

# THE BLACK DEATH AND THE FUTURE OF THE PLAGUE

MICHELLE ZIEGLER

THE GRAVITAS OF *Yersinia pestis*, unique among pathogens, is based more on its history than on modern case numbers. When new outbreaks of plague are reported in the media, journalists are quick to link these incidents with the horrors of the medieval Black Death—and then to claim that there is no real threat to society, because we now have modern antibiotics. Walking a thin line between stirring up interest and not causing panic, reporters are only half right on both counts. On the one hand, modern plague cases *are* caused by the same lethal bacterium, *Yersinia pestis*; and yet the phenomenon of the Black Death was far greater than any of the isolated cases or small outbreaks that usually attract such attention today. On the other, antibiotics are not a panacea that can wholly protect us from the next pandemic. Plague is re-emerging in a world of growing antibiotic resistance, economic interdependence, and rapid transit. *Yersinia pestis* is found in enzootic foci on every inhabited continent except Australia, and it was found in the arsenals of some states in the twentieth century. Political instability and weak economies can prevent the growth of adequate public health infrastructures that would enable rapid response to large infectious disease outbreaks, natural or not. Air travel makes pneumonic plague quickly transferable from one site to another. If public health officials and environmental services do their due diligence, an isolated case in the United States (or in most other countries) should not be cause for panic. However, the outbreak of over a hundred pneumonic plague cases, something that occurred in Congo in 2004 and 2005, was almost ignored by the media even though this was a serious risk to regional health. Sensationalizing the plague does not help us to deal with these realities, but neither does the lack of attention given to plague in areas of the world that are often beneath our notice.

This essay addresses three basic questions. First, what does it mean for plague to be classified as a re-emerging infectious disease? Second, what

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is the human incidence of plague around the world today? And finally, how do we unite study of the plague in the past and present to create a better understanding of plague dynamics, to better prepare for the future?

## A Re-emerging Infectious Disease

Frank Snowden (2008) has argued that the public health successes of the twentieth century led to an era of over-confidence in medical science: many supposed that the conquest and even eradication of pathogens was just a matter of time. Before the AIDs pandemic, it was unthinkable that this progress was illusory or temporary. But the growing awareness of the threat posed by the human immunodeficiency virus (HIV) in the 1980s was the first widely recognized indication that progress was neither inevitable nor irreversible. Then, between 1991 and 1995, the return of two old bacterial foes and the emergence of a terrifying new virus delivered a one-two punch to public confidence. Cholera had been undetected in the western hemisphere for a century when large new epidemics broke out in Central and South America, eventually claiming four thousand lives and raising fears of infrastructure failures. In 1994, a pneumonic plague outbreak in Surat, India, was followed by the discovery, the following year, of antibiotic-resistant strains of plague isolated in Madagascar. In 1995, spread of the Ebola virus in Zaire (now the Democratic Republic of Congo) also gained the attention of the global health community because of its gruesomely high fatality rate in a country without an adequate surveillance network. Within ten years, from the mid-1980s to mid-1990s, modern society's sense of security was shattered; hence, the new focus on "emerging and re-emerging" infectious diseases.

The 1994 plague epidemic in Surat has since become a textbook example of what can happen when a naturally occurring epidemic is not brought under control. Like many other countries, India had discontinued plague surveillance in the 1980s, believing that it was no longer necessary after the end of the Third Pandemic (Garrett 2000: 5; Barrett 2008; Sivaramakrishnan 2011).<sup>1</sup> As medical anthropologist Ron Barrett (2008) has argued, this outbreak appears to have resulted from a natural spillover, but it was greatly exacerbated by temporary and permanent human settlement patterns, insufficient healthcare and urban infrastructure, and other governmental failures. The outbreak was triggered by an earthquake that reactivated a bubonic plague focus in the rural village of Mamla, in the Breed

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<sup>1</sup> The Third Pandemic has never been officially declared "over," but there is a general consensus that it ended in the 1950s.

district. Social interactions (probably the movement of migrant workers) then transferred the plague to Surat, a city of over 1.5 million people, where it quickly became a pneumonic epidemic. Plague did not move through the city homogeneously: 78% of confirmed cases were first-generation immigrants to the city, living in slum communities (Barrett, 2008).

