PLAGUE (*YERSINIA PESTIS*)

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Plague is an infectious disease caused by the bacterium *Yersinia pestis*.[1] Its transmission is normally limited to wild rodent populations, but it is capable of catastrophic spillover events into human populations. It is still, as of the early twenty-first century, classified as a Class A pathogen, meaning that it can be easily transmitted and has the potential to cause high mortality. Although readily controlled by antibiotics if administered soon after exposure, most strains of the organism would be highly lethal in humans if untreated, with expected fatality rates between 50% to 100%. Of all the major infectious diseases, only Ebola and HIV (first discovered in 1976 and 1981, respectively) are known to produce fatality rates so high if untreated; even Ebola does not kill with the same speed.

Globally, plague has not ranked as a leading cause of human mortality for nearly a century. Yet its historical importance among infectious diseases is outsized. Not simply is *Y. pestis* now understood as the main agent involved in the Black Death (conventionally dated 1346-1353 CE), considered the most severe epidemic catastrophe in human history, and subsequent plague outbreaks in the early modern period (the Second Plague Pandemic), but its role has also been confirmed for the First Plague Pandemic, the so-called Justinianic Plague (conventionally dated 541-ca. 750 CE). These confirmations justify the ordinal designations vis-à-vis the so-called Third (or modern) Plague Pandemic (most commonly dated from 1894 to about the 1930s), when the bacterial cause was first identified. These three pandemics define plague's most visible periods in the historical record, when in each case the disease likely killed millions of people. The "historical record," however, is a cultural artifact that identifies events perceived and recorded by humans. Beyond human perception (that is, when passing solely through its normal wild rodent hosts and arthropod vectors), plague has

[1] My thanks to Thomas Booth, Timothy Brook, Nahyan Fancy, Christopher J. Philips, André Filipe Oliveira da Silva, and Justin Stearns for helpful comments on drafts of this essay.

had no historical record at all prior to twentieth-century ecological efforts to identify plague reservoirs (or foci).[2]

Now, however, plague has earned a special place in the history of science because its history is being reconstructed not from human observations only, but from the genetic history of the causative organism itself. The new evolutionary understanding of *Y. pestis* is not simply revealing a deeper history of the disease in humans than previously known (pushing it back into the Late Neolithic), it is also—in concert with revived inquiries based on traditional documentary sources—reframing the chronology and geographic definitions of the known pandemics. An evolutionary perspective reveals the connectedness of outbreaks across time and space, allowing historians, in turn, to better reveal the "disease regimes" that affected demographic patterns, political structures, and cultural behaviors of human populations across Eurasia and into Africa. As both fields, paleogenetics and history, better recognize the enormity of plague's imprint on the past, the importance of bioarchaeological methods and questions rise in importance, too.

Plague's history as an object of science, a topic in medicine, and a focus of historiography extends back many centuries. Although the disease garnered only passing mention in ancient Greek and Roman medical writings and has yet to be pinned down securely in either Indian or Chinese diagnostic categories before the later Middle Ages, in the Islamicate tradition (starting in the ninth century) plague became a regular topic of discussion in both medical and theological contexts.[3] Later, in both Europe and the western Islamicate world, plague treatises were written in response to the Black Death and they remained a common genre for centuries. By the early nineteenth century, plague transitioned in Europe from a topic of urgent public health concern to a historical question, with the Black Death being the prime focus of interest because of its demographic impact and resulting political or cultural changes.[4] Beyond clinical or epidemiological concerns, plague has played an important role in modern biomedicine as a "model organism" in the development of microbiology in the late nineteenth and twentieth centuries, largely because its exceptional virulence made it an important pathogen to study. Of most importance to the present analysis, *Y. pestis* has also played a leading role in the twenty-first century in the development of paleomicrobiology, a field concerned to construct the evolutionary histories of organisms on the basis of genomic fragments retrieved from historical burials. *Y. pestis* was the first pathogen to have its ancient genome sequenced, and subsequent successes in retrieving ancient *Y. pestis* genomes and modelling the relations between ancient and modern isolates have allowed a global history

[2] For example, da Silva, "Between Deserts and Jungles."

[3] Mulhall, "Plague before the Pandemics" and "Confronting Pandemic in Late Antiquity"; Green and Jones, "Evolution and Spread of Major Human Diseases"; Conrad, "Arabic Plague Chronologies"; Fancy, "Knowing the Signs of Disease."

[4] Varlık, "Plague in the Mediterranean and Islamicate World" provides a comprehensive bibliography on these questions.

of the organism to come into view. Plague was already the focus of on-going debates about "retrospective diagnosis" and how (or if) current scientific understandings of the natural world can be used to interpret past experiences. Those debates have taken a new direction now that science is itself contributing to the reconstruction of plague's history, and as humanistic and natural-historical approaches renegotiate their methods and claims.

YERSINIA PESTIS: A MODEL PATHOGENIC ORGANISM

The bacterium *Yersinia pestis* was first isolated and identified as the causative organism of plague in 1894, during what is now deemed the initial phase of the Third Plague Pandemic. This global transmission of plague, facilitated by steamships traveling out of Hong Kong's busy harbor, spread the disease to the Americas, Australia, and Madagascar, as well as taking new strains to the many port cities of Africa and Eurasia where plague had already circulated centuries before.[5] Both Kitasato Shibasaburō, a student of Robert Koch, and Alexandre Yersin, an associate of Louis Pasteur, had been sent to Hong Kong to isolate and study what was assumed to be a bacterial agent. Yersin proved to be more efficient in isolating the organism, and although he named the organism after his mentor in Paris, by the 1970s *Pasteurella pestis* was redesignated *Yersinia pestis*.[6] *Y. pestis*, it has now been established, is a clone of a relatively harmless organism, *Y. pseudotuberculosis*, that persists in soil and water and, if ingested, causes mild enteric distress before clearing from the body. Acquiring only a relatively small number of genetic changes, including functional gene loss and the acquisition of new plasmids (DNA structures that replicate separately from the main chromosome),[7] *Y. pestis* emerged as a pathogenic organism approximately 7400 years ago, most likely in northern Eurasia.[8] *Y. pestis*'s long-term persistence with relatively little genetic change, despite its extreme virulence, is considered a hallmark of what have been termed "genetically monomorphic pathogens." These are organisms that have found such an effective niche as readily transmissible pathogens that they seem to be under little evolutionary pressure to adapt.[9]

Plague's manifestations in the human body, as we understand them now, may be various.[10] Clinically, plague is differentiated according to the route it takes into its mammalian host's body. "Bubonic plague" refers to what seems to have been the most common manifestation

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[5] Echenberg, *Plague Ports*; Morelli et al., "Genome Sequencing."

[6] Bibel and Chen, "Diagnosis of Plague."

[7] Achtman et al., "Cause of Plague"; Wren, "Model Genus."

[8] The most recent estimate of *Y. pestis* emergence is Susat et al., "Hunter-Gatherer."

[9] Achtman, "Genomic Comparisons."

[10] Yang and Anisimov, *Yersinia pestis*; Demeure et al., "*Yersinia pestis* and Plague."

of the disease in historical times. This causes swift, painful swelling of the lymph nodes in the groin (inguinal), underarm (axial), or neck (cervical) areas. Taken into the body via the lymph system following the bite of a flea or other arthropod, *Y. pestis* essentially commandeers several types of cells in the immune system and is ferried to the lymph nodes where it replicates rapidly. The time from initial infection to septicemic infection of the entire bloodstream—which ultimately induces a cytokine storm (an overproduction of immune cells) inducing toxic shock—may be anywhere from six to ten days. In untreated cases, fatality rates are about 50%.

"Pneumonic plague" can be secondary to a bubonic infection, and is characterized by the particular speed with which the organism colonizes the tissues of the lungs. Primary pneumonic plague is acquired when an individual host, in whom *Y. pestis* has already colonized the lungs, coughs or sneezes, thus propelling the organism, via droplets, into the air, which are then inhaled directly into the lungs by a second host. This is one of the most lethal forms of plague, expected to result in close to 100% mortality if not swiftly treated with antibiotics. "Septicemic plague" occurs when the bacterium enters directly into the host's blood system, for example, via an animal bite or the cut of a knife used to slaughter an infected animal. Although less well studied, it is also believed that plague can be acquired when individuals eat the raw or undercooked meat of plague-infested animals.[11]

In the early twenty-first century, *Yersinia pestis* is found in wild rodent populations on all continents save Australia (where it arrived in 1900, but was driven out by the 1910s) and Antarctica (where it may never have been introduced). That plague no longer causes the catastrophic outbreaks it did in previous centuries is not due to the organism's successful eradication, as happened in the twentieth and early twenty-first centuries with the viruses that caused smallpox (Variola) and Rinderpest (a disease of livestock), nor to a uniform loss of virulence.[12] Clearly, certain lineages of the organism have gone extinct: that includes all the pre-bubonic forms of the organism recently retrieved from Neolithic and Bronze Age sites, as well as almost all strains that afflicted Europe in the Middle Ages and early modern period. In the latter case, there is now evidence that *Y. pestis* lost certain genetic characteristics, perhaps becoming less adapted it to its arthropod vectors or rodent hosts. Remarkably, strains late in both the First and Second Pandemic within Europe lost

[11] Ditchburn and Hodgkins, "Problem of the Past," collect some of the literature on what they distinguish as pharyngeal plague and gastrointestinal plague.

