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Demographic and Evolutionary Consequences of Pandemic Diseases

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ABSTRACT The ongoing COVID-19 pandemic has justifiably captured the attention of people around the world since late 2019. It has produced in many people a new perspective on or, indeed, a new realization about our potential vulnerability to emerging infectious diseases. However, our species has experienced numerous catastrophic disease pandemics in the past, and in addition to concerns about the harm being produced during the pandemic and the potential long-term sequelae of the disease, what has been frustrating for many public health experts, anthropologists, and historians is awareness that many of the outcomes of COVID-19 are not inevitable and might have been preventable had we actually heeded lessons from the past. We are currently witnessing variation in exposure risk, symptoms, and mortality from COVID-19, but these patterns are not surprising given what we know about past pandemics. We review here the literature on the demographic and evolutionary consequences of the Second Pandemic of Plague (ca. fourteenth–nineteenth centuries C.E.) and the 1918 influenza pandemic, two of the most devastating pandemics in recorded human history. These both provide case studies of the ways in which sociocultural and environmental contexts shape the experiences and outcomes of pandemic disease. Many of the factors at work during these past pandemics continue to be reproduced in modern contexts, and ultimately our hope is that by highlighting the outcomes that are at least theoretically preventable, we can leverage our knowledge about past experiences to prepare for and respond to disease today.

Keywords: plague; Black Death; 1918 influenza

The current COVID-19 pandemic, which at the time of writing (February 4, 2021) has caused 104,694,138 confirmed cases and 2,277,821 deaths worldwide (https://coronavirus.jhu.edu), is caused by a novel pathogen (severe acute respiratory syndrome coronavirus 2 or SARS CoV-2), but it is certainly not our species' first experience of a global pandemic. Many of the outcomes of the current COVID-19 pandemic, such as its rate of spread and the numbers of cases and deaths it is causing, are not inevitable. Indeed, much of what we are currently experiencing firsthand arguably could have been prevented if many of us, or our governments, had not ignored the behavior of disease epidemics in the past or the individual and societal responses to those epidemics. This is particularly clear if we examine the variation that exists among responses to COVID-19 and the repercussions thereof. Simply put, some countries, or local authorities within them, have handled the pandemic better than others by employing evidence-based strategies to reduce the spread of infection and prioritizing public health over short-term economic and political interests to the benefit of all inhabitants rather than a select few.

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Variation in responses to the COVID-19 pandemic has produced clear, dramatic differences in rates of infection and death. For example, Senegal has provided a model of success in the face of the pandemic as a result of a rapid, fact-based response by the nation's leaders who followed the guidance of scientific experts and provided clear communication about the virus to the public; curfews and travel bans were swiftly implemented, efficient testing capabilities were ramped up quickly, and health experts were completely transparent about rates of cases and deaths in an effort to undermine any doubts about the severity of the threat posed by the virus and to keep people mobilized and vigilant (Shesgreen 2020). As a result of these efforts, at the time of writing (February 4, 2021), Senegal has experienced 27,365 reported cases and 648 deaths from COVID. Senegal's population is about 0.21% of the world's total, yet their COVID deaths comprise only about 0.028% of the global total. Their success in controlling the spread of the disease and minimizing deaths is particularly impressive given that Senegal is designated by the World Bank as a lower-middle income country, and has a relatively low number of hospital beds and doctors. In stark contrast, in the United States, mask wearing, social distancing, and other non-pharmaceutical interventions that have proven to be effective in slowing disease transmission (see Hatchett et al. 2007) have not been sufficiently supported by the US government and have become politicized in ways that have severely undermined efforts to control the disease. The Trump administration failed to adequately control introduction of the virus into the country (e.g., by screening all travelers) (Hanage et al. 2020) and withheld information about the severity of the disease (Trump argued that he downplayed the danger of the virus to avoid causing panic [see, e.g., Kessler 2020]). Trump himself was likely the largest driver of misinformation spread about COVID-19 in the first half of 2020 (Evanega et al. 2020). As a result of these failures to respond adequately and the intentional distribution of misinformation, there have been over 26 million confirmed cases and 454,272 reported deaths from COVID-19 in the United States at the time of writing (February 4, 2021). It is shocking to note that the population of the United States represents about 4.25% of the total global population, yet cases of and deaths from COVID in the United States represent about 25.4% and 19.9% of the world totals, respectively (https://coronavirus.jhu.edu).

Emerging Diseases

COVID-19 is the most recent, and dramatic, example of an emerging disease pandemic, and highlights the short-lived and perhaps misguided nature of the general optimism in the mid-twentieth century that we were moving toward a future free from the threat of deadly infectious diseases (see, e.g., Burnet 1962). Emerging diseases are those that are completely new to human populations, have only recently been recognized and identified as distinct diseases, or are diseases that existed previously in a population but have, for a variety of possible reasons, increased rapidly in incidence or geographic distribution (Morse 1995). Examples of emerging infectious diseases within the last few decades include HIV/AIDS, West Nile virus, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), Ebola, Zika, and COVID-19 (Cleaveland et al. 2007; Morens et al. 2004). Reemerging diseases are those that experience a resurgence after they had been on a decline. There are several reasons for the emergence and reemergence of diseases including rural-to-urban migration, long-distance mobility and trade, encroachment into previously uncultivated environments, human-induced climate change, and over- and misuse of antibiotics (Weiss and McMichael 2004). Given that the factors that favor disease emergence and reemergence will likely continue unabated, our species will inevitably face new emerging diseases in the future.

Though the field of emerging disease research is relatively new (the dedicated journal, *Emerging Infections Diseases*, launched in 1995), the existence and impact of emerging diseases on human populations has a much deeper history. Emerging diseases, and the epidemics or pandemics they cause, were also important in the past, and we can study their behavior and repercussions to better understand the long-term biological, demographic, evolutionary, economic, and other consequences of such diseases in general as well as the context-dependent nature of the impacts they can have. Ideally, as a global community, we can carefully attend to data from and experiences of diseases in the past in ways that encourage and enable us to be proactive in the face of disease pandemics—i.e., learning about disease in the past has the potential to allow us to engage in effective disease prevention and preparedness rather than relying on disaster response mechanisms after diseases harm our bodies, lives, livelihoods, and communities.

Selective and Excess Mortality During Pandemics

Though disease pandemics can have myriad effects on human biology and genetic variation, demography, settlement patterns, ecology, and social, political, and economic conditions, the primary focus of

this paper is on their demographic and evolutionary effects. These consequences can often ultimately be traced to selective mortality or high excess mortality (or both) during pandemics. Selective mortality refers to the unequal distribution of deaths across various biological and social categories, such as age, sex, occupation, social status, ability status, and health status. Most causes of death, including diseases, tend to be selective and therefore disproportionately kill certain individuals, such as those with underdeveloped or compromised immune systems, people who are routinely denied quality health care, or those who are unable to remove themselves from threatening or hazardous situations. Because mortality tends to be selective, rather than indiscriminate, people who die at each particular age are unlikely to represent all of the individuals originally alive at that age. Instead, the sample of people who die at each age is biased toward the most frail and vulnerable individuals. The effects of selective mortality during a pandemic can produce a surviving population that differs demographically from the original population. For example, if older adults are more likely to die from a particular disease compared to younger individuals, the post-pandemic population may, over the short term, have an age distribution that is younger than that of the pre-pandemic population; or, if mortality is higher among women than men, sex ratios and patterns and levels of fertility might change in the aftermath of the epidemic. Selective mortality during disease epidemics can potentially also produce genetic changes in a population if mortality is selective with respect to genetic variants that confer resistance to the causative pathogens or elevate susceptibility thereto.

Excess mortality refers to a greater number of deaths than is typical for a particular population, i.e., excess mortality is the total number of deaths from all causes in a population, during a particular period, that are above and beyond the expected number of deaths for that same population based on the historical average. Excess mortality, in the absence of a selective effect, can produce the simple but important demographic effects of smaller population sizes and densities; depending on the severity of the excess mortality, it can take several generations for populations to recover from these effects. The deaths of relatively large proportions of a population at the local level can lead to changes in settlement patterns and migration, such as the relocation of people away from communities in England that were no longer sustainable following the fourteenth–century Black Death (Dyer 1982; see also archaeological evidence of site abandonment in Africa in the mid-fourteenth century, e.g., Chouin 2018).