But India's public health system was not up to the challenge, and officials even struggled to identify the individuals who were infected (Dutt, Akhtar, and McVeigh 2006). Physicians fled clinics in the most affected districts and antibiotic shortages were common (Barrett 2008). Meanwhile, the media—rehashing lore of “the Black Death” and invoking the loss of some ten to twelve million Indians during the plague pandemic of the early twentieth century—helped to spur a mass exodus from the city. Those traveling by train carried the plague to Delhi and Calcutta, 80 and 160 kilometers away from Surat, respectively; eventually, over half a million people fled to all parts of India, potentially bringing plague with them (Dutt, Akhtar, and McVeigh 2006). And yet the extent of the epidemic still cannot be reliably determined: all told, there were 5,150 suspected cases of pneumonic and bubonic plague but only 53 confirmed deaths, which suggests that over-diagnosis inflated the number of cases. During an epidemic, it is not uncommon for only a few cases to be confirmed by laboratory analysis, especially in developing countries, and the absence of adequate laboratory support means that every febrile case is assumed to be pneumonic plague and is treated as such with antibiotics (Barrett 2008: 53). In Surat, pneumonic plague was confirmed in eighteen patients whose cultures tested positive for *Yersinia pestis*, and this finding was confirmed by the World Health Organization in 1994 and then by genetic analysis in 2000 (Dutt, Akhtar, and McVeigh 2006).

That same subsequent analysis in 2000 also confirmed that the Surat outbreak was caused by a strain of *Yersinia pestis* descended from a Third Pandemic strain (1.ORI) now endemic in Indian foci (Kingston et al. 2009). In 1994, however, the U.S. Centers for Disease Control and Prevention (CDC) had reported that the Surat plague was caused by a previously unknown strain of the pathogen—and to Indian officials this unfortunately lent backing to rumors of bioterrorism that had begun to circulate early on. Surat's Muslims were accused of poisoning the city's water system and causing many more deaths than actually occurred (Barrett 2008). Indian officials even blamed a local Islamic group for the epidemic and transferred plague response to the Department of Defense (Price-Smith 2002: 242). Only two years before, Surat had been the scene of Hindu-Muslim clashes that had fueled distrust in the local government, on both sides; the rumor that officials were planning to quarantine the city was

therefore another factor that led Surat's citizens to flee. A lack of competent public health measures and pre-existing social tensions, heightened by fear and rumor, therefore exacerbated an outbreak of plague that could have been controlled.

Andrew Price-Smith (2002: 235) has argued that the psychological impact of the Surat plague was so great that it degraded the state capacity of India and impeded or weakened relations with countries around the world.<sup>2</sup> India paid a high price for the panic. Its neighbors (China, Nepal, Bangladesh, and Pakistan) completely closed their borders. Travel restrictions on people, imports, and in some cases mail were also imposed by other countries around the world. India lost an estimated 420 million dollars in trade from the United Arab Emirates alone (Barrett 2008). In the midst of the plague, the Indian stock market plunged, and costs of blocked exports and lost tourism revenues have been estimated at \$1.8 billion, a significant blow for a developing country (Price-Smith 2002: 242). Like the plague, an economic collapse in one country becomes rapidly contagious, triggering economic instability and consequently political instability around the world (Price-Smith 2002; Koblentz 2010).

Only one year after the outbreak in Surat, the first antibiotic-resistant strains of *Yersinia pestis* were discovered in Madagascar (Welsh et al. 2007). From 1995 to 1998, more antibiotic-resistant strains were isolated in that same offshore African island, including one that is resistant to all of the known antibiotics used for plague treatment and prophylaxis (Gali-mand, Carniel, and Courvalin 2006). Like other bacteria, plague gains its resistance from a process called "lateral gene transfer," acquiring genes from other species of bacteria that carry antibiotic resistance plasmids (small circular DNA shuttles). *Yersinia pestis* readily accepts such plasmids from other enteric bacteria like *Escherichia coli* and *Salmonella enterica*. For example, the multi-drug resistant (MDR) plasmid found in *Yersinia pestis* is "nearly identical" to those found in *Salmonella* (Welsh et al. 2007). Although similar antibiotic resistance has not been found in human cases outside of Madagascar, plague isolates must now be vigilantly screened for naturally occurring antibiotic resistance (Urich et al. 2012; Stenseth et al. 2008). At the media briefing for the CDC's first threat-assessment on antibiotic resistance, in 2013, its director Dr. Tom Frieden warned:

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**2** According to Price-Smith (2002: 339), "State capacity is the capability of the government, and its level determines the state's ability to satisfy the most important needs: survival, protection of its citizens from physical harm as a result of internal or external predation, economic prosperity and stability, power projection, and ideological projection."

"If we are not careful, we will soon be in a post-antibiotic era. . . And for some patients and for some microbes, we are already there" (quoted by McKenna 2013). Although Freiden was not speaking specifically of plague, antibiotics' capacity to play a role in plague containment can no longer be assumed (Oyston and Williamson 2013; Stenseth et al. 2008).