[12] There is one sublineage of *Y. pestis* non-virulent in humans, 0.PE4, found mostly in voles in China, Mongolia, and Kyrgyzstan. But it is neither the oldest nor the most derived of extant strains. Its loss of virulence is, in other words, an evolutionary fluke and not characteristic of the organism generally. Nevertheless, 0.PE4 played an undue role in early discussions of *Y. pestis* evolution because one isolate, 91001, was the third *Y. pestis* genome to be sequenced (Song et al., "Complete Genome Sequence") and was therefore used in all subsequent studies. Most recently on the classification of 0.PE4 lineages, see Nikiforov et al., "Population Structure"; and Kislichkina et al., "Rational Taxonomy."

comparable sections of genetic material before they died out.[13] Alternately (or concurrently), in the case of the Second Plague Pandemic, there is a question whether plague's constriction as a threat to humans is primarily due to public health surveillance and control measures that have disrupted the disease's transmission between rodents and humans via flea vectors.[14] The use of antibiotics to treat infected individuals and quarantine measures to prevent transmission to additional hosts has only been a factor in the control of plague since the mid-twentieth century.

Although it still causes an occasional human case among populations living near infected rodent populations, sometimes flaring up into sustained outbreaks in situations with poor public health infrastructures, plague is considered a relatively low-priority disease among global health concerns. Nevertheless, *Yersinia pestis* and its manifestations as plague remain a topic of vital concern both for the history of medicine and public health, and for the biological sciences. The factor that has made plague a major topic for historians is first and foremost its status as the cause of what has been deemed the most severe pandemic in human history, the mid-fourteenth-century Black Death.[15] There is an exceptional body of writing about the event, both academic and popular.[16] As explained below, the traditional framing of the Black Death's geography has, until recently, caused historical attention to focus solely on the epidemic's effects on Europe and the Middle East. For those areas, studies have had to draw on sources of inconsistent demographic representativeness and value. But repeatedly, the estimated mortality figures—or at least the drop in population levels in the latter half of the fourteenth century—have been in the range of 40-60%.[17] Although there was an extended debate in the later twentieth and early twenty-first century about the Black Death's cause, palaeogenetic work in the 2010s resolved the question in favor of *Y. pestis.*

Because of *Y. pestis*'s extreme virulence (making it an object of bioterrorism concerns), its broad prevalence, and its historic reputation as the world's most lethal epidemic disease,

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[13] Keller et al., "Ancient *Yersinia pestis* Genomes," and Spyrou et al., "Ancient Pathogen Genomics," in both cases drawing on only European samples, document the loss of a comparable section of the genome late in both the First Plague Pandemic and in the Second.

[14] Slack, "Perceptions of Plague." On modern plague surveillance systems, see, for example, Jones et al., "Living with Plague." On the technologies that controlled maritime transmission, Engelmann and Lynteris, *Sulphuric Utopias*.

[15] Rivalry for this dubious distinction is currently shared with the 1918-1919 Flu Pandemic, which may have produced more total fatalities in a more connected, more populous world, but whose total devastation likely did not exceed 2% of the world's population, with a case fatality rate estimated at 7.5%.

[16] Unlike the First (Justinianic Plague) and Third Pandemics, which are scarcely mentioned, the Black Death features in virtually all general historical texts, from middle school through college level surveys. See Green, "Learning How to Teach."

[17] Benedictow, *Complete History of the Black Death*; Lewis, "Disaster Recovery"; Borsch and Sabraa, "Refugees of the Black Death."

plague has remained an object of scientific interest. Due to extensive modern field surveys of *Y. pestis*'s behavior, hosts, and vectors in the Americas, Russia and countries formerly within the Soviet Union, China, the Middle East, and East Africa, plague is now an extremely well-studied disease. Through a series of more or less coincidental circumstances, *Y. pestis* also became the "model organism" for a new area of scientific research at the end of the twentieth century, a field variously called ancient pathogen genomics, palaeogenetics, or archaeogenomics.[18] *Y. pestis*'s prominence as the "star pathogen" in this emerging field is due not only to its geographic ubiquity, but to biological and historical factors.

Biologically, its virulence has made it attractive to laboratory researchers, even if it can only be studied in laboratories with the proper biohazard clearances. A particular characteristic of its virulence pathway has also contributed to its status as a "model organism" for palaeogenetic research. Palaeogenetics is a subspecialty of genetics focused on retrieving DNA fragments ("ancient DNA" or aDNA) from organisms of the past. Most aDNA research is done on hard tissues that survive after death: bones or the calculus (also known as "tartar") that builds up on teeth. These can preserve DNA of the organism itself (endogenous DNA), the microbial life within that host when it died (the neutral microbiome as well as pathogens), and the environmental organisms that colonize the tissues after death. Various bones have proved useful for retrieving endogenous aDNA, but to date nearly all *Y. pestis* aDNA has been retrieved only from human teeth. As described above, right before the host's death, *Y. pestis* is no longer contained within the lymph system but spills over into the general bloodstream. The tooth pulp, which is vasculated, will, like the rest of the body, be flooded with bacteria. The exceptionally hard tooth enamel, however, functions to protect the tooth pulp from post-mortem contamination and decay. Thus, while only a handful of genomes have been successfully retrieved from aDNA for other human pathogens (such as *Mycobacterium tuberculosis*, *Mycobacterium leprae*, malaria, cholera, *Salmonella*, and the DNA viruses variola and hepatitis B), nearly 200 *Y. pestis* genomes have been sequenced from aDNA.[19] Many more will likely come.

On the basis of this increasingly large dataset of premodern genomes (complemented by numerous projects sequencing modern *Y. pestis* genomes retrieved from field surveys and clinical samples which can be used to document *Y. pestis*'s biological diversity), it became possible, after 2010 and 2011, to posit a unified evolutionary history of the pathogen. As a "model organism" for studying what have been called "emerging and re-emerging diseases" in the context of Global Health studies, plague is belatedly being recognized as having no peer save for HIV/AIDS, whose epidemiological tracking via computer-enabled phylogenetics

[18] Bos et al., "Paleomicrobiology."

[19] On the increasing pace of recovery of *Y. pestis* sequences from aDNA, see Table 1 below.

served as a model for the field.[20] Should the SARS-CoV-2 virus become permanently established in wild animal populations, it is likely that the bacterium *Y. pestis* will, to some degree, serve as a model for that research, too.

HOW DO PANDEMICS HAPPEN? QUESTIONS AT THE INTERSECTION OF DOCUMENTARY AND NATURAL HISTORIES OF PLAGUE

As will be explained below, although the road was initially rocky, paleogenetics research on *Y. pestis* has developed with stunning speed and success since the turn of the twenty-first century. The fortuitous discovery in 2015 and subsequent years of the Late Neolithic and Bronze Age strains of *Yersinia pestis* has pushed the documentable history of plague as far back as the third or fourth millennium BCE,[21] while retrievals of *Y. pestis* from burial contexts where there was no prior reason to suspect the presence of plague have shown how surprisingly ubiquitous the disease was at times. Initially, as the fields of plague phylogenetics and paleogenetics developed, they did so by focusing either on certain characteristics of the pathogen that were already of interest to microbiologists, or on the already well-known plague outbreaks of the past. However, as new discoveries were made and as investigative methods honed, new questions have been put on the table.

For the Late Neolithic and Bronze Age periods, for example, major questions are being raised about the origin of *Yersinia pestis* as a highly pathogenic clone of *Y. pseudotuberculosis* and about plague's possible role in both a period of significant human migration in northern Eurasia and the genesis of human immune responses to this and other zoonotic diseases.[22] For the Third Plague Pandemic, it has been determined that only the strains involved in that dispersal carry a distinctive prophage (a virus that has been incorporated into the bacterial genome) which may have enhanced this strain's virulence.[23] However, at both those extreme ends of plague's history—the most distant and the most recent—there are factors that make the "multidisciplinarity" of research distinctive. For the prehistoric periods, geneticists and archaeologists are unconstrained in how they interpret their physical data since there is no need to correlate their theories with a documentary record of human outbreaks, for the simple reason that no such record exists for that period. For the very modern period, should

[20] Snowden, "Emerging and Reemerging Diseases"; Green, "Globalisations of Disease." Most recently on the historical reconstruction of the HIV pandemic on the basis of the phylogeny of the retrovirus, see Gryseels et al., "HIV-1 Genome."

[21] Swali et al., "Plague in Britain," summarizes the work to date, though see also Sikora et al., "Landscape of Ancient Human Pathogens."

[22] Sikora et al., "Landscape of Ancient Human Pathogens."

[23] Bonczarowska et al., "Ancient *Yersinia pestis* Genomes." This finding raises the question whether a Third Pandemic strain, CO92 (a 1.ORI sample obtained from human patient in Colorado in 1992), is suitable as the reference genome for *all Y. pestis* studies.

new evolutionary research questions develop, they will be pursued amidst an abundance of both documentary records (to investigate context) and laboratory samples (to reconstruct *in vitro* observations of the pathogen).

For the two medieval pandemics, in contrast, as well as for newly recognized incidents of sustained plague transmission that have not yet been formally circumscribed by historiographical conventions, issues are arising from the particular demands of both the biology of plague and human perception of plague's effects. This is uncharted territory, methodologically, and both fields have witnessed missteps. Since the Second Pandemic was likely the more deadly of the two medieval pandemics and happened in a period with much richer documentary records coming from a variety of affected societies, questions of how scientific and humanistic research agendas might work in tandem are of paramount concern.