The demographic consequences of pandemics can contribute to social, economic, political, and ecological changes in human populations. For example, changes to the age distribution or sex ratio of a population following a disease pandemic can potentially have economic effects by altering the ratio of consumers to producers and the number of available marriage partners, and thereby limiting feasible options for subsistence strategies, shaping household structures, and affecting economic growth. Pandemics can have positive or negative economic effects, depending on pre-pandemic conditions, as has been documented for medieval populations during the Second Pandemic of Plague (see, e.g., Alfani and Murphy 2017; Borsch 2005). The genetic consequences of pandemics might have long-term effects on patterns of health, such as potentially altering susceptibility to and thus the prevalence of some diseases among descendants of those who survive pandemics.

Though there have been many fascinating disease pandemics in human history, we focus here on the Second Pandemic of Plague (i.e., bubonic plague) and the 1918 influenza pandemic. Their causative pathogens still cause disease, so they have a clear, immediate relevance to living people. These historic pandemics produced extraordinarily high mortality—tens of millions of people died in a very short period of time both during the fourteenth–century inaugural outbreak of the Second Pandemic (now commonly referred to as the Black Death) and during the 1918 flu pandemic—and have therefore been the focus of a relatively rich literature focusing specifically on their short- and long-term health, demographic, or evolutionary effects. They are fascinating to scholars and the general public alike and are therefore referenced frequently in media reporting on current disease epidemics and pandemics. Thus, there is a need to thoroughly review what we know (and do not yet know) about their behavior and effects in order to enhance efforts to better educate the public about how human biology and demography are potentially shaped by pandemic disease.

The Second Pandemic of Plague

The fourteenth–century Black Death is one of the best-known pandemics in human history. It was the beginning of what is now called the Second Pandemic of Plague. The First Pandemic of Plague (also called the Plague of Justinian) began in the sixth century C.E. and lasted for about 200 years, and the Third Pandemic of Plague began in the nineteenth century and ended in the mid-twentieth century (Ziegler 2014). DNA evidence from historical burials

associated with the First and Second Pandemics have confirmed that they were caused by the same bubonic plague bacterium, *Yersinia pestis,* that was responsible for the Third Pandemic and that continues to cause plague around the world today (Bos et al. 2011; Bos et al. 2016; Keller et al. 2019; Spyrou et al. 2016; Wagner et al. 2014). The Black Death killed an estimated 30%–60% of affected populations (Green 2014). These mortality rates have been estimated from documentary sources, e.g., by comparing the numbers of death duty or head tax payments made before and during the Black Death (DeWitte and Kowaleski 2017). Further, this massive, rapid depopulation is also reflected in the archaeological record in some regions, allowing for reconstruction of the scale and geographic extent of the epidemic in areas without existing documentary evidence thereof. For example, archaeological research by Chouin and colleagues (see, e.g., Chouin 2018) in Ghana and Nigeria has revealed evidence of settlements that were abruptly abandoned in the second half of the fourteenth century. Gallagher and Dueppen (2018) similarly report archaeological evidence of settlement abandonment and thus depopulation in the fourteenth century in Mali and Burkina Faso. In the absence of documentary or molecular evidence, these archaeologists cannot yet say for certain that plague was the primary driver of abandonment, but evidence strongly suggests that it was. Lewis (2016) assessed trends in potsherd abundance across archaeological sites in England as a proxy for population size, and found that the number of test pits that yielded potsherds decreased, in general, by over 44% after the Black Death.

Following the Black Death, which ended in the mid-fourteenth century, there were recurrent plague outbreaks for hundreds of years, though none appear to have produced mortality levels as high as the Black Death. In England, for example, the outbreak of plague in 1361 killed an estimated 20%–30% of populations (DeWitte and Kowaleski 2017), and outbreaks in London in the seventeenth century (ca. 1603, 1625, 1636, and 1665) each killed approximately 20% of the city's population (Cummins et al. 2015). In addition to lower levels of mortality, there were other apparent changes in the epidemiology of plague following the initial epidemic. Earn and colleagues (2020) analyzed documentary data from London and found that the epidemic growth rate (a measure of the rate of spread of the disease) in the sixteenth and seventeenth centuries was four times that of fourteenth-century epidemics. The Second Pandemic ended at various times in different locations; for example, the last major outbreak of the Second Pandemic in England was the Great Plague of 1665–1666, and the Plague of Marseille in 1720–1721 is generally regarded as the last major outbreak in western Europe, but plague outbreaks were experienced in the Middle East until the nineteenth century (Varlık 2020).

Selective Mortality During the Second Pandemic of Plague

The extraordinarily high mortality levels produced by the Black Death and later outbreaks of plague during the Second Pandemic have raised questions about how excess mortality during these epidemics was distributed across various biological, demographic, and social categories, that is, whether everyone exposed to the disease faced the same risk of dying regardless of age, health condition, social position, gender, occupation, and other factors, or if there was variation in risk of death during the pandemic. The existence of the skeletal remains of people who died during the Second Pandemic has enabled bioarchaeologists to assess whether plague mortality was selective or indiscriminate using data derived directly from segments of the population not always represented in historical documents.

Selectivity with respect to age and frailty ("health")

Several bioarchaeological studies in England and France have analyzed differences between the age-at-death distributions within mass burials associated with the Black Death and/or later plague outbreaks vs. non-epidemic (attritional) burial assemblages or have compared the demographic profiles between plague burials and living age distributions. Some of these studies have concluded that mortality during these historical epidemics did not vary substantially by age and thus that death during medieval and postmedieval plague epidemics was indiscriminate with respect to age (Gowland and Chamberlain 2005; Kacki 2017; Margerison and Knüsel 2002). Conversely, Waldron (2001) found similarities in the age-at-death distributions between the East Smithfield Black Death cemetery in London and an attritional sample, and that both differed from a model living age distribution, which suggests that the Black Death was not an indiscriminate killer with respect to age. Similarly, analysis of sixteenth-century plague burials from Les Fédons in Lambesc, France, reveals an age-at-death profile that is similar to a living age distribution and also differs from age-at-death distributions found in attritional skeletal samples (Castex 2008). According to Castex (2008), these results indicate that plague mortality was not selective with respect to age in that context. Some studies have integrated paleopathological data to examine the "health" status of individuals killed during the

Second Pandemic compared to those who died under normal circumstances. Waldron (2001) found similar patterns of skeletal pathological indicators (osteoarthritis and other degenerative conditions, dental pathologies, trauma, and infections) between the English Black Death and attritional assemblages. In contrast, Kacki (2017) compared plague and nonplague burials from France (ca. fourteenth–sixteenth centuries) and found that frequencies of skeletal indicators of health (linear enamel hypoplasia [LEH], cribra orbitalia, endocranial lesions, and periosteal reactions) were lower in plague burials. Kacki (2017) interprets these results as indicating better health among plague victims (prior to death during the epidemic) compared to people who died under normal conditions of mortality, and thus that plague in these outbreaks was not selective with respect to preexisting health.

The disparity in these findings raises questions about the possible effects of age-estimation methods and the inherent difficulties with interpreting relative frequencies of skeletal pathological indicators (i.e., the Osteological Paradox). To address these possible confounders, other studies have used approaches that both circumvent some of the limitations of conventional skeletal age–estimation methods and explicitly address the potentially biased nature of skeletal stress markers, and they have revealed evidence of selective mortality during the Second Pandemic. Recent bioarchaeological studies of the East Smithfield Black Death cemetery in London by DeWitte and colleagues have used the method of transition analysis to estimate adult ages at death (applied to skeletal features described by [Boldsen et al. 2002] and using ADBOU software). This approach, in general, avoids the issue of age mimicry (which is characteristic of conventional methods), whereby estimated ages are biased toward the age distributions of known-age reference samples (Bocquet-Appel and Masset 1982). It also produces point estimates of age for all possible adult ages rather than open-ended terminal age categories, which prevent evaluation of demographic patterns at later adult ages (Milner and Boldsen 2012; Milner et al. 2018). DeWitte and colleagues have also applied fully and semiparametric hazards analysis and nonparametric survival analysis to reconstruct age patterns of mortality and to assess the effects of sex and the presence of a variety of skeletal stress markers on risks of death during the Black Death. This approach, in general, allows researchers to use age-structured data to directly address selective mortality and avoid making assumptions about what skeletal stress markers or other variables reflect about health. DeWitte and colleagues found that the risk of death during the epidemic increased with adult age, and that people with skeletal indicators of stress—including linear enamel hypoplasia, dental calculus, short adult stature, cribra orbitalia, and periosteal new bone formation (all of which were found to be associated with elevated risks of death under ordinary circumstances and thus reflective of underlying frailty)—faced higher risks of death during the Black Death compared to peers without them (DeWitte 2010a; DeWitte and Hughes-Morey 2012; DeWitte and Wood 2008; Yaussy and DeWitte 2019). In combination, these results suggest the Black Death was selective with respect to age and frailty.

