

# Tracing Ancient Plagues with Contemporary Genomic Tools

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Advances in genomics and computational power are heralding in a new age of discoveries in an unexpected place: ancient history. Until now, historians have had to rely on scientifically unverifiable historical and archaeological accounts to determine the causative agents and origins of many recorded plagues. Using novel techniques to isolate ancient, usually degraded, DNA from archaeological remains, scientists are beginning to learn more about some of history's deadliest pandemics.

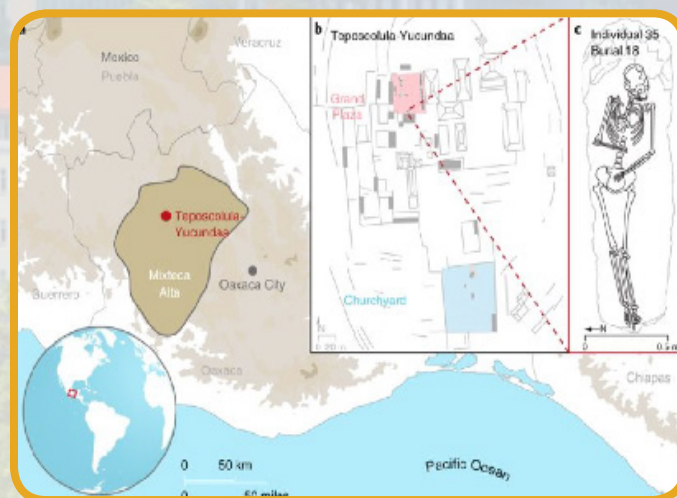
One such plague is the Cocoliztli Epidemic, which occurred in several waves in Mexico throughout the 16th century. This plague was responsible for the death of an estimated 8 million people, many of which were indigenous Aztec (Vågene et al., 2018). For the better part of a century, scholars have debated what pathogen could have killed so many people so quickly.

"This plague was responsible for the deaths of an estimated 8 million people."

An interdisciplinary team of researchers discovered a cemetery associated with the epidemic through written Spanish sources, the only one of its kind known to exist. They extracted ancient DNA (aDNA), which is often degraded or contaminated, from victim's teeth. Using damage pattern analysis to confirm the sample was in fact ancient and soil sequencing to check for contamination, the researchers sequenced the extracted DNA for analysis. The team was able to find a match between the samples collected and *Salmonella enterica* subsp. *enterica* serovar Paratyphi C, an enteric fever causing pathogen (Vågene et al., 2018). Scientists and historians alike now know the cause of the mysterious plague which killed so many.

Another famous plague occurred during the reign of Justinian I and then continued between the 6th and 8th centuries CE in and around the Byzantine Empire. The Justinian Plague was one of the earliest recorded major epidemics in history. According to Procopius, an ancient historian, the Justinian Plague killed 10,000 people daily. Many sources confirm that Constantinople was overrun with bodies and that crops failed due to a lack of living farmers. Victims suffered from fever, vomiting, buboes, and in some

cases, severe hallucinations (Ligon, 2006). While it was long suspected that *Yersinia pestis*, colloquially known as the plague, was the cause of these deaths, there was little empirical evidence to prove it. Researchers removed teeth from a grave in modern Germany wherein the individual had died from the Justinian Plague. aDNA was extracted and sequenced from the teeth, allowing researchers to reconstruct the disease genome. It was compared to known *Yersinia pestis* genomes and was determined to be a distant relative of the causative agent behind the Black Death



Map of graveyard where individual who died from the Cocoliztli plague was found at the archaeological site of Teposcolula-Yucundaa in Oaxaca, Mexico (Vågene et al., 2018).

(Wagner et al., 2014).

In fact, the plague arrived in Europe much earlier than previously thought. Strains of *Yersinia pestis* have been extracted from late Neolithic skeletons found in Southern Siberia. The late Neolithic

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period was characterized by rapid movement of ancient humans into and around Europe, both challenging and supplementing the local Neanderthal populations. Most of this movement came from the Eurasian steppe, a conclusion derived from the

analysis of ancient and modern genomes in these regions. *Yersinia pestis* thus appears to have come into Europe from steppe populations during their migration, triggering centuries of waves of the plague which hugely impacted the course of European history (Andam, Worby, Chang, & Campana, 2016; Andrades Valtueña et al., 2017)

Other plagues have been more difficult to research. The cause of the Athenian Plague is one of the most contentious cases in the field. The Athenian Plague occurred during the Peloponnesian Wars while Sparta held Athens under siege. Therefore, some, even Thucydides, suggest the outbreak was an example of early biological warfare (Papagrigrorakis, Synodinos, Stathi, Skevaki, & Zachariadou, 2013). The Plague of Athens has long been a point of fascination as it took the lives of many important historical Athenian leaders such as Pericles. Historical accounts give us vague and



Mass grave of ancient plague victims in modern day Martignes, France (Drancourt et al., 2007).