## Maintaining State Capacity and the Threat of Plague

Challenges to state capacity (the ability of the state to maintain basic functions) have existed since the beginning of settled civilization. The social and economic costs of these recent plague outbreaks are simply modern manifestations of trends that began with the sixth-century "Plague of Justinian," or First Pandemic. For the premodern world, as for our own, plague was not just a health crisis. All plagues are a threat to civil society; they jeopardize not just individuals but the fabric of communities and the institutions that maintain order. Plagues also decimate workforces, causing transformations in land use and the environment (see, e.g., Borsch 2014, in this issue). In the past, they spread through maritime economic networks: those of the Roman Empire in the sixth century, the mercantile empires of Italian city-states in the fourteenth century (Wheelis 2002; Horrox 1994: 14–26), and the British Empire at the turn of the twentieth (Echenberg 2007). Long-distance transmission of the next pandemic, if there is one, will likely be via airline networks, as was the case for the Severe Acute Respiratory Syndrome (SARS) pandemic in 2003 and which appears to be the case for the unfolding threat of MERS (Middle East Respiratory Syndrome). SARS has also directed our attention to the role played by "super spreaders": individuals who transmit disease to far greater degree than the average infected person (Stein 2011).<sup>3</sup> As Myron Echenberg has observed, "comparisons between the beginnings of the third [plague] pandemic in 1894 and the arrival of severe acute respiratory syndrome, or SARS, in 2003 are remarkable and suggest that we can do better at applying the experience of the past" (Echenberg 2007: 308).

Since the late 1990s, pandemics of all kinds have been considered matters of national and international security on the same level as military and terrorist threats, climate change, and refugee flows (Koblentz 2010). On January 10, 2000, the United Nations (UN) Security Council designated

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**3** When super-spreading is tied to a particular place, it is designated as a disease hotspot. For example, for plague, sites of grain storage are likely hotspots where infected rats and fleas are found in higher than average numbers, resulting in an increased number of human cases linked to that location. See further discussion below.

the HIV pandemic as a global security issue, moving it beyond the purview of the World Health Organization (WHO) (Price-Smith 2002). This set a precedent for allowing the UN to intervene in the governance of a sovereign state if it does not mount an adequate public health response to disease. Within this international security framework, plague is regarded as both a pandemic threat and a terrorist threat, given its potential to be used as a biological weapon. Indeed, *Yersinia pestis* is one of only three bacteria to have been labeled a “category A” biological weapons agent (the others being anthrax and tularemia). This top-level security designation is also shared by botulinum toxin, along with several hemorrhagic viruses and smallpox. Traits that define a “category A” agent include ease of distribution or transmission, high mortality rate, likelihood of causing social disruption and panic, and the necessity for special public health preparedness (CDC n.d.).

Major American initiatives are currently helping to build up global disease detection and response networks. For example, the United States has upgraded or rebuilt former Soviet anti-plague stations in the now-independent states of Kazakhstan and Uzbekistan, equipping them for improved surveillance and biosecurity (Koblentz 2012: 138; Pasternak 2013). The U.S. government also budgeted \$5.54 billion for biodefense and disaster preparedness in 2012–13, of which \$574.2 million was specifically dedicated to biodefense (Franco and Sell 2012). Some of this funding has already been used to answer historical questions relating to plague: ancient DNA (aDNA) confirmation of *Yersinia pestis* in specimens from a sixth-century Bavarian cemetery and the reconstruction of the ancient genome were supported in part by the Department of Homeland Security (Harbeck et al. 2013; Wagner et al. 2014). The latest advance in aDNA work, the Microbial Detection Array, which can screen aDNA for multiple pathogens, was developed in conjunction with the Lawrence Livermore National Laboratory (Devault et al. 2014). Of the full-scale federal response drills conducted to date, two of the exercises simulated plague attacks in multi-agent scenario exercises (TOPOFF 1 in May 2000 and TOPOFF 3 in April 2005; Inglesby, Grossman, and O’Toole 2001). These exercises involved thousands of participants, from local “first responders” to cabinet-level officials and governors.<sup>4</sup>

Yet pneumonic plague remains a bioterrorism concern for several reasons. With plague being endemic and enzootic in foci scattered around the world, natural sources cannot be fully identified or effectively controlled.

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4 For an accessible review of biosecurity drills, see Armstrong (2012).

Furthermore, many enzootic foci in Central Asia, the Middle East, and Africa are located in poor, politically unstable areas where basic national security and public health institutions are already vulnerable or underdeveloped, as well as in several states that have known programs or have used biological or chemical weapons in the past, such as Syria, Iran, and North Korea. Moreover, *Y. pestis* can be processed into a crude weapon without sophisticated technology or expensive equipment. In 2008, forty al-Qaeda operatives in Algeria were discovered to have died of plague, perhaps as the result of a failed experiment in biological weapons development (Lake 2009; “40 al-Qaeda Terrorists” 2009).