Godde et al. (2020) also focused on the East Smithfield Black Death cemetery, comparing it to other medieval London burial grounds. They estimated age at death using an approach different from, but adhering to the same underlying principles as, that used by DeWitte and colleagues (i.e., they used transition analysis applied to different skeletal age indicators). Nonetheless, they also found that skeletal evidence of previous stress (cribra orbitalia, short femora, and LEH) was associated with elevated risks of death during the Black Death. However, in contrast to DeWitte (2010a), they found decreased (rather than increased) odds of dying for individuals above the age of 65 during the Black Death. These findings with respect to age are also at variance with those for plague burials in sixteenth-century France; as detailed above, Castex (2008) found that the plague age profile was similar to that of a living population, suggesting that plague mortality was not selective with respect to age. It is important to note that Castex (2008) used conventional methods of adult age estimation and reported no ages above 29 years, and, further, did not use hazards analysis.

In England, the Black Death was followed soon after by the plague of 1361. Examination of selective mortality during this second wave of plague has been done using data from plague burials from the Cistercian Abbey of St. Mary Graces in London. Using age-at-death data (estimated using the method of transition analysis) from the 1361 plague burials, DeWitte and Kowaleski (2017) found by applying hazards analysis that the risk of death increased with adult age during the second outbreak of plague, as was previously observed for Black Death victims and for people who died during conditions of non-epidemic mortality. Analysis of the effect of periosteal new bone formation on risks of death revealed elevated risks of mortality for those with the skeletal lesion among the 1361 plague victims, similar to trends observed for the Black Death and suggesting that mortality during the 1361 outbreak was selective with respect to frailty as was apparently the case during the Black Death.

The findings with respect to the effects of preexisting health or previous exposure to physiological stress reported by DeWitte and colleagues and Godde and colleagues for the Black Death and the plague of 1361 in England contradict the conclusions drawn by Kacki (2017) for medieval and postmedieval France, as detailed above. Thus, the question remains whether these disparities reflect the use of a frequentist approach vs. hazards analysis or the possibility of geographic or temporal variation in plague mortality patterns.

Sex differences in plague mortality

None of the previous bioarchaeological research on Second Pandemic burial grounds revealed evidence of a significant difference in risk of death between the sexes (Castex and Kacki 2016; DeWitte 2009; DeWitte and Kowaleski 2017; Godde et al. 2020; Kacki 2017; Waldron 2001; see also the meta-analysis of sex ratios in plague burials by Bramanti et al. 2018). Waldron (2001) noted a higher proportion of males in the East Smithfield Black Death cemetery, but acknowledges that this is not sufficient evidence of a greater susceptibility of males to plague mortality. Research on the topic based on historical records has produced variable results, which might indicate the context-dependent nature of sex differences in historical plague mortality. Curtis and Roosen (2017) analyzed mortmain (death duty payment) records from the Southern Netherlands dating from 1349 to 1450 and found that sex ratios (male:female) declined during the Black Death and subsequent outbreaks of plague, which suggests that more women died during plague outbreaks than during periods of normal mortality and that there was a sex-selective effect of plague. Their analyses further suggest that the apparent disparity in excess mortality between the sexes during plague outbreaks was not the result of sex differences in exposure to the disease. In contrast, Lazzari and colleagues (2020) analyzed daily death records from the 1630–1631 plague outbreak in Venice, Italy, and found no evidence of a sex difference in mortality during the outbreak.

Pre-pandemic subsistence crises and social inequality

Some of the variation in risk of death that appears to have existed during the Black Death and the plague of 1361, at least insofar as has been estimated from London cemetery data, might have been shaped by social inequalities and experiences of severe famines in England before the Black Death. There were poor grain harvests in England in 1283 and 1293–1294, and the Great Famine of 1315–1317 killed an estimated 10%–15% of the population (directly via starvation or indirectly via increased susceptibility to disease as a result of poor nutritional status) (Alfani and Ó Gráda 2017), making it the worst recorded subsistence crisis in England's history (Campbell 2016; DeWitte and Slavin 2013). Shortly afterward was the Great Bovine Pestilence (ca. 1319–1320) that killed over half of bovine populations and led to a scarcity of dairy resources until the early 1330s (DeWitte and Slavin 2013; Jordan 1996; Slavin 2011). There were also severe harvest shortfalls in 1321, 1324, 1328, 1331, and 1339 (Campbell 2016). The harvest shortfalls in 1293–1294 and in 1339 occurred at a time of increased taxation (in support of military operations), which disproportionately negatively affected poor people (Campbell 2016).

The subsistence crises that occurred in the years or decades leading up to the Black Death might have had direct effects on the health of individuals (who ultimately died during the epidemic) by negatively affecting the development of their immune systems and thereby increasing their risk of death from infectious disease (see, e.g., Moore et al. 1999), as predicted by the developmental origins of health and disease (DOHaD) hypothesis (Barker 1990; Worthman and Kuzara 2005). Those crises that occurred a generation or more prior to the Black Death might have exerted intergenerational effects on health in the fourteenth century via epigenetic inheritance. Most studies of the potential intergenerational effects of famine conditions in humans (e.g., the effects of the Dutch Hunger Winter or the Great Chinese Famine) have examined links between epigenetic inheritance and noncommunicable diseases such as cardiovascular disease and diabetes (e.g., Fernandez-Twinn et al. 2015; Gomez-Verjan et al. 2020). However, a recent study by Cheng and colleagues (2020) found that prenatal and early life exposure to the Great Chinese Famine increased the risk of tuberculosis in adulthood across two generations. Regarding social inequalities, historical evidence from some contexts indicates that mortality during the Second Pandemic of Plague was higher among lower status and poorer people (Alfani and Bonetti 2018; Carmichael 1986; Cummins et al. 2015; DeWitte and Kowaleski 2017; Galanaud et al. 2020; see also, e.g., Alfani and Murphy 2017). Though the exact mechanisms contributing to heterogeneity in frailty within the populations affected by the Black Death have yet to be conclusively determined, the epidemic might provide a dramatic historical example of how the effects of a disease are not simply the result of the interaction of a pathogen with a human host's immune system, but rather reflect the synergistic effects of broader individual-level and societal conditions. That is, the

Black Death likely represents a syndemic (Singer and Clair 2003; Singer et al. 2017; Tsai et al. 2017).

Post-pandemic health and demography

Mortality during the Black Death appears to have produced, through either direct or indirect means, demographic changes that persisted at least over the short term following the epidemic. As mentioned above, the Black Death killed upward of 60% of affected populations, and in many locations, demographic recovery afterward was delayed for several generations; for example, it took about 200 years for populations to return to pre-pandemic levels in Denmark (Hybel and Poulsen 2007). Depopulation during the epidemic, and slow recovery thereafter, might have produced conditions that were favorable for health and well-being (though we emphasize that we in no way want to promote the view that the epidemic was ultimately good, regardless of the outcomes). For example, research has found evidence that adult mortality risk decreased while survivorship increased after the Black Death in London compared to pre-pandemic patterns (DeWitte 2015, 2017). Gamble (2020) similarly found that survivorship increased after the mid-fourteenth century in urban and rural contexts in Denmark. As detailed below, there is evidence for declines in fertility in parts of Europe following the Black Death, which raises the question of whether these mortality and survival analyses are confounded by changes in fertility. However, using the same skeletal data from medieval London that were used to estimate survivorship, DeWitte (2014, 2015) estimated fertility proxies (the ratio of individuals above the age of 30 to those above the age of 5 years, which is negatively associated with birth rates [Buikstra et al. 1986]), and the results indicated no significant changes across the medieval period. These findings suggest, at the very least, that the estimated changes in survivorship after the Black Death in London are not simply an artifact of declines in fertility. These demographic changes have been interpreted as potentially reflecting improvements in overall health that occurred because of increased standards of living and decreased social inequalities that were a consequence, at least in England and Denmark, of the depopulation produced by the Black Death (see, for example, dietary improvements described in historical documents as detailed by [Dyer 2002]) and subsequent reorganization of society (DeWitte et al. 2016).

