

Ye olde pathogen: Learning about evolution from ancient DNA

October 17 2022, by Vilhelmiina Haavisto



Skeleton showing effects of leprosy, from a medieval Danish leprosy cemetery, reputedly c.1350. Credit: Science Museum A635011/Wikipedia

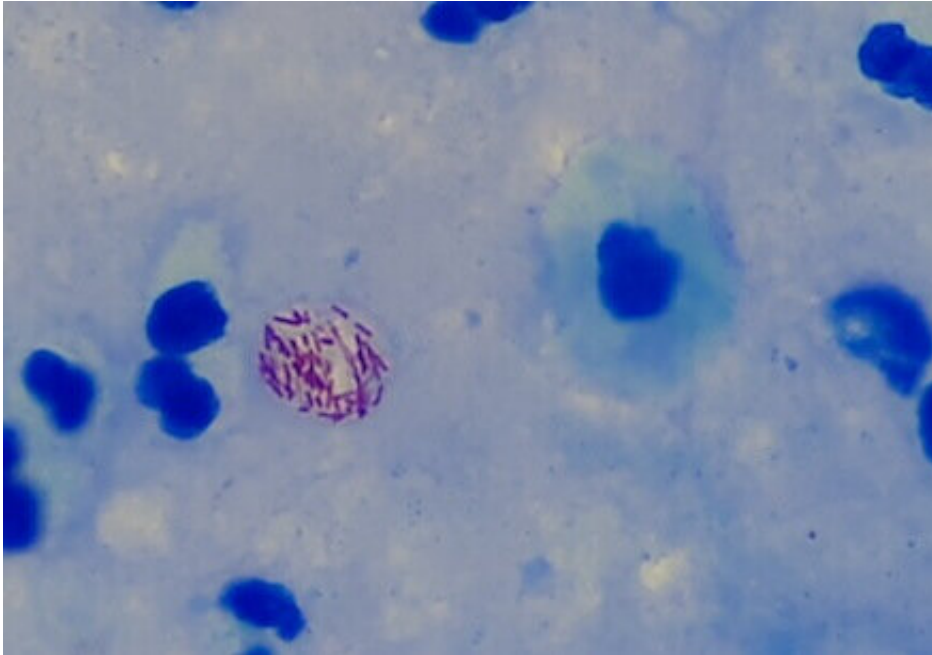
As long as humans have been around, there have been pathogens to make us sick. Some have achieved infamy in human history—the bubonic plague, for example, or smallpox—and with modern technologies, scientists can time-travel to find out what the bugs that caused these illnesses were like, and how they have evolved. With a bit of luck, and the correct alignment of environmental factors, the genomes of pathogens from time gone by can be sequenced from well-preserved

samples. By comparing these genomes to those of present-day pathogens, scientists can understand more about how pathogens have evolved and adapted throughout history.

Reconstructing [ancient genomes](#) is not easy, and has only become possible in the last few decades, thanks to advances in molecular techniques such as high throughput DNA sequencing. One central hurdle is the [damage](#) that DNA accumulates over hundreds of years. Time and exposure to the elements can fragment the DNA and lead to changes in the nucleobases that make up the molecule, which can, in turn, modify the sequence itself. However, there is great variation in the conditions that ancient bodies experience, meaning that in some cases, even very old samples can be relatively well-preserved.

When *Mycobacterium leprae* comes to town

One of the earliest documented diseases, leprosy, and its causative agent *Mycobacterium leprae*, are well-studied when it comes to ancient DNA. Though the disease became less common in Europe after the 16th century, it is still endemic around the globe, with almost [128,000 new cases reported in 2020](#). Back in 2013, researchers analyzed *M. leprae* DNA from British, Danish and Swedish skeletons dating back to Medieval times, and found that the [sequences were](#) remarkably similar to those from modern strains. The gene ML0411 has experienced the most change, perhaps in an effort by *M. leprae* to evade immune responses, as ML0411 codes for a surface antigen that our [immune system](#) can use to recognize the pathogen.