But as we have already noted in the case of Surat, plague does not have to be deployed as a weapon to be a threat. War and infectious disease have a reciprocal effect. War weakens a society’s ability to respond adequately to infectious disease by disrupting the social order, destroying civic infrastructure, and causing mass movements of people. Conversely, epidemics destabilize society and reduce state capacity, creating the conditions for political and social unrest. A recent instance of the former was the self-limiting outbreak of plague that occurred during the Libyan revolution in 2011, which could not be clinically confirmed or effectively treated because of ongoing hostilities (Cabanel et al. 2013). Plague outbreaks in the Democratic Republic of Congo—over ten thousand cases between 2000 and 2009—were also clearly exacerbated by ongoing political instability (Butler 2013). The violence and social disruption caused by the Vietnam War fostered a plague outbreak from 1966 to 1974, resulting in the loss of thousands of lives and the creation of endemic foci that persist to this day (Price-Smith 2009: 172–73). Outbreaks of plague and smallpox during the Korean War led to accusations that the United States had used biological weapons against North Korean and China. These accusations were later shown to be intentionally false; but here, again, environmental and institutional devastation contributed to the severity and persistence of disease (Hamblin 2013).

## Plague Incidence and Causes Today

Plague is considered a re-emerging infectious disease because the number of cases, overall, has been climbing since the 1980s (see, e.g., Neerinx, Bertherat, and Leirs 2010). Old plague foci are producing new cases after long intervals of quiescence. Moreover, endemic poverty and political unrest in developing countries with plague foci, the appearance of antibiotic-resistant strains of plague, and the potential use of plague as a biological weapon are major concerns.

The incidence, causes, and mortality rate of plague vary widely. Between 2000 and 2009, there were 21,725 cases reported to the WHO, with a case fatality rate of 7.4%. Of all these cases, 97% came from Africa (Butler 2013). Bubonic plague makes up the vast majority of these reported cases, but it can also manifest as primary septicemic plague, primary pneumonic plague, gastrointestinal plague, and plague pharyngitis. The most common of these presentations are perhaps better classified by their primary mode of exposure: insect bite or the entry of infectious bodily fluids through cuts and abrasions (bubonic and septicemic), inhalation (pneumonic), and ingestion (gastrointestinal and pharyngeal), respectively. While the “classic” rat-flea-human pathway is currently dominant, there is well-documented and long-standing evidence that other pathways of human exposure were common in past outbreaks and could become common again under certain conditions (Stenseth et al. 2008; Green 2014, in this issue; Carmichael 2014, in this issue). The human flea, *Pulex irritans*, has been implicated in Tanzanian plague outbreaks between 1986 and 2004 (Laudisoit et al. 2007) and may have been the agent of plague epidemics in medieval northern Europe, as well (Hufthammer and Walløe 2013). The human body louse has also been shown to be capable of transmitting *Yersinia pestis* and is another hypothetical medieval vector (Houhamdi et al. 2006; Drancourt, Houhamdi, and Raoult 2006). Here, it may be significant that combined epidemics of plague and louse-transmitted typhus were reported by contemporary physicians in Seville, in 1582 (Bowers 2013: 50). It may also be significant that aDNA testing of individuals buried in a Venetian mass grave and in graves from Bondy, France, have identified medieval cases of co-infection with *Y. pestis* and louse-transmitted *Bartonella quintana* (trench fever) (Tran et al. 2011a and 2011b).

Like cases of plague transmitted by human ectoparasites (fleas and lice), gastrointestinal plague and pharyngeal plague are relatively rare today. In the past, they may have been more common in areas where camels were the primary beast of burden (Christie, Chen, and Elberg 1980), and even a source of food. An outbreak of pharyngeal plague in 1997 was the first plague occurrence in Jordan since before the foundation of the modern state in 1921 (Arbaji et al. 2005). Three years earlier, a similar outbreak of pharyngeal plague occurred in Saudi Arabia, both caused by the consumption of infected camel meat (Bin Saeed, Al-Hamdan, and Fontaine 2005). An outbreak of gastrointestinal plague in 2007 is the first recorded outbreak in Afghanistan in the modern era and also the largest known outbreak to date. In December of that year, eighty-three individuals developed probable cases, some manifesting pharyngeal lesions, caused by consuming a visibly ill camel. The total case fatality rate was

20.5%, and the attack rate among those who ate the cooked camel meat was approximately 80% (Leslie et al. 2010). Gastrointestinal plague from consumption of camel meat has also been reported in Libya, and from the consumption of guinea pigs in Ecuador and Peru (Leslie et al. 2010; Stenseth et al. 2008). Consumption of diseased meat was not uncommon during the Middle Ages (Newfield 2012), and this should be considered as a possible route of infection for historic plagues, too, especially during food shortages. Moreover, gastrointestinal plague is not necessarily rare among other animals. Carnivores can contract the plague from the blood of their prey as well as from the prey's fleas. Pharyngeal plague is also not uncommon in cats, which can in turn then transmit plague pneumatically to humans (Gage et al. 2000).