It is also possible that post-pandemic demographic (and, by inference, health) changes were produced by a short-term harvesting effect or a longer-term selective effect of the pandemic (DeWitte 2017). The former has been suggested as an explanation for changes in estimated sex differentials in mortality in London: prior to the Black Death in London (ca. 1349–1350), adult males and females apparently experienced similar mortality risks, but afterward (1350–1540 C.E.), adult males experienced lower risks of mortality (DeWitte and Yaussy 2019; Yaussy et al. 2016). Coupled with evidence from DeWitte (2010b) that more frail males died during the epidemic than did frail females, the apparent change over time in sex differences in risks of mortality might reflect the effects of selective mortality during the Black Death. That is, excess mortality of frail males might have resulted in lower average frailty among males compared to females following the Black Death.

Recently DeWitte and Lewis (2020) examined changes in the average age at menarche in medieval London. This study was motivated by previous findings that adult tibia length (a proxy for achieved stature, which is associated with health and exposure to stress) increased significantly among males after the Black Death in London, but decreased among females (DeWitte 2017). Given evidence that survivorship, and likely health, improved for both sexes after the Black Death, the apparent increase in male stature is perhaps unsurprising, but the seemingly contradictory decrease in female stature begged further study. Studies of some living populations have found that average age at menarche (which is generally viewed as a reflection of population health and socioeconomic conditions) (Cho et al. 2010; Lehmann et al. 2010) declines in some populations that experience improvements in nutritional status and reductions in disease burdens. Furthermore, in some contexts, an earlier age at menarche is associated with shorter stature in females (e.g., Kang et al. 2019; Onland-Moret et al. 2005; Petersohn et al. 2019; Schooling et al. 2010). Thus, it is possible that if health conditions truly improved substantially in general following the Black Death, adolescent girls may have experienced an earlier age at menarche and earlier skeletal maturation. Cessation of long bone growth may have resulted in shorter stature for healthier adult females after the Black Death compared to pre-epidemic conditions. Analysis of skeletal indicators of pubertal events from medieval London suggests that the average age at menarche did, in fact, decrease after the Black Death (importantly, this decrease was not an artifact of changes in the underlying age-at-death distributions among adolescents).

These changes theoretically could have positively affected fertility following the Black Death by increasing the reproductive lifespans of women. However, quite the opposite trend appears to have actually occurred, as some historians (see Bailey 1996) have

argued that fertility rates declined after the Black Death. At least in some contexts, these declines might have been driven by economic conditions. There is evidence that in northwestern Europe, the European Marriage Pattern was widely adopted after the Black Death. The European Marriage Pattern is characterized by a relatively late average age at marriage and high rates of people never marrying, both of which contribute to limiting fertility. Some scholars attribute this change to the economic opportunities that opened up for women because of the severely reduced labor pool produced by the epidemic; employment for women was, in some cases, conditional on celibacy (de Moor and Van Zanden 2009; Voigtländer and Voth 2013). According to Voigtländer and Voth (2013), adoption of the European Marriage Pattern led to 25%–40% reductions in fertility.

Another important demographic variable to consider is migration, particularly its effects on population health, social and economic conditions, its potential role in the emergence and effects of the Black Death, and how migration patterns might have changed in the aftermath of the pandemic. For example, migration can have effects on age and sex structures in both sending and receiving populations, and might affect health patterns in receiving populations as a result of "migrant selectivity" (Lu 2008), due to exposure to novel (to the migrants) pathogens, and/or poor housing conditions following migration (see Galanaud et al. 2020). According to Dyer (2005), migration likely increased after the Black Death, and there is evidence that rural-urban migration in medieval England in general was disproportionately female (Goldberg 1986; Kowaleski 2013). Klunk et al.'s (2019) paleogenetic analyses of human skeletal remains from medieval London and cities in medieval Denmark revealed evidence of high mitochondrial DNA diversity in these contexts before, during, and after the Black Death. These findings might reflect consistent, high levels of female migration into cities before and after the epidemic. Kendall et al. (2012) found, using isotopic data, that over 15% of sampled Black Death victims (n=30) in London were immigrants to the city. To date, bioarchaeological work on migration in this context has been limited, so there is great potential for further work integrating historical, genetic, and isotopic data on migration before and during the Second Pandemic of Plague.

Evolutionary consequences of the Second Pandemic

The very high mortality levels produced by the Black Death and/or the evidence, at least in some contexts, that risks of mortality were not uniform during the epidemic has motivated researchers to seek evidence of its effects on human genetic variation—i.e., to assess whether the Black Death produced observable evolutionary effects—or to attribute patterns of genetic variation found within living people to the effects of the epidemic. For example, Moalem et al. (2002) hypothesize that high frequencies in people of northern and western European descent of a genetic mutation (C282Y) that causes hereditary hemochromatosis reflects the selective effect of medieval plague epidemics. Hereditary hemochromatosis (HH) is a disease of excessive iron storage that can be fatal if untreated, but because it is characterized by low iron levels in macrophages and reticuloendothelial cells, it may be protective against intracellular pathogens that require iron (such as *Yersinia pestis*). Iron storage disease has not been found to confer resistance to plague in mouse models (Quenee et al. 2012). There are, however, other pathogens against which HH might confer protection, such as *Salmonella typhi* and *Mycobacterium tuberculosis* (Moalem et al. 2002; Weinberg 2008).

Another genetic mutation that has been suggested as reflecting selective pressures during Second Pandemic outbreaks (see, e.g., Stephens et al. 1998) is CCR5-Δ32, a deletion mutation in a chemokine receptor gene that is found at relatively high frequencies in Europe, Russia, the Middle East, and the Indian subcontinent (but rare or absent elsewhere) and that confers resistance to HIV (Bouwman et al. 2017). However, ancient DNA studies of skeletal samples from Europe have not found substantial changes in frequencies of the allele before, during, or after the Black Death, and thus fail to support a link between the Black Death and modern frequencies of the allele (Bouwman et al. 2017; Hummel et al. 2005; Kremeyer et al. 2005). Further, studies using animal models have indicated it is unlikely that the CCR5-Δ32 allele protects against *Y. pestis* (Mecsas et al. 2004). Laayouni and colleagues (2014) suggest that plague outbreaks during the Second Pandemic drove convergent evolution (with respect to Toll-like receptors) in Rroma and European/Romanian populations. Recently, Park and colleagues (2020) have argued that the Plague of Justinian and the Black Death produced selective pressures favoring genetic variants, now at relatively high frequencies in the Middle East and Mediterranean basin, that cause familial Mediterranean fever.

1918 Influenza Pandemic

The 1918 influenza pandemic is one of the most well-studied examples of pandemic disease. It erroneously became known as the "Spanish" influenza pandemic

even though the virus did not originate in Spain; nor did Spain suffer the highest death rate. The moniker likely arose due to governmental censorship during World War I; officials in the United States and several countries in Europe suppressed information about the outbreaks to maintain wartime morale. Spain, however, remained neutral during the war, allowing the press to report on the growing number of cases in their country, thereby making it appear that Spain was the initial epicenter of the epidemic. Furthermore, the Spanish King Alfonso XIII was among the first rulers to contract the influenza, and public interest in the illness of a monarch focused attention on Spain as the site of the outbreak (Trilla et al. 2008). The geographic point of origin of the 1918 virus remains debated (Barry 2004; Humphries 2014; Langford 2005; Oxford 2001; Oxford et al. 1999); however, much of the historical and epidemiological evidence suggests that the virus emerged in Haskell County, Kansas, US, in January 1918 (Barry 2004, 2005; Jordan 1927; but see Olson et al. 2005; Patterson and Pyle 1991). Epidemiologists have traced the spread of the virus from Haskell County to Camp Funston, a nearby army training facility. From there, the virus spread among military personnel who were moving freely among army bases in the US and Europe and then to the civilian population (Barry 2004).