The Black Death as traditionally defined from documentary sources was the sudden and catastrophic diffusion of plague out of southwestern Russia (the territory of the Mongol Ulus of Jochi, or Golden Horde) starting in 1346 and ending, in virtually all areas of Europe, by 1353 if not before.[24] Descriptive accounts, like the scenes of social breakdown evoked by the Italian writer Giovanni Boccaccio (1313-1375) in his famous *Decameron*, or the bleak descriptions of civilizational decay by the historian Ibn Khaldun (1332-1406), have been combined with documentary records (such as probated wills and records of property transfers) as well as medical treatises offering advice on avoidance or treatment of the disease, to show incontrovertibly that a massive catastrophe visited regions from modern-day Iran and southern Russia westward all the way to the Atlantic Ocean.[25] The documentary record for Europe and the Middle East make clear that this sustained plague regime lasted until the eighteenth or nineteenth century.[26]

This traditional understanding of the Black Death is so pat that one often forgets to ask the most basic biological question: how could a vector-borne bacterial disease replicate so far

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[24] The most recent reassembly of this documentary record from Arabic, Persian, Russian, and Latin sources is Jackson, *Genghis Khan to Tamerlane*, chapter 5.

[25] The bibliography on the Black Death, in many languages, is massive; Alfani and Murphy, "Plague and Lethal Epidemics" provides a recent survey focusing mostly on Europe; Varlık, "Plague in the Mediterranean and Islamicate World" expands her purview into the Islamic world; while Roosen and Green, "Mother of All Pandemics" provides a continuously updated bibliography in fields ranging from climate science to economic effects of both the First and Second Plague Pandemics. Dols, *Black Death in the Middle East* and Benedictow, *Black Death* provide what are still the most comprehensive overviews for the Middle East and European experiences of the Black Death, respectively, though it should be kept in mind that both accounts predate all the major work on *Y. pestis* aDNA. Borsch and Sabraa, "Refugees of the Black Death" offers important updates on Dols' work estimating mortality levels in the Middle East. DeWitte and Kowaleski, "Black Death Bodies" focuses specifically on England, and is particularly valuable for integrating documentary and bioarchaeological evidence. Horrox, *Black Death* is the single best collection of primary sources, though there are others.

[26] Conrad, "Arabic Plague Chronologies"; Stearns, *Infectious Ideas*; Shoshan and Panzac, "Wabā'"; Varlık, *Plague and Empire*; Fancy, "Signs of Disease"; Varlık, "Plague in the Mediterranean and Islamicate World."

and so fast in an era before motorized transport? This question is of particular urgency if, as has been claimed since the fourteenth century, the above phenomena were simply the westernmost manifestation of a new, pan-Eurasian diffusion of the disease. Although it is likely there are some fictive elements of the medieval "It Came From the East" narratives, a series of recent historical studies have now suggested similar epidemic phenomena in late-medieval China.[27] For sub-Saharan West Africa, where plague's presence has not yet been confirmed either genetically or from documentary records, it has nevertheless been proposed on the basis of extensive archaeological evidence that plague-like depopulation occurred in the late fourteenth and fifteenth centuries, perhaps in two epidemic waves.[28]

Importantly, on the side of phylogenetics, the new evolutionary approach to plague's history has only heightened the question of the late medieval pandemic's geographic extent and originating processes by proposing that a major evolutionary event occurred in *Y. pestis* ecology. The "Big Bang" is an apparently sudden polytomy or evolutionary divergence of a particularly lethal strain of the plague bacterium associated with marmot populations. (Fig. 3 below captures the basic notions of the concept.)

Two separate questions are on the table: Where did it happen? And when did it happen? The focal point out of which the "Big Bang" lineages emerged, it is now believed, was in or near the area where predecessor strains to the polytomy can still be found to this day: the Tian Shan range bordering western China and Kyrgyzstan.[29] The "Big Bang" created four new lineages of *Y. pestis*, each moving to a new ecological niche. Branch 1 spread the furthest, having been involved in events in Europe (and presumably also the Middle East) from at least the fourteenth to the eighteenth centuries. But Branch 1 is also present in East Africa (as Lineage 1.ANT) and the Tibetan Plateau and Yunnan Province (Lineages 1.IN and 1.ORI). Branch 2 is currently found across all of central Asia and the Middle East; Branch 3 is found in north-central China and Mongolia; and Branch 4 has been documented along the border between Mongolia and Siberia.[30]

Given the permanent imprint that this event left on *Y. pestis*'s phylogeny, one might think it had left a clear signature in the historical record. Yet its timing remains in dispute, with estimates ranging anywhere from the fourteenth to the thirteen centuries, or possibly even

[27] Hymes, "East Asian Beginnings," "Tale of Two Sieges," and "Buboes in Thirteenth-Century China"; Brook, "Comparative Pandemics."

[28] Chouin, "Plague in African History"; Chouin and Lasisi, "Crisis and Transformation"; Dueppen and Gallagher, "Collectivism and New Identities."

[29] Green, "Putting Africa on the Black Death Map" and "Four Black Deaths"; Spyrou et al., "Source of the Black Death."

[30] Green, "Putting Asia on the Black Death Map" summarizes this evidence from modern phylogenetic studies.

considerably earlier.[31] In fact, the whole evolutionary history *Y. pestis* was said in 2023 to be characterized by a "cryptic clock." Why the issue remains convoluted can be found within the history of the evolutionary microbiology of *Y. pestis* itself.

THE EMERGING SCIENCE OF *Y. PESTIS* EVOLUTION

Histories of plague can be traced back at least to the ninth century, when Islamic hadith scholars began to use various outbreaks of plague in Islam's first two centuries as historical markers in the religion's development.[32] Litanies of plague outbreaks became standard features in the Arabic plague treatises of the fourteenth century, and comparable historiographical traditions developed in Europe about two centuries later.[33] From the eighteenth century, histories of the Black Death, and to a lesser extent, the Justinianic Plague, were a staple of both general history and histories of medicine.[34] There was nothing unusual, therefore, about the late nineteenth-century bacteriologists musing about plague's history as they pondered the significance of their new discoveries. The German microbiologist Robert Koch (1843-1910), Kitasato's mentor, was not directly involved in the discovery of *Yersinia pestis* in 1894, or in the recognition several years later of the rat-flea mode of transmission. Yet he did have occasion to study the newly discovered organism both in India and in East Africa, when he visited what was then German-controlled Tanzania in 1897. European colonials learned from locals in East Africa that plague was already endemic there: in several languages, it had not only a local name, but a well-developed cultural tradition that suggested its presence in the region for a considerable time.[35] Trained themselves in the classical languages of Greek and Latin, European colonialist scientists of the period went beyond the testimony of East Africans themselves and drew on references in ancient Mediterranean chroniclers like Evagrius and Procopius to construct a history of plague that situated its origin not in northern Eurasia (as now understood), but in Africa.

Koch's thinking that plague had existed in sub-Saharan East Africa "since time immemorial" was carried forward to new generations of plague researchers in the twentieth century. One of these was the physician René Devignat (1907-1991), who for several decades conducted researches in what was then the Belgian Congo, honing techniques for cultivating *Y. pestis* in the laboratory.[36] Devignat was in constant communication with other field researchers

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[31] Fourteenth century: Spyrou et al., "Source of the Black Death"; Thirteenth century: Green, "New Definition" (and literature cited therein); earlier: Eaton et al., "Cryptic Clock."

[32] Conrad, "Arabic Plague Chronologies."

[33] On Arabic traditions, see Arıcı, "Silent Sources"; on Italian traditions, Martin, "Medieval Plague in Renaissance Italy."

[34] Varlık, "Plague in the Mediterranean and Islamicate World."

[35] Green, "Putting Africa on the Black Death Map."

[36] Boné, "René Devignat."

working in Russia and Asia. Collectively, their observations showed that what in Yersin's and Koch's day had simply been a generic "plague" bacillus could be phenotypically differentiated into distinct strains according to their biochemical properties of fermenting glycerin and reducing nitrates. In a bold move, Devignat assigned the label "Antiqua" to isolates found both in Africa and Central Asia, "Medievalis" to isolates from the Middle East and Central Asia, and "Orientalis" to new strains that had come out of China in the nineteenth century.[37] In other words, each of his three strains (which he called "biovars") was associated with a historical pandemic, fixing in biological thinking what had previously been carved out from the written historical record. Devignat's classification scheme was taken up and popularized in plague science by Robert Pollitzer who, under the auspices of the then recently founded World Health Organization, literally wrote the book on plague in 1954.[38]

This, then, was the scientific-historical understanding that Mark Achtman, a specialist in bacterial population genetics, started with when he began his own research on *Y. pestis* in the 1990s. The discovery of the structure of DNA in 1953 had revolutionized many fields of biological research, and Achtman's work was done on the basis of molecular analysis, not biochemical. In 1999, in association with colleagues at the Max Planck Institut for Molecular Genetics at Berlin and the Yersinia laboratory at the Institut Pasteur in Paris, Achtman established definitively the clonal nature of *Y. pestis* vis-à-vis its parent species, *Y. pseudotuberculosis*. In this first study, he also affirmed the correctness of Devignat's three biovars schema, associated, respectively, with the three historical pandemics. (Fig. 1.)

[37] Devignat, "Nouvelle hypothèse" and "La peste antique."

[38] Pollitzer, *Plague*. This was originally published in installments in the *Bulletin of the World Health Organization* between 1951 and 1953.