Meanwhile, a recent upsurge in cases of bubonic plague heralds the re-emergence of very old plague foci around the Mediterranean and in Central Asia: in Algeria (2003 and 2008), Libya (2009 and 2011), and Kyrgyzstan (2013). The 2009 Libyan outbreak has been shown to be completely distinct from those of Algeria, and also different from those of the entire Third Pandemic (1.ORI strains). Instead, the plague in Libya was caused by the reactivation of an ancient plague focus (Cabanel et al. 2013). Such foci, having gone unmonitored for decades, are now showing signs of life in other places as well: plague has recently been confirmed in a western Iranian focus that had not been surveyed in thirty years (Esamaeili et al. 2013). Currently, the most active plague focus in the world is in the Ituri region of the Democratic Republic of Congo, which produces approximately one thousand bubonic cases per year (Butler 2013; Neerinckx et al. 2010). Large outbreaks often display multiple presentations of disease. For example, a 127-case Ugandan outbreak in 2006 produced 88% bubonic and 12% pneumonic cases (CDC 2009).

Clearly, though, diagnosis and case reporting are still a major problem in resource-poor countries, which have widely divergent diagnostic abilities and levels of treatment. This can lead to over-diagnosis that lowers the reported case fatality rate (Neerinckx et al. 2010). Late diagnosis and delayed treatment can also cause extreme differences in case fatality rates between the beginning and end of a single epidemic. So if the reported case fatality rate is cumulative, it will not distinguish between fatalities that occurred before and after antibiotic treatment began.

The incidence and case fatality rates reported to the WHO meeting in Antananarivo, Madagascar, in April of 2006 illustrate this problem (WHO 2008). At that meeting, the host country reported that plague cases between 2000 and 2005 were 94% bubonic with a fatality rate of 19%. The Democratic Republic of Congo reported a prevalent plague but

could not offer reliable statistics for the years 2000 to 2005, because no records were kept between 2002 and 2003. Tanzania reported that about 90% of its cases were bubonic with an approximately 10% fatality rate. It also reported that deaths in family units were the result of secondary pneumonic plague caused by delayed treatment,<sup>5</sup> and that the human flea, *Pulex irritans*, was suspected as the vector in the absence of cat and dog fleas. Mongolia reported that 90% of its 160 cases between 1971 and 2000 were bubonic, with an astounding 40% developing secondary pneumonic plague due to lack of treatment. However, its officials also reported that only 4.2% of cases were primary pneumonic and reported a fatality rate of “up to 70%” due to lack of treatment and healthcare infrastructure. Neighboring China reported 630 cases between 1994 and 2004 with a case fatality rate of only 6.67%. China also reported that *Y. pestis* from southern foci (transmitted by the rat flea *X. cheopis*) caused bubonic plague with a very low fatality rate due largely to the relatively rapid provision of antibiotic treatment; yet *Y. pestis* from its northern foci was primarily transmitted to hunters who skinned animals, causing pneumonic and primary septicemic plague with a fatality rate over 50% due to the “remoteness” of the territory and delays in seeking and obtaining treatment. Little information on the Americas was offered at the meeting, but Peru did report an epidemic of 1,248 cases between 1992 and 1994. Peruvian representatives identified risk factors as “grain storage in the open air, which favors an abundance of rodents and fleas; promiscuity in housing; absence of rodent-proof devices, beds on the floor and infested with fleas; and the custom of raising guinea-pigs for their flesh” (WHO 2008: 20).