Mycobacterium leprae (pink), pictured here in sputum, has caused leprosy in humans since at least 2000 BCE. Credit: Chaurasiya A.K./Wikipedia

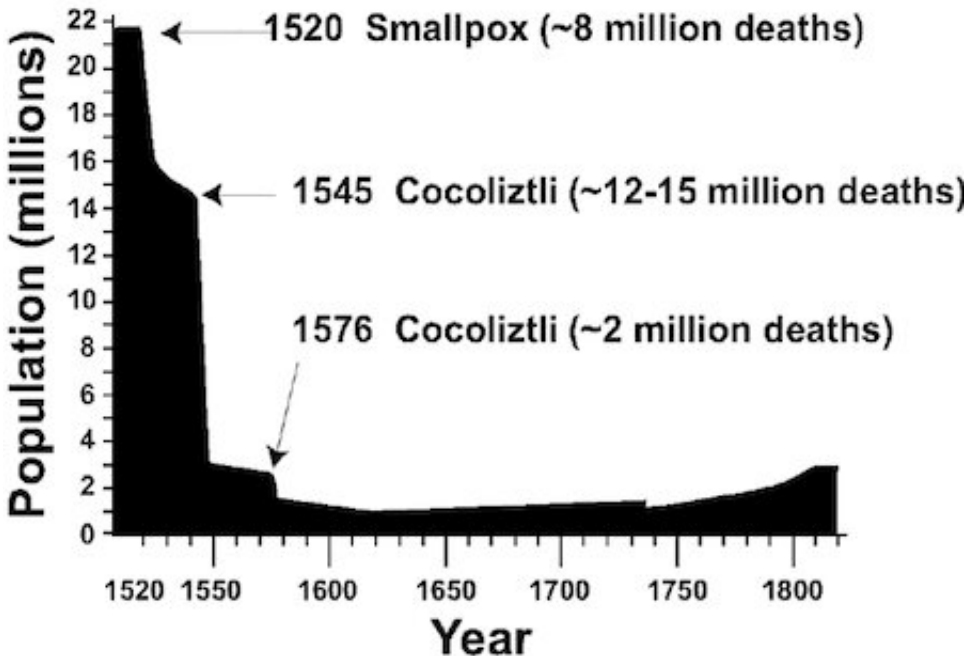
By [comparing ancient and modern DNA sequences](#), the researchers could also glean some insight into why leprosy suddenly declined in Europe during the 16th century. In a 2018 study [of 10 ancient *M. leprae* genomes from Britain](#), they suggest that a loss of virulence—a pathogen's ability to cause disease—was probably not to blame, as the ancient and modern strains are so genetically similar, with the latter still being capable of causing disease. Instead, external factors such as improvements in hygiene practices following other pandemics of the time, such as cholera and tuberculosis, may have contributed to the decline, as *M. leprae* is primarily spread via droplets over recurrent, close contact.

In another study from 2021, researchers paid special attention to understudied regions within Europe and analyzed DNA from [11 more ancient *M. leprae* genomes](#). They analyzed several samples from a

leprosarium, where infected individuals were confined, in Barcelona. There they found a menagerie of *M. leprae* strains, suggesting that beyond serving [local populations](#), the leprosaria also welcomed individuals from abroad, carrying different strains of *M. leprae*. This also raised questions about the importance of migration in spreading the disease.

Using bioinformatics approaches, the researchers were able to link historical expansions in *M. leprae* populations to significant events in [human history](#), showcasing the power of human movement and connectivity in influencing infectious disease dynamics. For example, the ongoing expansion of the Roman Empire co-occurred with an *M. leprae* population boom around 250 AD. The researchers hypothesized that, as humans migrated, they could have introduced *M. leprae* to previously unexposed populations, who may have been more susceptible to the disease. This would explain the increase in disease incidence, as *M. leprae* may have had a relatively easy time infecting humans with no prior exposure.

