the archaeological record. Turns out that the precise time in which plague started to diversify and spread, overlapped with the period in which humans started to build large-settlements in Europe, in the current region of Ukraine, Moldova and Romania (6,100-5,400 years ago). For the first time in the European history, we find between 10 and 20 thousand people living relatively packed and in close contact with their cattle, pets and even vermin. In other words, for the first time we find the perfect conditions for the emergence of an infectious disease such as plague. These settlements were repeatedly burned down around 5,400-5,000 years ago, to finally disappear during the Neolithic decline. Was this due to confrontations, as previously proposed, or could it also be for getting rid of epidemic events?

Interestingly, by around the same time (5,500-5,000-years-ago) important technological innovations such as wheeled transport, animal traction and metallurgy largely expanded all over Eurasia. This, for instance, brought the opportunity to expand trade networks over very long distances, but also opened the gate for the rapid and extensive spread of diseases.

Finally, the analysis of hundreds of ancient human genomes from this period of time indicated that massive human migrations could not explain the observed the initial spread of the disease over Eurasia. We thus concluded that it was rather small-scale human interactions (such as trading) that more likely spread the pathogen.

Gathering all evidences together, we built a new model of the early history of plague, which proposes that plague could have emerged in the first European Mega-Settlements and rapidly expanded over long distances favored by animal-powered wheeled transports. Because this scenario became first possible in this historical period, we hypothesize that this could have well been the first human pandemic of history.

Although still hypothetical, if confirmed, the implications of this model are profound. The decline of Neolithic populations in Europe and the massive genetic and cultural changes that came after, with the massive invasions of people coming from the Steppe, significantly bent the curse of human history. We now propose that maybe a single and microscopic bacterium may have played an important role on this, by decimating Stone age European populations or even promoting movements of people escaping from Steppe plagues.

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