Until the recent resurgence of interest in pandemics, the 1918 pandemic had largely faded from the global collective memory (Crosby 2003), which is surprising given its high global mortality. An estimated 50 million people died worldwide (Barry 2005; Johnson and Mueller 2002; Murray et al. 2006; but see Spreeuwenberg et al. 2018), and approximately one-third of the global population became infected with the virus and was symptomatic (Crosby 1976; Taubenberger and Morens 2006). The global mortality rate has been estimated to be ~2.5% (Johnson and Mueller 2002; Taubenberger 2005), though the mortality rate in the United States may have been as low as ~1% (Viboud et al. 2013). These estimates are biased toward Europe and North America, though more recent studies have begun investigating the morbidity and mortality rates in previously understudied areas (Chandra 2013; Ranjan 2020; Reyes et al. 2018). The majority of the deaths were not caused by the influenza virus itself, but by secondary bacterial pneumonia (Klugman et al. 2009; McAuley et al. 2007; Shanks and Brundage 2012).

Selective mortality during the 1918 influenza pandemic

Despite the global distribution of the 1918 pandemic, not everyone was equally likely to contract the disease or die from it. Contemporary physicians and epidemiologists immediately noticed that certain segments of the population seemed more vulnerable than others. By analyzing various historical data sources, historical demographers have further assessed how variation in sex, gender, occupation, socioeconomic status, geography, ethnicity, and preexisting health affected morbidity and mortality. While relatively abundant, historical records from the early twentieth century do not capture the disease experiences of all sections of society; they are less likely to contain information from people of lower socioeconomic status, African American and Indigenous communities, and countries with less developed disease reporting systems.

Selective mortality with respect to age

Perhaps the most well-known fact about the 1918 pandemic is the unusually high mortality rate in healthy young adults. Seasonal influenza is typically most deadly to infants, young children, and the elderly (Ahmed et al. 2007), producing a U-shaped mortality distribution (Fig. 1). However, the 1918 ◂F1 pandemic (and indeed other influenza A H1N1 viruses such as the 2009 pandemic virus) caused unprecedented mortality among adults between the ages of ~20 and 40 years (Barry 2005; Crosby 2003; Karageorgopoulos et al. 2011; Simonsen et al. 1998; Taubenberger and Morens 2006). Compared to previous non-pandemic years, the death rates for pneumonia and influenza during the pandemic were more than 20 times greater for those between the ages of 15 and 34 (Taubenberger and Morens 2006). The infamous W-curve age-at-death distribution (see Figure 1) reflects high death rates among infants and older individuals, as typical, but with an additional spike in mortality among young adults (Ahmed et al. 2007; Shanks and Brundage 2012; Taubenberger and Morens 2006). Gagnon et al. (2013) found that the mortality rate for young adults in 1918 peaked at age 28 in the United States and Canada (see also Hallman and Gagnon 2014; Wilson et al. 2014; Yang et al. 2014). Taubenberger and Morens (2006) found that individuals younger than 35 years of age also experienced higher influenza morbidity in 1918 compared to older age groups. Less often discussed is the relatively low excess mortality in people over 65 years of age. Mortality due to influenza and pneumonia among those 74 years and older was actually lower in 1918 than in prior, non-pandemic years (Lukacs et al. 2001), and 99% of the excess deaths due to influenza and pneumonia in 1918 were among those younger than 65 years (Simonsen et al. 1998).

There are many theories regarding the unusually high death rate for young adults. Among the most

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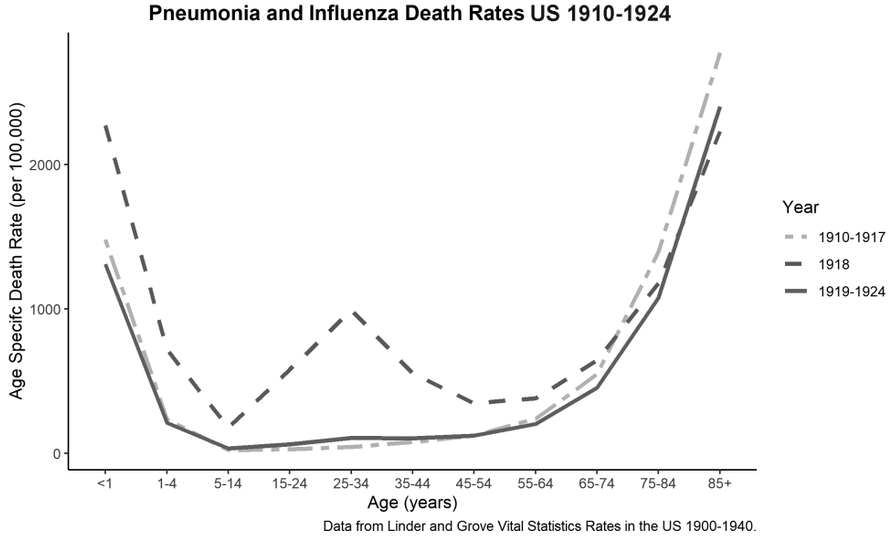

Figure 1. Pneumonia and influenza death rates in the US, 1910–1924 (Linder and Grove 1947).

popular is the "cytokine storm" hypothesis. A cytokine storm occurs when the immune system mounts an overly aggressive attack, releasing many more pro-inflammatory cytokines than is necessary. In the lungs, the excessive inflammatory processes cause alveolar damage and tissue scarring, edema, and fluid accumulation that restricts lung function (Liu and Ying 2020; Liu et al. 2016). The overabundance of pro-inflammatory cytokines can overflow into the circulatory system, causing systemic damage, organ failure (sepsis), and host death (Chousterman et al. 2017; Liu et al. 2016). Scholars hypothesize that the 1918 influenza virus may have triggered a cytokine storm in infected hosts (de Wit et al. 2018; Kash et al. 2006). As young adults have the most robust immune systems, they may have experienced a higher likelihood and proportion of cytokine storms and therefore a higher risk of death (Ma et al. 2011). Studies using animal models infected with reconstructed versions of the 1918 H1N1 influenza virus were done to explore its virulence and unusual behavior (Kash et al. 2006; Kobasa et al. 2004, 2007) and revealed atypical immune responses that included "high and sustained release of pro-inflammatory cytokines" consistent with a cytokine storm (Loo and Gale 2007:268). Animal subjects developed widespread alveolar damage, pulmonary edema and bleeding, and decreased lung function leading to a high probability of death—reminiscent of the symptoms sustained by 1918 influenza victims.

A second possible explanation for the high mortality rate among young adults during the 1918 pandemic is the influence of prior influenza exposure (Gagnon et al. 2015; Hallman and Gagnon 2014; Shanks and Brundage 2012). According to the "original antigenic sin" hypothesis, the immune system imprints on the first strain of a virus it encounters—usually in utero or during infancy. The individual is able to fight off that particular viral strain, but is left with a decreased ability to resist other strains (Davenport et al. 1953; Francis 1955; Kim et al. 2009). Gagnon and colleagues proposed that exposure to the 1889–1890 "Russian Flu" pandemic—which swept around the globe exactly 28 years prior to 1918—caused the immune systems of those born at the time to imprint on that particular viral strain (possibly an H3N8 strain). Having become particularly adapted to fight the 1889 strain, the immune systems of young adults around 28 years of age were unable to respond accordingly to the 1918 virus, increasing the likelihood of an adverse outcome (Gagnon et al. 2013; Hallman and Gagnon 2014). Worobey et al. (2014) argued that a single previous pandemic would not produce the unique age-at-death distribution seen in 1918, which included not only large numbers of young adults, but fewer older adults than expected. In the decades preceding 1918, several influenza viruses had circulated globally, notably an H1N1 in 1830–1847, H1N8 in 1847–1889, H3N8 in 1889–1890, and H1N8 in 1900–1918. The authors hypothesized that previous exposure to similar hemagglutinin (H) and neuraminidase (N) subtypes conferred increased immunity in the 1918 H1N1 pandemic. Individuals born during the 1889–1890 pandemic, exposed only to the H3 and N8 subtypes, were not able to adequately combat the H1 or N1 subtypes. Adults born in the

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1830s—who were in their eighties in 1918—had greater than expected survival due to exposure to both the H1 and N1 subtypes. Meanwhile those born between 1847 and 1889 were exposed to H1, conferring partial immunity and contributing to the lower than expected morality rate among older adults.