Population Collapse in Mexico



The mysterious cocoliztli epidemic caused massive population declines in what is now Mexico. Credit: Acuna-Soto R. et al./Wikimedia

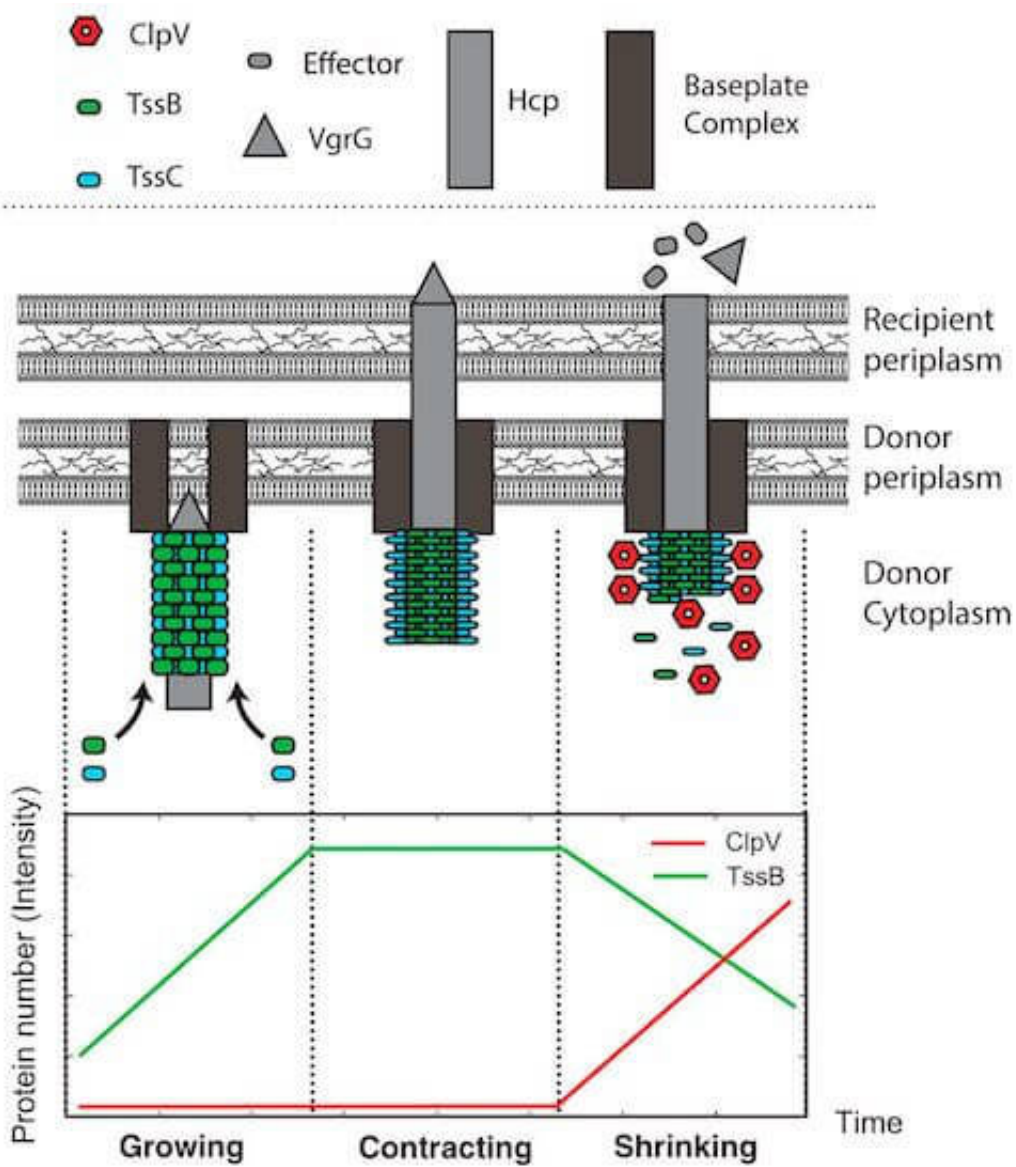
New answers to old questions

Besides shedding light on pathogen evolution, sequencing ancient DNA can also help to clarify the pathogens responsible for mass mortality events where other historical evidence is scarce. For example, the cause of cocoliztli, an epidemic that affected large parts of what is now southern Mexico between 1545 and 1550, remained a mystery for over 500 years. The descriptions of symptoms that have survived are non-specific, including vomiting and red spots on the skin, making it difficult to infer what could have caused the epidemic.