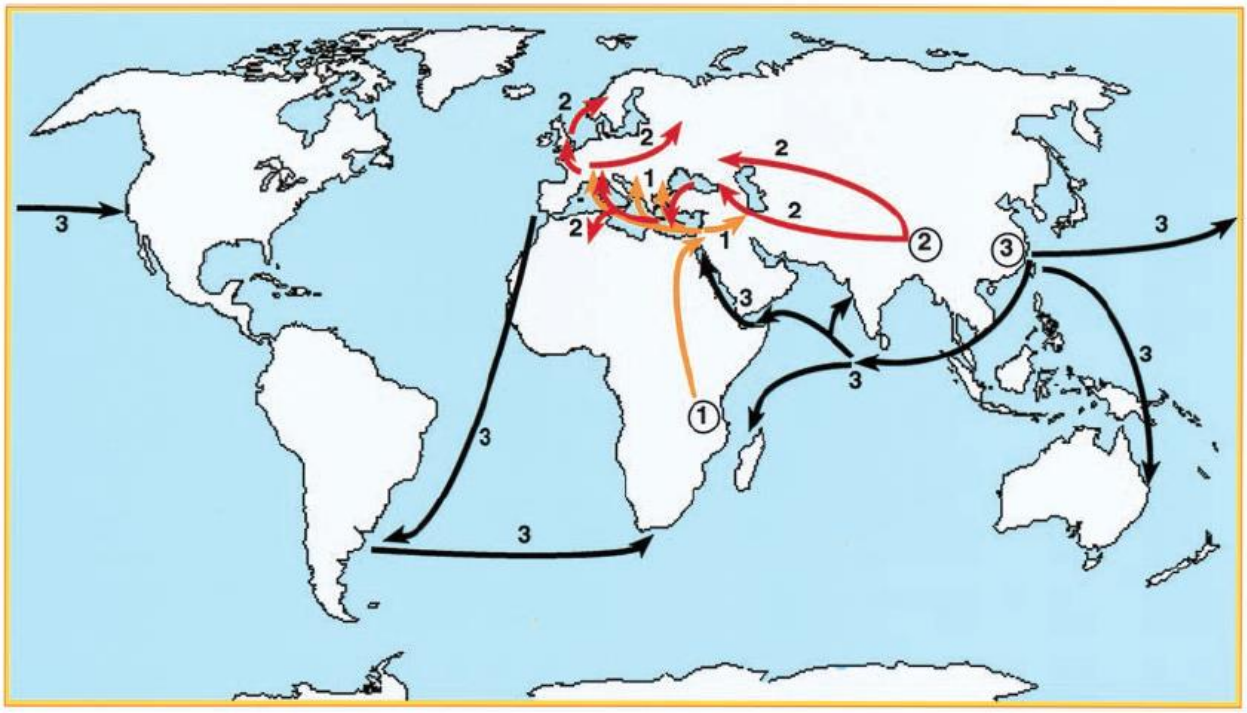

Figure 1: From Achtman et al., "Cause of Plague," fig. 1: "Routes followed by the three plague pandemic waves, labeled 1, 2, and 3. Circled numbers indicate the regions thought to be the origins of these pandemic waves." Note that the First Pandemic was assumed to have an origin in Africa.[39] By 2004, Achtman had abandoned his adherence to Devignat's three biovars-three pandemics theory, and suggested that *Yersinia pestis* originated as a clone of *Y. pseudotuberculosis* in Central Asia.

By the time Achtman returned to *Y. pestis* work in 2004 with a new team of colleagues, however, the organism had been fully sequenced three times: first in 2001 (the same year that the first draft human genome was published), from a sample from Colorado (an "Orientalis" isolate, in Devignat's scheme); then in 2002, from a sample from Iran or Kurdistan ("Medievalis"); and a third time, in 2004, from an isolate from Inner Mongolia which, it became obvious, didn't fall into any of Devignat's three biovar groups and would end up being assigned to a new biovar category, *microtus* (from the Latin for vole, its chief rodent host).[40] In addition to these three whole genomes, Achtman and his colleagues were working

[39] Why Achtman et al., "Cause of Plague" placed the origin of the Second Pandemic in the region of Tibet was not explained. They do not cite McNeill, *Plagues and Peoples*, but that work had been the most influential popularizer of the Tibetan origin theory.

[40] Song et al., "Complete Genome Sequence" demonstrated that although isolate 91001 behaved chemically like a Medievalis strain, genetically it had little in common with the one Medievalis isolate sequenced by that point, KIM. In Achtman et al., "Microevolution and History," it was newly designated 0.PE, to signal its position on the 0 stem of the phylogenetic tree.

with 153 partially sequenced *Y. pestis* and *Y. pseudotuberculosis* isolates to confirm the genomic variants (SNPs, or singular nucleotide polymorphisms, substitutions at particular points along the genome of the bases adenine [A], cytosine [C], guanine [G], and thymine [T]) that could be used as distinct markers of different lineages. Their conclusion was that there were not three different "biovars," as Devignat had supposed, or even four or five, but at least eight populations of *Y. pestis*. They concluded: "Thus, Devignat's hypothesis is no longer convincing, and we can only hope for direct data from ancient DNA."[41] In explicitly asking that a new kind of evidence—DNA of *Y. pestis* retrieved from "ancient" (i.e., historical) remains—be factored into phylogenetic analyses, Achtman and colleagues definitively opened the door to paleogenetics as a contributor to plague's history.

PALEOGENETICS AND THE TRANSFORMATION OF PLAGUE'S HISTORY

In the latter part of the twentieth century, even while microbiologists were continuing their field and laboratory studies of *Yersinia pestis* and its biological character and evolutionary history, a very different take on the principal historical outbreak of plague, the Black Death, was coalescing. Coming from quite different backgrounds (zoology, population studies, and demographic history), a variety of researchers, starting in the 1970s, began to question whether scientists and historians had been right to follow Yersin and others in identifying *Yersinia pestis* as the causative organism of the Black Death. Several concerns underlay these doubts, but most of them centered on seeming discrepancies between the ways plague had manifested itself in the Third Plague Pandemic (particularly in India, which was well studied by several Plague Commissions established by the occupying British) and the written and archaeological evidence for the Black Death. The identification of two new highly lethal diseases in 1976 and 1981—Ebola and HIV/AIDS, respectively—was especially influential in fueling this doubt whether plague was really the most plausible diagnosis to make. Inconsistencies in symptoms described, seeming exaggerations in mortality levels, questions about whether rats (assumed to be the most important intermediate hosts of the disease) were even historically present—all these issues and more caused researchers to question whether *Y. pestis* was really the cause, or rather some other organism, perhaps one (like hemorrhagic fevers or retroviruses) historians in the early years of germ theory hadn't even known to postulate. These new doubts had a dampening effect on plague studies within the field of History for three decades. Although demographic historians could and did continue work attempting to quantify demographic shifts, while cultural historians looked at changes in social structures during epidemic crises, plague denialism essentially brought plague historiography to a halt because historians and demographers had asked a question they (working with written documents produced in a pre-microscopic age) could never answer: which *microorganism* caused the most severe pandemic in human history?

[41] Achtman et al., "Microevolution and History," 17842. In addition to *microtus*, a fifth group, Pestoides, had been identified in 1998.

At the same time these doubts were being raised by historians and demographers, the shifts already examined above were taking place in biology. While most microbiologists continued to work with modern samples, those who had embraced molecular genetics recognized that, like all fields concerned to study evolution, a challenge beckoned to pursue questions of change over time. Palaeogenetics emerged in an inchoate form in the 1970s, initially focused on recently extinct animals but soon expanding its ambitions into the deeper past and higher taxa.[42] As early as 1994, interest turned to whether the fragmentary genomes of microbial organisms colonizing human hosts might also be retrievable from ancient remains. One of the first claims to have retrieved ancient DNA (aDNA) fragments from a pathogen was Salo and colleagues' isolation of a distinctive gene of tuberculosis (*Mycobacterium tuberculosis*) from mummified remains from pre-Columbian South America.[43] In 1998, the first claim was made that diagnostic fragments of *Yersinia pestis* DNA had been retrieved from bodies associated with a 1590 plague cemetery and a 1722 burial ground near Marseille, site of the last known plague outbreak in mainland Europe.[44] In 2000, the same group announced recovery of *Y. pestis* fragments from a site in Montpellier which, they said, dated from the time of the Black Death.[45] Both these studies appeared in the American journal, the *Proceedings of the National Academy of Sciences*, and therefore received considerable attention. The most vocal opponents of the findings were microbiologists themselves, who were not persuaded of the validity of the claims; the most pressing concern was whether the researchers had properly controlled for contamination in their lab. Most damningly, it was asserted that their results were not replicable. The famous plague controversy of 2003-2004—which played out in the pages of *Lancet Infectious Diseases*—addressed questions of laboratory methods and replication.[46]

Even had there not been these technical controversies, however, something larger was amiss. Simply proving the presence of *Y. pestis* had never been the sole goal for the biological researchers. Rather, since Devignat had already put on the table the idea that specific strains of *Y. pestis* correlated with the different pandemics, aDNA findings should have confirmed his hypothesis and yielded insight into the biological character (and potentially, the evolution) of the pandemic strains. They didn't. Even before Achtman and colleagues parted ways with Devignat in 2004, the Marseille group, in its first publication in 1998, claimed it had recovered an "Orientalis" strain from the 1590 burial site in France, potentially troubling Devignat's assumption that that strain was in fact of east Asian (and presumably modern) origin. When they announced their recovery of a Black Death genetic fragment in 2000, the

[42] Jones, "Ancient DNA" and *Ancient DNA*; Orlando et al., "Ancient DNA Analysis."

[43] Salo et al., "Identification of *Mycobacterium tuberculosis*."

[44] Drancourt et al., "Diagnosis of Ancient Septicemia."

[45] Raoult et al., "Molecular Identification."

[46] Little, "Plague Historians in Lab Coats" recounts this in full.

Marseille researchers said nothing of its biovar classification. In a 2002 piece summarizing their achievements to date, they said that while phylogenetic studies had thus far supported Devignat's three biovar schema, "[f]urther support using molecular typing of ancient strains is, however, yet to be provided."[47] Palaeogenetics remained at odds with phylogenetics.