Another explanation proposed for the unusual age-at-death distribution in the 1918 pandemic is coinfection with influenza and pulmonary tuberculosis. In the early 1900s, tuberculosis was most prevalent among those between the ages of 15 and 44 (Rothman 1994; Shryock 1977). Infection with influenza can impair both T-cell and innate immune responses against bacterial infections (Walaza et al. 2019). For example, research suggests that influenza A viruses alter the behavior of alveolar macrophages—cells of the innate immune system responsible for clearing the lung tissues of dust, bacteria, and other pathogens (Califano et al. 2018; Ghoneim et al. 2013; McCullers 2014)—therefore reducing their ability to fight tuberculosis bacteria (Braciale et al. 2012; Mendy et al. 2019). As many deaths during the pandemic of 1918 were caused by secondary pneumonia infection, it is possible that coinfection with influenza and tuberculosis may explain the high mortality rate in young adults. Walaza et al. (2019) note that more studies using lab-confirmed cases of influenza and pulmonary tuberculosis are needed to determine causal relationships between the two diseases. Further details about the interaction between influenza and tuberculosis are provided below.

Selectivity with respect to social race, ethnicity, and indigeneity

Indigenous populations throughout the world, including in the continental United States, Hawaii, Canada, Norway, Australia, Fiji, and Tahiti, experienced significantly worse morbidity and mortality in the 1918 influenza (Dahal et al. 2018; Mamelund 2001, 2003; Schmitt and Nordyke 1999; Shanks et al. 2012; Wilson et al. 2012). Some Inuit communities in Alaska and Labrador experienced up to 90% and 78% mortality, respectively (Herring and Sattenspiel 2007; Mamelund 2011). Indigenous people of Western Samoa lost 22% of their population (Tomkins 1992), and the Māori of New Zealand experienced mortality rates over seven times greater than non-Māori (Pool 1973; Wilson and Baker 2008). Structural racism, poor nutrition, poverty, decreased access to healthcare, high housing density, and inadequate hygiene likely all played a role in the high fatality rate among Indigenous peoples (Dahal et al. 2018; Mamelund 2003). Mamelund (2011) found that native communities who lived far from major roads and cities had greater mortality, suggesting that a lack of immunity from previous influenza outbreaks and from the less virulent 1918 spring wave likely contributed to their high mortality.

Some uncertainty exists regarding whether African Americans and white Americans experienced different morbidity and mortality rates during the pandemic. In 1918, the United States was highly segregated; African Americans were more likely to live in crowded areas, have less access to healthcare and sanitation, and lower income—all factors that are expected to contribute to greater morbidity and mortality during an epidemic. There is, however, abundant anecdotal evidence reported in newspapers and oral histories that African Americans experienced lower rates of morbidity and mortality than white Americans (Anon 1918a; Anon 1918b; Anon 1918c; Anon 1918d) such that it was widely held to be true among laypeople and physicians alike (Gamble 2010). Several epidemiological studies found that African American populations had lower incidence, lower morbidity, and lower mortality rates from the influenza (Anon 1919; Britten 1932; Frost 1920). This occurrence is rendered more unusual as both prior to and after the pandemic, African Americans had greater morbidity and mortality from pneumonia and influenza. Indeed, 1918 was the sole year in the twentieth century in which mortality from pneumonia and influenza was lower for African Americans than white Americans (Økland and Mamelund 2019). Økland and Mamelund (2019) investigated this unusual reversal and found that in the fall of 1918, white Americans did have much higher influenza morbidity, yet African Americans had higher case fatality.

Differences in morbidity and mortality between African Americans and white Americans were due to unequal social conditions. African Americans were more likely to experience crowded living conditions and decreased access to sanitation services. They were therefore at increased risk of exposure during the first (milder) wave of the pandemic in the spring of 1918, which conferred some immunity to the deadlier fall wave (Crosby 1976, 2003). It is also highly possible that the lower impact of influenza on African Americans may be an artifact of underreporting; African Americans had less access to medical care and were therefore less likely to have their cases counted and included in official records (Gamble 2010).

Selectivity with respect to tuberculosis

In addition to being a potential explanation for the unusual age-at-death distribution in 1918, pulmonary tuberculosis may also have been a significant risk factor for morbidity and mortality. Numerous studies have investigated the relationship between active tuberculosis infection and influenza mortality, with

mixed results (Espersen 1954; Herring and Sattenspiel 2007; Mamelund and Dimka 2019; Noymer and Garenne 2000; Oei and Nishiura 2012; Tripp et al. 2018; Zürcher et al. 2016). Oei and Nishiura (2012) showed a statistically significant association between patients with tuberculosis and death by influenza, although their sample size was extremely small. Mamelund and Dimka (2019), however, found that coinfection with tuberculosis and influenza had only a small effect on mortality for females aged 20–29 and no effect for males at all. In their landmark paper, Noymer and Garenne (2000) argue that "TB infection was a significant risk factor for contracting influenza" (573). They also find that the proportion of deaths from pulmonary tuberculosis decreased noticeably immediately after 1918: there were 500,000 fewer US deaths by tuberculosis in the years after the pandemic than expected if the normal trajectory of tuberculosis morbidity and mortality had continued (Noymer and Garenne 2000). The authors hypothesize that the 1918 pandemic may have been a "harvesting" event whereby individuals with active tuberculosis were more likely to die than those without tuberculosis, leaving fewer individuals with tuberculosis afterward (Noymer 2010; Noymer and Garenne 2000). Noymer (2009) builds on these interpretations, arguing that the post-1918 decrease in tuberculosis morbidity and mortality was not necessarily due to "active selection" whereby tuberculosis directly predisposed one to dying of influenza. Instead, the decline may have been due to "passive selection," in which people who were more likely to have tuberculosis coincidentally were also more likely to die from influenza. The pandemic removed such a large number of individuals from these overlapping pools that the number of subsequent tuberculosis deaths dropped. The association between tuberculosis infection and influenza mortality may have been "due to the tuberculous population being 'in the wrong age group at the wrong time'" (Noymer 2009:1607). Tripp and Sawchuk (2017) argue that while influenza infection may have played a role in changing the prevalence of deaths from tuberculosis, it was not the primary impetus. In their study area of Malta, they found that tuberculosis mortality began to change in 1917, a year before the pandemic. The authors concluded that a decline in living conditions and food shortages caused by World War I are the most likely causes of changes in tuberculosis deaths.

Selectivity with respect to socioeconomic status

Contemporary anecdotal accounts reported that the influenza scourge was "classless" and struck "rich and poor alike" (Brainerd and Siegler 2003; Sydenstricker 1931). As the virus was a newly emerged pathogen to which no one had adaptive immunity, it is possible that all were equally susceptible. Indeed, many studies both immediately following the pandemic and in recent years found no or only a slight association between socioeconomic status and increased morbidity and mortality during the pandemic (Johnson 2001; Patterson and Pyle 1991; Rice 1988). Others, however, have found notable associations between high influenza morbidity and mortality and indicators of low socioeconomic status. Influenza tended to be worse among those with lower incomes (Murray et al. 2006), smaller domiciles (Mamelund 2006), less schooling (Grantz et al. 2016; Tuckel et al. 2006), and less-skilled jobs (Bengtsson et al. 2018; McCracken and Curson 2003). Mamelund (2018) examined the relationship between socioeconomic status and influenza on a more fine-grained level, testing whether apartment size was associated with influenza morbidity in the different waves of the pandemic. Results demonstrated that overall morbidity was lower among those who lived in smaller apartments. More specifically, however, those in smaller apartments had greater morbidity in the earlier first wave, while morbidity was greater for those in larger apartments in the second, fall wave. The author suggests that these results reflect a greater risk of exposure for those of lower socioeconomic status in the early days of the pandemic while those of higher socioeconomic status were protected from the first wave and were then more likely to become ill in the second wave.