Plague reporting on routes of infection (or presentations) is similarly problematic. All individuals with fatal cases of plague develop a secondary septicemia before death. To put it simply, primary septicemic plague skips the initial inoculation phase that creates a bubo or manifests as pneumonia, and instead develops the systemic (body-wide) blood-borne infection immediately. The total rate of primary septicemic plague is therefore unknown, because it is usually only diagnosed by blood culture in the United States, where it represents approximately 30% of all cases (mostly contracted by handling or skinning animals) (Butler 2013). This suggests that primary septicemic plague is significantly under-diagnosed globally. It can be acquired while skinning or butchering animals via small cuts in the skin, giving *Y. pestis* direct access to the bloodstream. People handling

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**5** Secondary pneumonic plague is the development of plague pneumonia in a case of primary bubonic plague. Primary pneumonic plague outbreaks are begun by a case of secondary pneumonic plague in a human or animal index case.

plague victims or corpses could also be vulnerable to septicemic plague by extant wounds coming into contact with infected body fluids. In short, variations in modern standards of diagnosis and reporting mean that the data reported to WHO is suspect, serving as a further reminder that we need to be cautious when we use medieval data, too.

Although the vast majority of contemporary global cases appear to be bubonic, there have been a couple of recognizable pneumonic plague outbreaks in every recent decade. During this past winter of 2013–14, a pneumonic plague outbreak in Madagascar was widely reported in the news, but as of this writing it has not been formally reported to the scientific community. There was a pneumonic outbreak in Ecuador in 1998, and two nosocomial (hospital-acquired) pneumonic cases in Peru in 2010 (Schneider et al. 2014). Between 2000 and 2009, there were five natural pneumonic outbreaks affecting a dozen or more people: India (2002), Congo (2005 and 2006), Uganda (2006), and China (2009) (Joshi et al. 2009; Butler 2013; Bertherat et al. 2011; and Wang et al. 2010). The 2002 Indian outbreak in the Shimla district of Himachal Pradesh was caused by a strain distinct from the 1994 pneumonic epidemic in Surat (Kingston et al. 2009). The 2009 Chinese outbreak was chosen as a case study for a microbial forensic investigation (Yan et al. 2014) and was characterized as a 1.IN2 strain of *Yersinia pestis* (evolutionarily intermediate between the Second and Third Pandemic strain) and localized to Xinghai, in the Qinghai region of northwestern China.

The study of Yan and colleagues (2014) allows us to glimpse what future plague tracking and surveillance will look like when resources and databases mature. The unusually low genetic diversity of *Yersinia pestis* requires the comparison of whole genome sequences with reference to a global database of samples collected from animals and humans over the last century, in order to localize the source of the outbreak strain. This could be critically important for the success of a public health response. In the case of a biological attack, furthermore, the ability to trace the source of infection would also help the international community to identify the responsible state or terrorist organization (Koblentz and Tucker 2010). The seemingly random aspects of pneumonic plague transmission are typical of pathogens that spread by heterogeneous transmission (Lloyd-Smith et al. 2005). Like other respiratory “super-spreading” diseases, pneumonic plague is a high-impact, low probability event that can be explosive and catastrophic, as it was in Manchuria in 1910–11 (Summers 2012; Hinckley et al. 2012). With the variety of transmission methods, multiple vectors, and the potential for super-spreading events, existing plague foci are fertile grounds for initiating the next large epidemic, or even a pandemic, if the correct conditions emerge.

## Uniting the Study of Past and Present, for the Future

Learning what we can from past epidemics is the best way to predict and prevent the next major epidemic. The careful analysis and contextualization of historical sources are therefore vitally important to our understanding of how plague functions as an epidemic pathogen. Combining historical data with a modern scientific knowledge also has the advantage of providing checks and balances to both humanistic and scientific study. It prevents researchers in all disciplines from stopping at the easy answers and being stymied by a mysterious aetiology.

Ancient and modern *Y. pestis* genetics suggest that current *Y. pestis* strains are good candidates for investigation by researchers in historic epidemiology. But while our understanding and use of aDNA data will continue and expand, it is still unlikely that a “smoking gun” will be found in the genome to explain its virulence or transmission patterns. Plague is created, amplified, and transported in man-made environments, whether it is transmitted by commensal rat fleas, human ectoparasites, or personal contact. The global distribution of plague reflects human movements more than any other host (Achtman 2012; Green, forthcoming). Plague epidemics have human fingerprints all over them, and that is why we need to know as much as we can about human interactions and global connectivity in the distant past: hence, this special issue of *The Medieval Globe*.

In the *Unnatural History of Emerging Infections* (2013), medical anthropologists Ronald Barrett and George Armelagos identify sustenance, settlement, and social order as primary drivers in the emergence of epidemic disease throughout human history. They reintroduce the metaphor of “seed and soil” (first used by physicians of the late nineteenth and early twentieth centuries, “who increasingly believed in Germ theory but continued to practice environmental medicine”) to explain the relationship between microbes and the environment (Barrett and Armelagos 2013: 11). Whether or not genetically identical seeds (i.e., microbes) flourish is dependent upon the conditions of the soil (i.e., the environment). Understanding these conditions—of settlement, social order, nutrition—are historical issues that science alone cannot address. If the human components of epidemics are not understood (or are misunderstood), then our expensive preparations for the future will fail to mitigate not only the widespread return of diseases like plague, but also new emerging infectious diseases (Barrett 2006). The long history of plague gives us the rare opportunity to study a single disease over an unprecedented period of time.