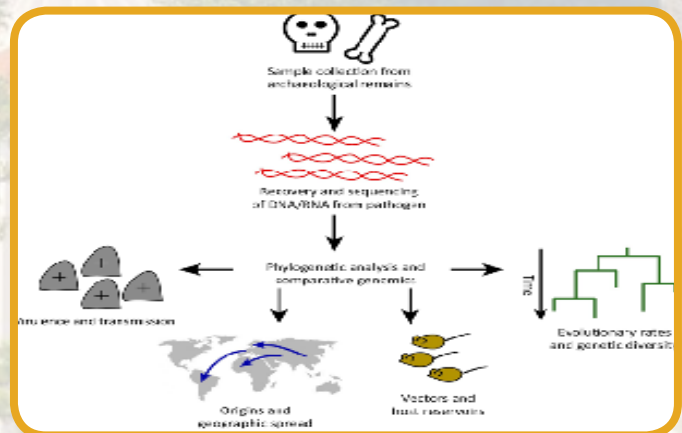
nonspecific symptoms in victims, and lack references to their exact burial sites. Some symptoms described by Thucydides, who was a victim himself, include high fever, extreme thirst, diarrhea, and restlessness (Thucydides; Smith, 1831). Historians have attributed the outbreak, which killed an estimated 25% of the Athenian population, to many different diseases: typhus, smallpox, measles, toxic shock syndrome, and even various hemorrhagic fevers (Littman, 2009; Olson, Hames, Benenson, & Genovese, 1996) To settle this debate, bioarchaeologists have sequenced multiple samples from skeletons associated with the city during the Peloponnesian War and received mixed results. Some have found evidence of typhoid and others of smallpox (Papagrigrorakis, Yapijakis, Synodinos, & Baziotopoulou-Valavani, 2006; Shapiro, Rambaut, & Gilbert, 2006; Spence). As both typhoid and smallpox were endemic in the area, some believe that they would not have caused the devastation described by ancient historians without serious mutations that increased their virulence.

Without historical sources connecting researchers to cemeteries associated with the plague, scientists are unable to definitively determine its cause.

Developments in genomics and computational analysis have allowed scientists to have a deeper understanding of our past. However, some believe that studying ancient diseases may come with a deadly price. Most researchers publish the genomic information of ancient diseases freely online for other

"Some believe that resurrecting ancient diseases may come with a deadly price."

researchers to access. This open access is invaluable to ancient disease researchers who are often investigating similar questions. Some point out that other recent developments in biology may make it possible for terror organizations to inexpensively recreate deadly pathogens with only a few specialized tools given this genomic information. This would allow individuals to release a new epidemic at any time (van Aken, 2006). To mitigate this risk, new ethical safeguards need to be put in place. The National Science Advisory Board for Biosecurity in the United States helps establish codes of conduct when working with



Process of genomic paleopathology and resulting avenues of research (Andam et al., 2016).

pathogens. Additionally, they have worked with the US Department of Health and Human Services to evaluate individual cases to mitigate risk and assess potential benefits of the research being conducted. Another group, the National Research Council Committee on Genomics Databases for Bioterrorism Threat also provide recommendations to reduce bioterrorism risks (Council, Affairs, Studies, Sciences, & Agents, 2004; DeWitte, 2016).

Many believe that understanding the genomic history of pathogens, some of which still plague millions around the world, is extremely beneficial to

medical research. Knowing how pathogens change over time provides insight into their evolutionary history, transmission, and vectors. Ancient data can help scientists understand how diseases spread in the past and apply that information to fight the spread of modern emerging diseases such as SARS and Ebola (Andam et al., 2016). This real-world data from antiquity can also contribute to the creation of statistical models used to predict pandemics and understand how emerging diseases might change over time (Anastasiou & Mitchell, 2013; DeWitte, 2016). While its applications and ethical dilemmas are still being debated, there is significant value in using genomics to understand our history. Historians, archaeologists, and biologists are beginning to have a more complete and nuanced understanding of ancient disease's role in ancient society that will continue to impact our view on the past for years to come.

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