In 2004, in announcing additional *Y. pestis* fragments they had retrieved from historic burials, the Marseilles group now claimed boldly that all their ancient samples, from the sixth century up through the eighteenth (all from western Europe), were indeed of the "Orientalis" biovar.[48] With even a Justinianic Plague sample falling into the "Orientalis" group, Devignat's three biovars-three pandemics theory was invalidated as a description of plague's history, not simply from the side of phylogenetics (through Achtman and his colleagues) but also from palaeogenetics. The Marseille group's study came out just as Achtman and colleagues' 2004 phylogenetic study was going to press, in fact; the latter group attached a coda to acknowledge the concurrent finding. Devignat's labels live on today, of course, as confusing relics of a discarded bio-historical narrative of the mid-twentieth century. Achtman's labeling schema would restrict the designation "Orientalis" (now abbreviated to "ORI") to strains associated with the Third Pandemic coming out of south China. And when, a decade later, a Justinianic Plague genome was first sequenced, it ended up falling amid (Asian) strains previously designated as "Antiqua."[49] But these were accidents of chemistry, not a description of evolutionary descent.

Discarding Devignat's biovar system did not, however, secure the status of a biomolecular approach in explaining plague's *history*. Clearly, both for palaeogenetics and for phylogenetics, increasing the number of samples analyzed was key to achieving robust results. (See Table 1.) The Marseille Group had drawn on two whole genomes and 35 partially sequenced isolates for their 2004 study. Achtman and colleagues had drawn on three modern genomes and 153 isolates in the same year. When Achtman next engaged with *Y. pestis*'s phylogeny in 2010, he and his team drew on a world-wide sample of 17 whole genomes and 286 partially sequenced isolates.[50] This increase in the number of isolates studied allowed an increasing depth of the branches that could be placed on *Y. pestis*'s ever bushier phylogenetic tree, while geolocation data, in Achtman's work, raised the profile of western China as the region showing the greatest diversity of strains (including ones deemed

[47] Drancourt and Raoult, "Molecular Insights," 106.

[48] Drancourt et al., "Genotyping."

[49] Wagner et al., "*Yersinia pestis* and the Plague of Justinian."

[50] Morelli et al., "Global Phylogenetic Diversity." Achtman's name appears as the last of the 24 authors here, in the principal investigator's position.

very old), suggesting that it was likely the region that served as *Y. pestis*'s birthplace and long-term home.[51]

Table 1. Number of complete, published genome sequences of *Yersinia pestis* available for research at key points from 1998 to 2019.[52]

Year	Modern genomes	Ancient genomes
1998	0	0
2001	1	0
2004	3	0
2010	17	0
2011	17	2
2013	131	2
2015	138	9[53]
2016	141	10
2019	237	72

However, the collective project of investigating *Y. pestis*'s history still lacked any clear chronological parameters. In 2004, Achtman and colleagues had speculated that the two main branches of the phylogenetic tree may have split 5000-6000 years before present, though (incongruously) they also postulated that *Y. pestis*'s overall history could extend as far back as 20,000 years or be as recent as 1,500 years, just before the advent of the Justinianic Plague. The field stood at this impasse for the next six years. Even the 286 modern isolates

[51] Achtman et al., "Microevolution and History."

[52] The following studies serve as benchmarks for their respective years: Drancourt et al., "Diagnosis of Ancient Septicemia" (1998); Parkhill et al., "Causative Agent of Plague" (2001); Achtman et al., "Microevolution and History" (2004); Morelli et al., "Global Phylogenetic Diversity" (2010); Bos et al., "Draft Genome" (2011); Cui et al., "Historical Variations" (2013); Rasmussen et al., "Early Divergent Strains" (2015); Spyrou et al., "Historical *Y. pestis* Genomes" (2016); Spyrou et al., "Phylogeography of the Second Plague" (2019).

[53] Rasmussen et al., "Early Divergent Strains" produced seven new aDNA sequences from their own study. Other aDNA used for comparison were the composite basal genome from the London Black Death Cemetery and the Justinianic Plague genome that had been sequenced in 2014. They did not, however, incorporate London 6330 into their tree. See Rasmussen et al., "Early Divergent Strains," Supplemental Information, Table S2.

and 17 whole genomes used for the global diversity study of 2010 could only produce an estimate of "728–8,006 ya [years ago]" as the date range for the split between Branch 1 (the former "Orientalis" branch) and Branch 2 ("Medievalis").

In order for a new fine-grained epidemiological and evolutionary history of *Y. pestis* to be pursued, two things were needed: precise geolocation of samples and precise timing. Both factors were embedded in the sampling methods used to collect *Y. pestis* isolates in field studies in the twentieth century, of course, which (usually) recorded the site and date of collection. For historical samples, geolocation was likewise easy, because all came from well-recorded archaeological digs.

Dating, however, was the issue. Historical epidemiological tracking (that is, tracking specific outbreaks in human populations) could not be done on the scale of the broad estimates of biologists' "molecular clocks." Narrower estimates could be had from radiocarbon dating of archaeological samples, usually on the order of about a century, but for epidemiological tracking they were still unsatisfactory. Even if retrieval methods now met a firmer standard of proper anti-contamination protocols and replicability, the addition of more poorly dated, phylogenetically undiagnostic results for *Y. pestis* retrievals could not move the field forward.[54]

While the global diversity study was being prepared for *Nature Genetics* in 2010, another paper that had been in the works at the same time, and again included Achtman as one of its co-authors, appeared in *PLoS Pathogens.*[55] With Stephanie Haensch, then at the Johannes Gutenberg University in Mainz,[56] as lead author, this second major study of 2010 returned to the work of identifying phylogenetically diagnostic elements of *Y. pestis* aDNA. Working with the samples from three burial sites of the fourteenth century, the authors were able to sequence diagnostically relevant SNPs from Bergen op Zoom in the Netherlands (whose date they reported as "AD 1349-50?"); Hereford, England, for which they had carbon-14 dating (calAD 1281-1389 [95% probability]); and Saint-Laurent-de-la-Cabrerisse, in southern France (calAD 1279-1389 [95.4 % probability]). Remarkably, for both the Hereford and the Saint-Laurent-de-la-Cabrerisse samples, Haensch and colleagues found that "the genotypes map

[54] For example, Wiechmann et al., "Late Medieval Skeletal Finds" would be cited by Schuenemann et al., "Targeted Enrichment" as a positive result, with its claims to have found *Y. pestis* DNA in 10 of 33 skeletal remains from the mass grave beneath the sacristy of the Bavarian town of Manching-Pichl. The dating offered was based on the architectural style of the church (1250–1500 CE); no diagnostic SNPs were called. The Manching-Pichl samples were reanalyzed by Spyrou et al., "Ancient Pathogen Genomics," now accompanied by carbon-14 dating. Even this dating method, however, only produced a century-wide range.

[55] Morelli et al., "Global Phylogenetic Diversity": received 11 January, accepted 8 October, and published online 31 October 2010 in *Nature Genetics*. Haensch et al., "Distinct Clones of *Yersinia pestis*": received 28 May, accepted 7 September, and published 7 October.

[56] In published work, she has variously used "Haensch" and "Hänsch."

to that part of the phylogenetic tree where branches 0, 1 and 2 separate."[57] In other words, it seemed that the Black Death—the great historical event in *Y. pestis*'s history—was also the divergence, its greatest evolutionary event.