Exploring the effects of nutrition on plague dynamics is a prime example of the need for interdisciplinary research. The expertise of historians is

essential to the identification and analysis of sources that provide data on agricultural yields and practices of animal husbandry, food shortages and famine, trade networks and the diversification of foodstuffs, and all of the other activities that cultivate and sustain a food supply (e.g., Newfield 2012 and 2013). These efforts should dovetail with those of biologists working on the effects of nutrition on human immunology, *Y. pestis* itself, and rodent population dynamics (e.g., Crespo and Lawrenz 2014, in this issue; La Cava and Matarese 2004; Schaible and Stefan 2007). Biological anthropologists contribute, in turn, by analyzing bones for signs of malnutrition and disease, and tracing the sources and proportions of nutrients via isotopes (DeWitte 2014, in this issue). The work of climatologists provides a broader context for all of this historically informed research, by analyzing long- and short-term climate changes and their environmental and economic impact (e.g., Campbell 2010 and 2011). To understand the full complexity of plague, we need to pull together—rather than talk past each other.

A fine example of cross-disciplinary collaboration is that of anthropologist Sharon DeWitte and economic historian Philip Slavin (2013), who recently co-authored a study on the impact of the Great Famine (1315–17) and the food shortages resulting from the Great Bovine Epizootic (1319/20), which lasted until at least 1332. Their goal was to determine whether these catastrophic events had an impact on plague mortality, as reflected in London's East Smithfield cemetery, where victims of the Black Death were buried and where the full genome of *Y. pestis* was reconstructed in 2011. Slavin analyzed manorial accounts in order to document the depth and length of the famine and the subsequent food shortages resulting from the loss of cattle, while DeWitte assessed the ages and nutritional status of those individuals who lived through these privations only to die in the Black Death pandemic. Their failure to find a strong correlation between cohorts of people who survived the famine and food shortages, and increased susceptibility to the plague several decades later, is a good example of the checks and balances that the sciences and humanities can provide each other. The authors worked together to reach common conclusions, pose new questions, and suggest the next steps. Comparing bioarcheological evidence from one cemetery in the capital city of England to historical evidence from rural manorial accounts is a good start, but it does not settle the question of the influence of previous malnutrition on plague mortality, as they have noted. Many more collaborative studies of this kind are needed.

Settlement patterns, the conditions in which people live, and social stratification encompass another vast set of variables which must be understood from an historical perspective. As we saw in the case of Surat

in 1994, socio-economic status can explain how plague moves through a large urban environment. What is the thread of social proximity that links together the earliest cases and therefore shapes the epidemic? Were some occupations at greater risk than others? What aspects of poverty might make people more vulnerable to plague? How are existing social, political, and religious tensions catalyzed by the stress of an epidemic disaster? How well does urban planning and the built environment correlate with plague incidence? What external factors (trade networks, new commodities, immigration) play a role in introducing or spreading disease? These are questions that historians and anthropologists are best suited to answer. Genetics and microbiology tell us little about these issues.

In turn, the methods and observations of modern epidemiology can illuminate the study of historic epidemics. The transmission of infection is now understood to be a continuum across hosts and environments (Lloyd-Smith et al. 2005). Heterogeneous transmission<sup>6</sup> is defined as “variability in the contribution of specific hosts or locations to the overall rates of pathogen spread” (Paull et al. 2012); extreme cases are better known by the more common term “super-spreading events” (SSE). *Yersinia pestis*, as we have observed, spreads by heterogeneous transmission, and the pneumonic form produces such super-spreading events (Lloyd-Smith et al. 2005). It is therefore possible that some historic outbreaks of bubonic plague were also super-spreading events fueled by disease hot spots.

Comparing plague to other insect-vector zoonotic diseases provides further insight into transmission dynamics. Super-spreading events of Dengue fever, which like plague is transmitted by an insect vector that remains close to the place where it hatches, have been linked to sites where vector super-production intersects with human density (Padmanabha et al. 2012). In this study, vector super-production sites were as heterogeneous as would be expected of infection super-spreaders. Moreover, human density or traffic to these sites was as critical to disease transmission as vector production. Short distance or circular movements over the course of a day or week by humans has also been linked to increased risk of zoonotic disease transmission. For example, children at play or visiting friends can be exposed to more aspects or corners of a community than adults (Stoddard et al. 2009). A similar super-production of rodent fleas at sites of grain storage, which also draws in high human traffic, seems reasonable. It has often been remarked that outbreaks of plague

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<sup>6</sup> In contrast, homogenous transmission occurs when all hosts have an equal chance of becoming infected. See also Lambin et al. (2010) and Paull et al. (2012) for a discussion of some general principles of landscape epidemiology.