However, in 2018 a team of researchers [identified *Salmonella enterica Paratyphi C*](#), a bacterium that causes potentially lethal enteric fever, in

the teeth of 10 bodies excavated from the only confirmed cocoliztli-era cemetery in Mexico. Using state-of-the-art analysis tools to search for ancient pathogen DNA, the researchers could provide evidence that *S. Paratyphi C* was circulating at the time of the epidemic, and may have caused, or at least contributed to, the catastrophic population declines associated with cocoliztli.

While the identity of the bacterium was resolved, its origins still remain murky. Given the devastation that cocoliztli caused, a leading hypothesis is that it was introduced by Europeans to indigenous Mesoamerican populations without pre-existing immunity. A *S. Paratyphi C* genome has also been found in the remains of a Norwegian woman, who died in 1200, showing that the bacterium was present in Europe before contact was made with indigenous populations in Mesoamerica. However, the researchers could not be certain of from where the *S. Paratyphi C* they detected had come.



Mechanism of a type 6 secretion system (T6SS) that bacteria such as *Escherichia coli* can use to directly inject proteins into neighboring cells. Credit: Corbitt J. et al. *Journal of Bacteriology*, 2018

Potential pathogens hiding in plain sight

While historically infamous and important, not all targets of ancient genome reconstruction are nasty pathogens. Earlier this year, a team of

researchers working in Canada, Italy, Australia and France reconstructed a [16th-century Escherichia coli genome](#) from the mummified gallstone of an Italian nobleman. What was special about this bug, though, is that it was not responsible for large-scale mortality events, like the [bubonic plague](#) or cocoliztli. Instead, it made its living as an opportunistic pathogen—one that strikes only when its host is already weakened.

These kinds of pathogens can be harder to identify because of what the authors of the study call "burden of authentication," as they could also have been introduced as exogenous contaminants from the environment, or during excavation and sample processing. In these cases, DNA damage can actually be helpful, as scientists can differentiate ancient genomes from potential modern contaminants by looking for tell-tale molecular signatures. These include degradation at the ends of DNA fragments, whereby the nucleobases making up DNA lose key functional groups, changing their chemical structure.

The ancient *E. coli* genome included virulence genes, which contribute to its ability to cause disease. For example, several copies of genes encoding type VI secretion system (T6SS), which lets bacteria directly inject proteins such as toxins into their neighbors, point to possible exchange of these genes with other bacteria. Indeed, the T6SS gene cassette appeared to have been acquired from *Klebsiella aerogenes*, a fellow opportunistic bacterium that co-occurs with *E. coli* in certain types of infections. However, most virulence genes that the researchers identified are also carried by *E. coli* K12, the harmless laboratory workhorse strain. Moreover, when the researchers used a strain with a genome similar to the ancient reconstruction, they found that it could not successfully infect mice. Altogether, these pieces of evidence support this strain's primary role as a commensal bacterium that only turns pathogenic if the opportunity presents itself.

Learning from pathogens of days past

The fossils of the microbial world, the genomes of ancient pathogens, can tell us much about the past, and present, of how microbes make us sick. Molecular evidence, combined with information from other branches of research, including archaeology and history, can help us better understand both the evolution and epidemiology of past infections. As technological advances in DNA sequencing and analysis are made, the window of opportunity for sequencing and learning from all kinds of ancient DNA widens.

Provided by American Society for Microbiology

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