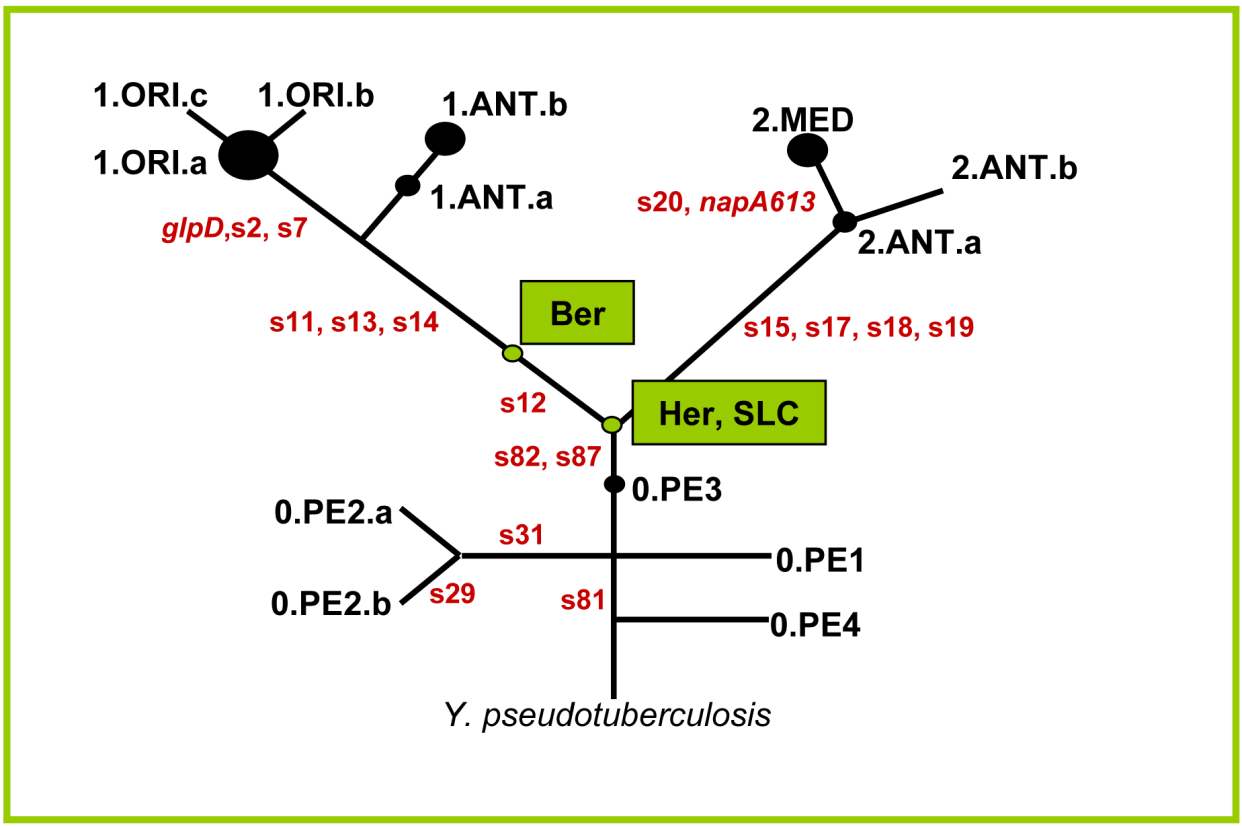

Figure 2: From Haensch et al., "Distinct Clones of *Yersinia pestis*," fig. 2: Schematic phylogenetic tree of *Y. pestis* derived from Achtman et al., "Microevolution and History," which was based on data from 3 complete *Y. pestis* sequences and 153 partial sequences. Branch 0 is the stem of the "Y," Branch 1 is the upper left, and Branch 2 the upper right. The positions of the fourteenth-century archaeological strains sampled for SNP calling (in red)—from Hereford (Her), Saint-Laurent-de-la-Cabrerisse (SLC), and Bergen op Zoom (Ber)—are indicated in green. This captures the understanding of *Y. pestis* phylogeny as of 2010, when only fragments of aDNA were available.

Haensch and colleagues did not claim, however, that western Europe (the site of their samples and the locus of the Black Death as traditionally described from historical sources) was the original site of these new developments in *Y. pestis*'s evolution. Historical descriptions of the Black Death from Europe and the Middle East had always described it as an imported disease: it came from "the East," "the land of darkness," elsewhere. Whatever credence should be given to or withheld from individual chroniclers' accounts, it was

[57] Haensch et al., "Distinct Clones of *Yersinia pestis*," 4.

incontrovertible that the disease, in western Eurasian eyes, was coming from somewhere else, a new import. Haensch and colleagues likewise worked on the assumption that plague was imported. In fact, they suggested that there might have been two paths of importation: one from the south, via the Mediterranean, and one from the north (to account for the derived sample they found at Bergen op Zoom in the Netherlands).

As suggestive as the 2010 study by Haensch and colleagues was, it also showed the impasse the field had reached, as long as it had to rely on genetic fragments only. Just as the transition from partially sequenced isolates to whole genomes had made the inadequacy of Devignat's schema clear to phylogeneticists in 2004, the ability to move beyond partial aDNA sequences (which could only show SNPs haphazardly) to a whole genome became the new Holy Grail. Amazingly, that milestone was reached the very next year, and it brought greater historical clarity to the question of how the Black Death, at least in Europe, related to the divergence between Branches 1 and 2. In 2011, Kirsten Bos, then a graduate student at McMaster University, working with colleagues at Tübingen, addressed the continuing unease about modern contamination in sampling work. She and her colleagues refined tests, which were applied to samples taken from the East Smithfield Black Death Cemetery in London, which had been partially excavated in the 1980s. The result was the confident reconstruction, first, of one of the key virulence plasmids of *Y. pestis*, pPCP1, and then the sequencing of the full chromosomal ancient genome of *Yersinia pestis*.[58] *Y. pestis* thus became the first pathogen to have its genome completely sequenced from archaeological samples, just a decade after the modern genome itself had been sequenced.

Upon publication of Bos and colleagues' study in October 2011, announcements were carried in newspapers around the world. Most praised the technical achievement and celebrated the work as "confirming" *Yersinia pestis* as the cause of the Black Death. In fact, by 2011, there really wasn't much doubt on that point, since study after study had by then yielded either immunological or (partial) genetic evidence for *Y. pestis* in mid-fourteenth-century graves.[59] Rather, the two studies by Bos and her team marked a turning point in *Y. pestis* studies for a different reason: having a complete genome *and* having precisely dated samples made it possible to pin specific evolutionary changes to specific points in time. This transformed the history of the Black Death.

First, the complete genome allowed Bos and colleagues to set aside one hypothesis proposed by the plague deniers, that is, that even if it was *Y. pestis* that caused the Black Death, it must have been a much more virulent strain. Having the complete chromosomal genome as well as that of a main virulence plasmid demonstrated that, in fact, the Black Death genome wasn't all that much different from strains that could be found in the world

[58] Schuenemann et al., "Targeted Enrichment"; Bos et al., "Draft Genome."

[59] Tran et al., "Plague Waves in Medieval Venice," fig. 2, summarized the findings through March 2011, some of which were still unpublished at that point.

today. Indeed, Bos and colleagues' work proved what the Marseille group had inferred in classifying their premodern European samples as "Orientalis" right from the start: that the Third Pandemic strains seemed to be descendants of the Black Death genome.

Second, and just as importantly, the McMaster-Tübingen studies affirmed the finding of Haensch and colleagues that plague's evolutionary development was intimately connected to the Black Death as a historical event. Bos and colleagues' decision to base their palaeogenetic study on samples taken from the East Smithfield Black Death Cemetery in London meant that they could exploit the exceptional historical record of that burial site. It had been created late in 1348 when Londoners heard that a "great mortality" was moving through Europe, and it was closed in 1350 when the epidemic passed and the land was sold. Together with its large size (it has been estimated to have held at least 5000 people), it was the ultimate prize in Black Death studies because it held the promise of giving *Y. pestis*'s phylogeny an absolute time-stamp.[60] Rather than placing the Black Death right at the point of divergence of the two main branches, however, as Haensch and colleagues had done in 2010, Bos and colleagues found that two SNPs separated the more basal of the two genotypes they sequenced in London from the most recent common ancestor shared by Branch 1 ("Orientalis") and Branch 2 ("Medievalis"). The great divergence of *Y. pestis*'s two major branches thus could now be dated, not to 6000 years ago, but to a point soon before the fourteenth-century Black Death itself.

In a follow-up paper in 2012, Bos and colleagues added in more genetic data (most of it supplementary data from Morelli and colleagues' global plague study in 2010) to make their phylogenetic tree's branches bushier, its roots deeper. Now, for example, they acknowledged the existence of a third branch produced at the same time as the split between Branches 1 and 2, which had already been announced (from unpublished data) in the 2010 study.[61] A subsequent study in 2013 by Yujun Cui and colleagues (a team that again included Mark Achtman) revisited *Y. pestis*'s phylogeny yet again, this time adding in data from 127 additional whole modern genomes (mostly from China) that had been sequenced specifically for this study.[62] They identified a fourth new branch originating in the late medieval divergence, which affirmed again that the Black Death, as documented in London, was a later event. The pre-Black Death split into four branches (a polytomy) was now given the memorable epithet, the "Big Bang." By 2013, therefore, the combined efforts of molecular phylogenetics and palaeogenetics had shown that the 1340s Black Death as

[60] Schuenemann et al., "Targeted Enrichment"; Bos et al., "Draft Genome"; Bos et al., "New Evidence for an Old Infection." It had already been unsuccessfully investigated for *Y. pestis* aDNA in 2004 by a previous team of researchers; see the account of Little, "Plague Historians in Lab Coats."

[61] Morelli et al., "Global Phylogenetic Diversity"; Bos et al., "New Evidence for an Old Infection."

[62] Cui et al., "Historical Variations."

experienced in western Eurasia—the story told by Boccaccio and Ibn Khaldun and so many others—wasn't the Big Bang. It was an aftershock.

COUNTING SNPS, TRACKING CHANGE

The overall shape of the *Y. pestis* phylogenetic tree—the two-pronged divergence having now become four-pronged—held firm throughout the rest of the decade, even as new palaeogenetic studies and hundreds more modern genomes (enabled by the dropping costs of sequencing) made the tree thicker and gave new contours to the understanding of plague's history in the Common Era. (Fig. 3.) The Justinianic Plague genome, first documented from genetic fragments and protein signatures in the mid-2000s, was fully sequenced in 2014.[63] Even the announcement of the discovery of Bronze Age lineages in 2015 didn't alter the shape of the main tree, since these extinct strains were believed to be on a whole separate branch, one where (apparently) *Y. pestis* had not yet developed the capability to be effectively transmitted by fleas.[64] Whereas the field had started off the 2000s debating methods and protocols for aDNA retrieval, after 2011 aDNA sequences were given as much ontological authority on phylogenetic trees as modern genomes.[65]

[63] On pre-2011 work on the Justinianic Plague, see Little, "Plague Historians in Lab Coats." On sequencing, see Keller et al., "Early Diversification" and the literature cited therein.

[64] Again, see Swali et al., "Plague in Britain" for a summary of the literature to date.

[65] Zhou et al., "EnteroBase User's Guide."