Selectivity with respect to urban and rural areas

Residing in a less populated small town or rural area may have conferred some measure of protection against influenza (Johnson 2001; Ohadike 1991). Those living in rural areas almost certainly had a lower risk of exposure compared to urban dwellers. Nonetheless, some studies have shown that populations in rural areas had higher morbidity and mortality compared to urban areas (Afkhami 2003) or that rural/urban living played no role in influenza illness and fatality (Nishiura and Chowell 2008). McSweeny et al. (2007) found that the mortality rate was generally greater in cities compared to rural counties, but, among non-rural spaces, mortality rates decreased with increasing population size. The authors attribute this to greater access to medical care and community assistance in larger urban areas. Additional study is needed to clarify whether the general tendency for higher mortality in urban areas reflects characteristics of the urban environment (e.g., crowding, sanitation, pollution) or inherent greater susceptibly in urban

dwellers themselves. Paynter et al. (2011) compared mortality records from rural and urban civilians with those of military personnel who were mixing together in military training areas or overseas. They found that among civilian populations, people from urban areas had higher mortality than those from rural areas; in the military, soldiers who were from urban areas had a lower risk of mortality compared to soldiers from rural areas. The authors conclude that people who were from cities may have had some level of protective immunity compared to those from rural areas and that the primary reason rural areas had lower morbidity and mortality was due to low population density.

Other causes of selective mortality

In addition to those described above, scholars have investigated other factors that may have contributed to selective mortality during the 1918 pandemic. Most epidemiological surveys have concluded that males generally suffered worse mortality than females (Ammon 2001; Brennaman 2019; Collins 1931; Rice 2018; Tuckel et al. 2006; Winslow and Rogers 1920; Wilson et al. 2014), though this association is often confounded by age and geography (Erkoreka 2010; Langford 2005; Pinnelli and Mancini 1999; Viboud et al. 2013; Viktoria Kolte et al. 2008). Lower morbidity and mortality among females may have been due to biological differences between males and females. Estrogens stimulate immune system functions (Bouman et al. 2005; Foo et al. 2017; Nalbandian and Kovats 2005). As a result, females generally elicit more vigorous immune reactions to disease and trauma (Choudhry et al. 2007; Giefing-Kröll et al. 2015; Kovacs et al. 2002) and may have been better able to combat influenza infection. Gendered differences in social roles may also have played a part. In 1918, males were more likely to work outside the home and may have had greater risk of exposure. On the other hand, females were more likely to occupy caretaker roles and would have been charged with tending to sick individuals, bringing them in closer contact with the sick (Paskoff and Sattenspiel 2018; Pinnelli and Mancini 1999).

Pregnancy may have increased the risk of poor health outcomes from influenza (Bland 1919; Harris 1919; Woolston and Conley 1918). Paskoff and Sattenspiel (2018) showed that males in Labrador and Newfoundland suffered greater mortality in the first wave of the pandemic whereas females had greater mortality in the second wave. They suggest that greater male morbidity early in the pandemic left fewer susceptible males in the later waves. Dimka and Mamelund (2020) investigated disability as a risk factor for increased morbidity and mortality in 1918 by comparing disabled patients and nondisabled staff at Norwegian institutions. Staff members had higher morbidity than the patients, but patients had significantly greater case fatality demonstrating that individuals with disabilities had an increased susceptibility to the virus.

Post-influenza pandemic health and demography

Despite the enormous body of literature on the 1918 flu, relatively few papers have explored the long-term impacts of the pandemic on health, demography, and economy. The disproportionately high mortality rate among reproductively aged young adults during the 1918 pandemic caused numerous long-term changes to the global population structure. For example, in the 1918 pandemic, so many adults between 15 and 34 years died that the average life expectancy dropped by several years in 1918 (Tumpey et al. 2005).

Influenza infection also represents a substantial risk to pregnant women and their offspring (Gunnes et al. 2020; Mertz et al. 2019; Rasmussen et al. 2008). During the pandemic, there was a substantial increase in maternal mortality, preterm labor, and the risk of miscarriage and stillbirth (Bland 1919; Harris 1919; Woolston and Conley 1918). The loss of so many births upset the expected population structure for years. Dahal et al. (2018) reported a 43% drop in births about 9–11 months after the peak of the pandemic in the state of Arizona. The Māori of New Zealand experienced a lower child:woman ratio in the 1921 census not only due to the loss of so many infants but also disrupted marriages due to the loss of a spouse (Pool 1973). In the US and several Scandinavian countries, Bloom-Feshbach et al. (2011) noted a decrease in the annual birthrate of 5%–15% 6 months after the height of the pandemic.

Infants who survived the 1918 pandemic may have faced significant long-term disadvantages that would have had enduring effects on society. A number of studies have examined the possible effects of influenza infection on those who were in utero during the pandemic. Numerous studies have found that offspring of women who were pregnant during the pandemic had an increased likelihood of poor health outcomes in adulthood, including heart disease and diabetes (Almond and Mazumder 2005; Mazumder et al. 2010), shorter stature (Lin and Liu 2014; Mazumder et al. 2010), functional limitations (Almond and Mazumder 2005), and early mortality (Fletcher 2018; Helgertz and Bengtsson 2019; Myrskylä et al. 2013). Furthermore, those who were in utero during the pandemic may have been more likely to have less education and lower wages later in life (Almond

2006; Beach et al. 2018; Lin and Liu 2014; Neelsen and Stratmann 2012; Nelson 2010). Other studies, however, found only weak or no associations between being in utero in 1918 and later life deficits, arguing that other life circumstances are responsible for any differences in later life attainment (Brown and Thomas 2018; Cohen et al. 2010; Palloni et al. 2020; Vollmer and Wójcik 2017).

Pandemic disease can affect the epidemiology, prevalence, and circulation of existing pathogens. This can be caused by selectively removing certain segments of the population, by altering the risk of morbidity and/or mortality from coinfection, by predisposing survivors to later disease, or by disrupting normal access to healthcare and vaccinations. As detailed above, research suggests that the 1918 flu may have also permanently altered the trajectory of tuberculosis in the United States. Further, Azambuja and Duncan (2002) hypothesized that the rise of cardiovascular disease in the early twentieth century may be directly related to the 1918 pandemic and subsequent influenza outbreaks. Arguing that the increase in heart disease cannot be fully explained by changes in traditional risk factors, they contend that exposure to an earlier pathogen triggered an inflammatory immune response that caused survivors to be more susceptible to coronary heart disease. They found a correlation between birth cohorts who suffered high morbidity and mortality in 1918 and later mortality from coronary heart disease. Tate et al. (2016), however, refuted their conclusions, finding that changes in heart disease mortality varied more by age-cohort rather than from exposure to the 1918 virus.

Perhaps the greatest way that the 1918 influenza changed the global disease landscape is by acting as a founder virus. The 1918 H1N1 virus emerged with an entirely novel set of eight influenza genes to which no one was completely immune (Morens et al. 2009). Over the past 100 years, these eight genes have remained in the influenza gene pool and continue to circulate in both seasonal and pandemic influenza viruses. The 1957, 1968, and 2009 pandemic influenza viruses are all descendants of the 1918 H1N1 virus (Taubenberger et al. 2012). Globally, the 1957 pandemic caused an estimated 1.1 million deaths (Viboud et al. 2016), the 1968 pandemic an estimated 1 million deaths (Honigsbaum 2020), and the 2009 pandemic over 200,000 excess deaths (Dawood et al. 2012; Simonsen et al. 2013). Furthermore, these pathogens continue to impact health and mortality long after the pandemic has passed. For example, survivors of the recent 2009 H1N1 epidemic exhibited prolonged sequelae including decreased respiratory function years after infection (Luyt et al. 2012; Toufen et al. 2011; Zarogoulidis et al. 2011).

Bioarchaeology and the 1918 flu

Nearly all the studies of the 1918 flu rely on data from historical documentation such as census and death records, insurance claims, or military archives. While these records contain a wealth of valuable information, they usually do not include individual-level data on health and disease over the life course. Researchers have therefore been limited in their ability to explore factors influencing morbidity and mortality on a population scale from a biological perspective. By aggregating individual health and demographic data, bioarchaeological research on the 1918 flu has the potential to expand our knowledge not only of the pandemic, but of broader concepts in demography and paleopathology.