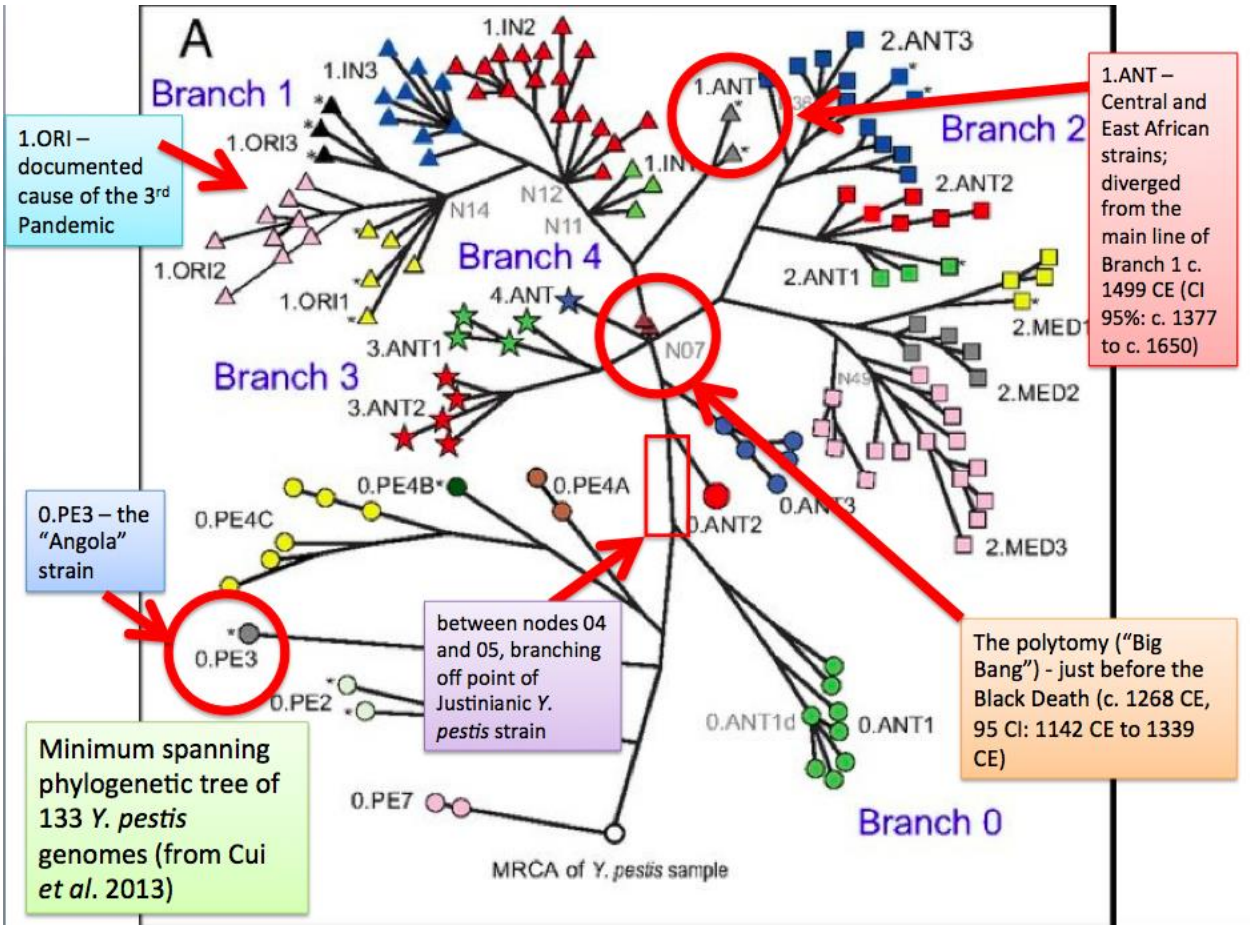

Figure 3: The global phylogeny of *Yersinia pestis* as it was understood in 2013, with estimated times of divergence for the Big Bang and the African lineage, 1.ANT. Minimum spanning phylogenetic tree of 133 *Yersinia pestis* genomes, with major historical events marked. (The branching off point for the Justinianic Plague would be established by Wagner et al., "*Yersinia pestis* and the Plague of Justinian"; in 2015, Rasmussen et al., "Early Divergent Strains" would announce the discovery of what has come to be known as the Late Neolithic/Bronze Age lineage, which they would situate at a basal position to 0.PE7.) From Cui et al., "Historical Variations," with annotations by the present author.

As noted above, the 2011 Black Death genome study was often misunderstood in the popular press as being confirmatory, simply proving what species of microorganism might have killed millions of people in the mid-fourteenth century. But increasingly, just as molecular genetics proved that modern *Y. pestis* had many more forms than Devignat's three biochemical biovars, so palaeogenetics now had the potential to identify strains in the past. These could be tied to specific times and places, and thus could be used to track plague's movements across landscapes and through time. Palaeogenetics was not simply a laboratory testing service; it was capable of doing real "shoe-leather epidemiology." This potential was enhanced even further with the development, by 2016, of a new method of retrieving and analyzing microbial aDNA. Whereas the "targeted capture" techniques used

for studies in 2011 and 2014 had proved tremendously fruitful, they could only be used to determine the presence of an organism the researchers already knew they wanted to look for. By 2016, a newer technique was available. Next Generation Sequencing (NGS) technologies, which employed enhanced (and much cheaper) computational methods, began to make possible so-called "shotgun sequencing," which enabled researchers to capture DNA of any type (host, pathogen, microbiome, or post-mortem environmental organisms), and tag all fragments in libraries, which could then be consulted repeatedly for different DNA fragments. The first study to employ this technique for *Y. pestis* appeared in 2016, announcing the complete sequencing of five genomes from burials from the last major plague outbreak in Europe, the plague of Provence in the 1720s.[66]

And yet, there was still a fly (or flea) in the ointment. Precise dating down to the year was the promise the 2011 East Smithfield study held out, and that was the attraction, too, of the precisely dated Marseille site. *Y. pestis*'s evolutionary state at the ostensible beginning and end of Europe's medieval and early modern experience with plague were now revealed. It was particularly intriguing, therefore, that of the two different genotypes that Bos and colleagues had reported from the London Black Death Cemetery—three identical to each other while the fourth was derived (further evolved) from that—the Marseille genomes, nearly 400 years later, were derived from the earlier one. Since historical (written) descriptions of plague's sudden arrival and spread into Europe in 1347-48 were quite consistent, it had been assumed that the evolutionary change that Bos and colleagues documented in 2011 in the fourteenth-century genotypes had happened within the two-year period when the East Smithfield cemetery was actively in use. Indeed, the derived London genome (coming from sample 6330) had the distinctive SNP that Haensch and colleagues had documented at Bergen op Zoom, leading Bos's team to assume that there likely had been no second transmission of plague into Europe, but rather a local genetic development. It was assumed, in other words, that *Y. pestis*'s evolution had at last been "caught in the act" in a single well-documented historical outbreak of less than two years' duration. The development of the Marseille genome from the less derived London genotype therefore seemed puzzling. Biologically, it was not an impossible result. The evolutionary development of the 6330 sample may have happened only in northern Europe and had no effect on plague as it evolved in later centuries in southern Europe. But epidemiologically, it was curious.

Immediately upon publication of Bos and colleagues' findings in early 2016, a medical historian, Monica Green, noted two things. First was the oddity of the divergence of the Marseille lineage (which she would call Branch 1A) and the London 6330 lineage (Branch 1B, which constituted all the rest of Branch 1 up to and including the Third Pandemic strains). Second, she noted that the two-SNP interval separating the London Black Death genome from that in sample 6330 was the same amount of "genetic time" that separated the Black

[66] Bos et al., "Long-term Persistence." This was the same burial site from which the Marseille group had first reported partial *Y. pestis* fragments in 1998 (Drancourt et al., "Diagnosis of Ancient Septicemia").

Death from the polytomy, which was presumed to have happened in Central Asia, half a continent away from London. This prompted her to double-check the burial location of the anomalous London sample, to see if it signaled something about when during the 1348-50 outbreak this individual had been buried. Surprisingly, further investigation of sample 6330 showed that this seemingly healthy woman of around 25 years of age had been buried in a different, later London cemetery. This wasn't a Black Death burial at all. This later cemetery was St Mary Graces, which was established on the land that the East Smithfield Cemetery had occupied and which was sold at the end of the initial epidemic in 1350 to the newly founded Cistercian abbey. St Mary Graces likely took in bodies buried during a second outbreak of plague (the *pestis secunda*) in the early 1360s. Apparently due to a clerical error, the remains for sample 6330 had been assumed to come from the London Black Death Cemetery.

By separating sample 6330 from the period of the Black Death, Green was able to open up, at minimum, a 12- to 13-year gap in the evolutionary development of Branch 1 of *Y. pestis*.[67] Bos and colleagues would revise their study of the Marseille findings in light of this new information.[68] Additionally, a further publication from Bos's lab in 2016 announced an additional Black Death genome from western Europe (Barcelona, in this case) that was said to be identical to the London Black Death genotype, and a later fourteenth-century genome from western Russia (Bolgar City) that seemed to be further derived along the London 6330/Bergen op Zoom lineage.[69] Together, the two studies from 2016 brought new relevance to historian Ann Carmichael's musings, from 2014, whether the patterns of plague observable in documentary records from northern Italy and Switzerland might not signal focalization of the disease in upland regions within western Europe itself.[70] New questions had been put onto the table—*historical* questions, potentially involving human actors—with this recognition that sample 6330 represented a separate historical event. The discovery of the later provenance of London 6330 put back into play Haensch and colleagues' earlier suggestion that two separate transmissions had brought plague to Europe in the fourteenth century. Scientific analysis of the history of plague, it turned out, still remained inseparable from historical analysis of context.

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[67] Green and Schmid, "Tiny Changes with Huge Implications."

[68] Bos et al., "Long-term Persistence." This was published in two versions: an initial draft (dated 21 January 2016) and then a second draft (dated 11 March 2016) that incorporated the information (communicated to them from Monica Green, via Sharon DeWitte, in February 2016) that sample 6330 was in fact from a different burial site.

[69] Spyrou et al., "Historical *Y. pestis* Genomes."

[70] Carmichael, "Plague Persistence in Western Europe." Subsequent strains of this apparently "within Europe" lineage (Branch 1A) are reported in Spyrou et al., "Phylogeography of the Second Plague."

EXPANSIVE GEOGRAPHIES AND DISCORDANT CHRONOLOGIES: TOWARDS A NEW INTERDISCIPLINARITY IN DISEASE HISTORY

As of early 2024, the timing of the Big Bang remains as contested an issue as it was in 2013. So, too, are the histories of the new lineages it produced, as methods of deriving phylogenetic trees remain in flux and as historians and archaeologists present evidence that troubles the simple Black Death narratives that saw it as a sudden "attack" on western Eurasia in the 1340s with no precursory focalization.[71] The drawbacks of paleogenetics' Eurocentric focus have become clear; due largely to where archaeological digs have been or can be made, and even to the funding infrastructures of where the science is performed rather than any deliberate attempts to exclude evidence, such limited sampling has nevertheless produced an ascertainment bias that stymies interpretative vision and robustness of data. At the moment, the lack of any medieval aDNA from China or Mongolia (or anywhere in Africa) hampers investigation.

Despite these limitations, the palaeoscientific contributions to plague's history cannot be denied, the most important singular achievement being to reveal *Yersinia pestis* as an efficient invader of vast landscapes. By moving beyond written documentation of known human outbreaks of plague and onto the physical evidence of the microbial pathogen itself, the genetics turn in plague research has pushed plague's documentable history back into the Neolithic, and has created the framework to outline the disease's hemispheric pre-modern history, prior to global dissemination during the Third Pandemic. Indeed, it is likely that the histories of the premodern (pre-laboratory) and modern (bacteriologically-verifiable) ages of plague will now merge, since archived isolates from the twentieth century are now regularly being incorporated into *Y. pestis*'s global phylogeny.[72]

Within the history of medicine, oddly, there has been a notable split between modernist historians, who have remained mostly unaware of, or aloof to, these developments in the sciences, and premodernists, who have been more willing to embrace a new source of information. Between 2011 and 2017, five major essays written by historians (all medievalists) described the transition in understandings of the Black Death (or plague studies generally) that the palaeogenetic approach had made possible.[73] Among modernists, even during the COVID pandemic, the "genetics turn" in disease history had not registered.[74]

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[71] Green and da Silva, "Shifting Paradigms"; Hensch, "'Ungewöhnliche im Grab.'"

[72] For example, the extensive work on the 2.MED lineage around the Caspian Sea; most recently, Eroshenko et al., "Retrospective Analysis."

[73] Little, "Plague Historians in Lab Coats"; Bolton, "Looking for *Yersinia pestis*"; Green, "Taking 'Pandemic' Seriously"; Toubert, "La Peste Noire"; Dameron, "Identificazione di un killer." On the special importance of the medieval period for the incipient globalization of several major infectious diseases, see Green, "Climate and Disease in Medieval Eurasia."

[74] Green, "Pandemic Arc."

The reticence to engage with an evolutionary approach to disease history has partly been a function of the field of medical history itself, where methodological developments in the 1970s and 1980s, particularly in Anglophone traditions, left practitioners hesitant to engage in what has been called "retrospective diagnosis." Was it not irresponsible (or at least unduly positivist) for the historian to use modern disease categories to diagnose diseases of the past when historical actors were using medical terms and concepts in no way comparable to modern biomedical ones?[75] Obviously, these questions were initially posed at a time when microbiological analysis was only possible on living (or recently preserved) samples, and historical "diagnoses" were based primarily on written texts. The laboratory of the palaeogenetics age, in contrast, has no such barrier.

Yet impasses remain, many of them having to do with the incompatible chronometrics of the different disciplines involved in pathogen studies. It has been significant that prior to 2016, historians, who have the most immediate interest in coherent stories about one of the world's most devastating killers, were left off of the research teams producing either phylogenetic or palaeogenetic studies of plague.[76] Since then, efforts to develop holistic, interdisciplinary histories of plague have exposed a rather ironic but predictable truth. That is, that in piecing together the global history of a single-celled bacterium that only periodically presents in human populations, there has not been due acknowledgement of two fundamental facts about our modes of knowledge acquisition about plague: 1) that because phylogenetically diagnostic aDNA retrievals have thus far come exclusively from human remains, the genetic record is skewed toward the unusual stages of plague ecology (human infections, often in urban settings) rather than the usual ones (enzootic transmissions in the wild); and 2) that our inherited *narratives* of this history (which have informed scientific approaches as much as traditional humanistic ones) have significant gaps due to fallible human perception of a pre-microscopic world. Given that it is now well-demonstrated that *Y. pestis* has been present in many parts of Eurasia over the course of the last six millennia, tracking its routes from fragmentary, randomly distributed molecular data is an inherently challenging enterprise.[77]

To some extent, a "normal science" state (in the Kuhnian sense) has already been achieved in the disciplines contributing to either molecular or archaeological approaches to plague's history. With the transition to shotgun sequencing, a number of aDNA laboratories are producing newly retrieved *Y. pestis* genomes of considerable quality on a regular basis. Archaeologists, too, have honed their range of questions and techniques: while

[75] Cunningham, "Transforming Plague"; Benedict, "Framing Plague in China's Past."

[76] Michael McCormick, a historian of late antiquity and the early Middle Ages who had predicted the future potential of palaeogenetics as a source of historical information in 2001-2002 (McCormick, "Molecular History of the Justinianic Pandemic"), was the first historian to be a co-author on a *Y. pestis* palaeogenetics paper: Feldman et al., "High-Coverage *Yersinia pestis* Genome"; he was also a co-author on Keller et al., "Early Diversification."

[77] Green, "Out of the East."

"confirmation" of *Yersinia pestis*'s presence is left to geneticists, bioarchaeologists focus on isotopic, paleopathological, and taphonomic analyses of human remains to investigate the demographic profiles of plague victims and other approaches to reconstructing the lives they lived.[78] Discoveries of plague victims in times or places where no documentary records had previously indicated the disease's presence are expanding the general understanding of plague epidemiology; for example, the discovery of the early presence of plague in post-Roman Britain (sixth century) is now transforming questions about the Justinianic Plague's reach and demographic impact.[79]

Yet fundamental questions remain unresolved about the research trajectories ahead, largely because each discipline has limits not simply to the evidence they can retrieve, but to the degree of refinement they can bring to their analyses. As the age of pathogen paleogenetics now moves into its third decade, questions such as the following still loom large:

- **Why do some plague histories seem to have been hidden in the historical record?** Prompted by Cui and colleagues' 2013 delineation of the Big Bang and their suggestion that it *may* have occurred in the thirteenth century, several historians began re-reading thirteenth-century documentary records (including the accounts of physicians and stories of sieges waged by the Mongols). Obviously, plague must have existed *somewhere* in the thirteenth century. But was it in active transmission through human communities? These historians reported that mass mortality events could indeed plausibly be ascribed to plague, particularly incidents where buboes were reported. However, even in finding these hints, historians were puzzled why no *narratives* of these outbreaks had established themselves in the historical canons, even in societies that had strong chronicle traditions.[80] Although partly this question relates to cultural literary traditions (for example, what kinds of human experiences are deemed worthy of recording), in another sense it points to limited visions of what phenomena historians should be looking for. Plague cannot cause *sustained* outbreaks in a region if it has not already focalized: it has to have already embedded itself in the local arthropod and rodent landscapes. Yet what does that process *look like* in terms of human reporting? Just because plague is not causing Boccaccian-level catastrophes does not mean it is not present nearby.[81] It is emerging, for example, that the widespread persecutions of minority groups in fourteenth-century Europe, which started three decades before the Black Death, focused on "well-poisoning" because the apparent randomness of affliction did not immediately

[78] de Lépinau et al., "Entre peste et famine"; Cessford et al., "Beyond Plague Pits"; Kacki, "Digging up the Victims of the Black Death"; DeWitte and Lewis, "Medieval Menarche."

[79] Keller et al., "Early Diversification"; Sarris, "New Approaches to the 'Plague of Justinian.'"

[80] Hymes, "East Asian Beginnings," "Tale of Two Sieges," and "Buboes in Thirteenth-Century China"; Green, "Four Black Deaths"; Fancy and Green, "Plague and the Fall of Baghdad" and "CORRIGENDUM."

[81] Green, "Putting Asia on the Black Death Map."

fit more common miasmatic understandings of "pestilence." Yet *pestilencia*, plague, was already there.

- **How will archeology and genetics, which rely largely on radiocarbon dating (with its inherent imprecisions), address historians' need for annually-resolved dating to time specific plague outbreaks?** The well-poisoning accusations in Europe put in particularly sharp relief historians' need for annually-resolved dating to track developments in human affairs. A typical radiocarbon date for Late Neolithic remains has a span of about 200 years; a typical date for the fourteenth century is about 100-110 years. Yet in every instance, the humans in whom Y. pestis has been retrieved died on a specific day. And since plague epidemics are generally of short duration (a couple of weeks to a few months), annual resolution of data is in fact absolutely necessary for the historian to tie outbreaks to specific political regimes, trade networks, urban regulations, or social responses to environmental changes. In contrast, for evolutionary biologists this focus on annual resolution may have a distorting effect. If anything, there has been a tendency to force too much bacterial genetic data onto a Procrustean bed of human narratives, while at the same time overlooking the diversity in the data already at hand.[82]

With present-day climate change threatening to alter the habitats of many animal species, and potentially alter host-vector relations, too, understanding plague's ecologies—both past and present—will be a continuing global health concern.[83] Whether or not plague reasserts itself as a global threat, it will likely continue to be a "model organism" in historical investigations of emerging diseases.

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[82] Green, "Out of the East."

[83] Carlson et al., "Plague Risk in the Western United States."

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