Despite this, the 1918 influenza pandemic remains remarkably un(der)studied within bioarchaeology. A few studies have assessed how specific biological proxies for ill-health—such as short stature (Lin and Liu 2014; Mazumder et al. 2010) or preexisting disease (Noymer 2009; Oei and Nishiura 2012; Zürcher et al. 2016)—impacted mortality and survival of the 1918 pandemic. However, they relied on data from historical records, not directly from human remains. The viral RNA used to sequence and re-create the 1918 virus was obtained from the lung tissue of exhumed victims of the 1918 pandemic (Basler et al. 2001; Reid et al. 1999; Reid et al. 2004; Taubenberger et al. 1997), which also could be considered under the purview of bioarchaeology. To date, the only research on the 1918 pandemic designed within a bioarchaeological framework is that of Wissler (Wissler 2019, 2021). Using the Hamann-Todd documented collection at the Cleveland Museum of Natural History (which includes individuals who were born between 1825 and 1910 and died between 1912 and 1938), she assesses how preexisting frailty may have increased the risk of mortality from influenza and how the pandemic impacted survivorship in the years following the pandemic.

There are likely numerous reasons for the dearth of bioarchaeological studies on the 1918 flu. Bioarchaeological research is predominantly done in contexts that are many hundreds, if not thousands, of years old. Comparatively, the 1918 pandemic is a recent event and historical bioarchaeology is relatively scarce. Influenza does not leave direct evidence on the skeleton, so scholars studying the historical, social, and biological determinants of morbidity and mortality risk from the 1918 virus would likely not

consider using skeletal remains. Paleoepidemiology—the branch of paleopathology that aims to understand the distribution and determinants of disease in past populations—is a relatively young and still evolving field. The guiding methods, research practices, and historical and archaeological contexts in which we can learn about past health are still being discovered.

Another reason for the lack of bioarchaeological research on the 1918 flu may be the paucity of available skeletal material. The overwhelming majority of the remains of individuals who died of the flu are inaccessible; most people were buried in existing "attritional" cemeteries using burial practices that did not differ from those used under normal circumstances. A few mass burials attributed to the pandemic have been uncovered, but these individuals have all since been reburied (Lewis 2015). On the other hand, many of the documented osteological collections from around the world (e.g., Hamann-Todd, Luis Lopes, and Coimbra) were formed in the early 1900s and thus represent an untapped source of knowledge on the pandemic. The combination of large samples of individual-level biological data from the skeleton, documentation on age, cause, and date of death, and broader historical records presents an excellent opportunity to examine the social, cultural, and biological dynamics of the 1918 flu. This is not to say, however, that historic documented collections are perfect. There are, for example, issues regarding sample representativeness and inaccuracies in documentation (Hunt and Albanese 2005; Lovejoy et al. 1985). Furthermore, most were created using unjust and often racist collection procedures that must be confronted (de la Cova 2010; Muller et al. 2017).

There are less well-known skeletal assemblages throughout the world that include individuals who died in the early 1900s, such as the osteological reference collection at the University of Antioquia, Medellín, in Colombia (Monsalve and Isaza 2014), the Milwaukee County Poor Farm Cemetery (Richards et al. 2016), the Santa Clara Valley Medical Center in California (Hall 2017), and the Frassetto osteological collection of Sassari at the Museum of Anthropology, University of Bologna (Cameriere et al. 2007). However, the number of individuals in each of these collections who died in 1918 is generally small, and most have no information on the age of the individual or cause of death. Depending on one's research question, these factors may be limitations to using these collections to study the 1918 flu.

Multiple new contexts for investigating the 1918 flu would be ideal, but they are not necessary to enhance our understanding of that influenza in particular or pandemics in general. Bioarchaeological studies of the Black Death have greatly expanded our knowledge of the event, yet the majority have relied on a handful of European skeletal assemblages. It is more important for scholars to design creative research programs that draw on multiple disciplines, including skeletal biology, demography, historical archaeology, epidemiology, and disease ecology. Additional research on the 1918 flu through the lens of bioarchaeology could help clarify the virus's unusual age-at-death distribution, how the risk of illness and death varied according to other biological and social factors, and the impact the pandemic had on the population structure over both the short and long term.

Further research on the 1918 pandemic through the lens of bioarchaeology can also contribute to greater engagement of the general public with the science of bioarchaeology and anthropology. The 1918 flu is a subject of enormous popular interest; many people have a personal connection to the pandemic—having grandparents, great-aunts or -uncles, or cousins who were its victims; for example, the first author's (SND) great-aunt was a victim of the epidemic, and her death had long-term effects on health behavior and perceptions within her family. The current COVID-19 situation has also demonstrated to everyone the powerful ways in which pandemics shape human behavior, culture, and biology and reveals the importance of learning from the past. Additional anthropological study of the 1918 pandemic as well as nineteenth- and twentieth-century epidemics can show that anthropology remains relevant and is poised to make vital contributions to public health, policy, and education.

Conclusion

What emerges from this review of the literature on the Second Pandemic of Plague and the 1918 influenza pandemic is a general picture of variation in risks of exposure to and mortality from past pandemics and the importance of preexisting biological, environmental, and social conditions in shaping outcomes during and after pandemics. For both historical pandemics, there does not yet appear to be evidence of universal patterns with respect to several axes of potential difference. For example, it is not clear whether sex differences in mortality were a consistent characteristic of plague outbreaks during the Second Pandemic. Similarly, there is variation among findings regarding selectivity of the 1918 flu with respect to socioeconomic status and the effect of urban vs. rural habitation on morbidity and mortality.

Nonetheless, even though there are inconsistencies in findings regarding variation (or lack thereof) in risk of death during the Second Pandemic and the 1918 flu, the idea that either killed indiscriminately is not generally well supported. Certainly, further work using previously unexplored lines of evidence and in contexts that have not yet been studied is warranted. For example, emerging work on newly excavated plague burials or integrating isotopic, DNA, and proteomic data into bioarchaeological studies may clarify whether the discrepancies in previous findings regarding sex, age, and socioeconomic differences in plague mortality and the effect of frailty on risks of death are an artifact of methodological approaches or genuinely reflect geographic or temporal variation in historical plague mortality patterns. These lines of evidence will also potentially allow bioarchaeologists to assess the effects of migrant status or racial discrimination on risks of death during the Second Pandemic. Further, as described above, bioarchaeology is poised to make major contributions to our understanding of variation in risks during the 1918 flu.

As important as further study on past pandemics is for clarifying their effects at the individual and population level, it is also crucial for the general public, scholars, and policy makers today to gain and sustain awareness of what we *already* know about our previous experiences of diseases, attend to those factors that affected morbidity and mortality in the past and that persist today, and devote resources toward maintaining and building pandemic responses in the future. For example, previous research has revealed the possible effects of poverty on risks of death during the Second Pandemic and the 1918 flu, and we are witnessing the ways in which poverty, structural racism, and social marginalization are increasing susceptibility to and risks of death from COVID-19 (Laster Pirtle 2020; Patel et al. 2020; Rodriguez-Lonebear et al. 2020). These effects are both predictable and theoretically preventable. The positive impact of non-pharmaceutical interventions such as mask wearing, social distancing, and banning large gatherings is evident from studying the course of the 1918 pandemic. Philadelphia's failure to cancel a citywide parade in September 1918 is widely believed to have been responsible for their extremely high death toll. Other US cities, such as St. Louis, that imposed more aggressive and sustained public health measures, including school closures and banning public gatherings, had far fewer excess deaths (Hatchett et al. 2007; Markel et al. 2007).

As a society and as individuals we must improve our pandemic preparedness. It is imperative to work toward bettering the health and well-being of people in order to reduce the burden of disease and death during disease epidemics and the long-term sequelae they can produce. It is our hope that bioarchaeological research on the Second Pandemic of Plague and the 1918 flu—past pandemics that garner a tremendous amount of interest from the general public—will inform efforts to prepare for and respond to diseases that threaten people now and in the future. Expanding our knowledge of how interactions between culture and biology impact variation in morbidity and mortality allows anthropologists to contribute to issues of health inequality and demonstrate the value of anthropological perspectives.

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