(past and present) disproportionately affect the poor more than the affluent (e.g., Wrightson 2011; Carmichael 1986), and it has been suggested that poverty-induced grain hoarding in crowded homes of poor construction create an environment where plague can flourish: this was the case in Surat (1994) as well as in Peru (1992–94) and in more recent outbreaks in Madagascar (Andrianaivoarimanana et al. 2013; WHO 2008). Testing such a hypothesis for historic epidemics requires good urban environmental histories of multiple locations and time periods, as proposed by Guy Geltner (2012) and Carole Rawcliffe (2013). We cannot rely on the traditional assumption that medieval cities were seething sites of filth and vermin; the historical reality is not only much more positive than these modern prejudices would credit, it is also more complex (Rawcliffe 2013).

So if there *were* historic plague hotspots in the medieval world, it will take much more research into the historical shaping of urban and rural environments in order to identify them: and this will require pulling together all available evidence, historical and scientific. So far, the eastern Mediterranean has been the most fruitful place to look for such sites, with the possible identification of an enzootic focus in the late antique Levant (Tsiamis 2010) and an environmental and documentary analysis of plague in Ottoman Egypt (Mikhail 2008). Indeed, Nükhet Varlık (2014, in this issue) argues convincingly for the Ottoman empire's central place in an historical understanding of plague. And importantly, Ann Carmichael (2014, in this issue) makes the first historical argument for a *European* plague focus. As part of an ongoing effort, the Environmental History Network for the Middle Ages is beginning to gather the environmental studies that are necessary to a contextualization of the plague and other medieval epidemics and epizootics.<sup>7</sup> Patterns of land use constitute another critical factor in creating an environment suitable for the establishment of plague. In modern Madagascar, for example, deforestation and bush fires (to clear land for agriculture) have been associated with plague outbreaks because they appear to disturb enzootic foci (Andrianaivoarimanana et al. 2013). Looking at plague incidence and severity in regions where the demographic effect of the Black Death substantially changed land use and agricultural methods could test these observations.

Related environmental change tends to occur after natural disasters like earthquakes and floods. An earthquake and monsoon flooding were both key catalysts for the 1994 outbreak in Surat (Barrett 2008). China has learned the importance of plague surveillance after earthquakes

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7 ENforMA <<http://www.medievaleh.org/>> [accessed September 22, 2014].

around the Tibetan Plateau, where the plague is endemic and enzootic (and probably originated). The association between plague and earthquakes goes all the way back to the First Pandemic: Tsiamis and colleagues (2013) found an association between five earthquakes in the territories of the eastern Roman (Byzantine) empire and five plague outbreaks that occurred within a year of these respective events, in the era between 557 and 713. Extensive flooding was also associated with plague in Ottoman Egypt (Mikhail 2008), and the breakdown of infrastructures meant to regulate flooding and irrigation would have made matters worse (see Borsch 2014, in this issue). The first quantitative study of long- and short-distance transmission during the entire Third Pandemic in China showed that wet conditions facilitated spread of the plague: displacement of people and rodents by floods was proposed as a major factor in the increased velocity of transmission in South China (Xu et al. 2014). Indeed, a key feature in all of these natural disasters is that they displaced potential hosts (people, animals, rodents, insects) from their normal settings.

Environmental histories should accordingly make historical epidemiology more robust and comprehensive, because plague transmission is dependent upon the environment. It is necessary to approach the study of transmission from both the environmental context and the epidemiological result. Looking at one variable in isolation will not produce an accurate picture of transmission. If the epidemiological results do not match an expected plague pattern, then there is a missing piece to be found somewhere in the environment. For too long, plague researchers in both the sciences and the humanities were content to focus solely on the black rat and its flea, but we now know that over two hundred rodent species and their parasites carry and transmit *Yersinia pestis*; the black rat may be a common host but it is far from alone (Eisen and Gage 2011; Gage and Kosoy 2005). Moreover, fleas may be less abundant in the winter but some, such as *Oropsylla montana*, transmit *Yersinia pestis* effectively at temperatures as low as 6° C (42.8° F)—better, in fact, than at 23° C (73.4° F) (Williams et al. 2013). We must remember that *Yersinia pestis* evolved on the cold meadows of the Tibetan Plateau. It is not a tropical or near tropical disease.

Another environment that needs to be accounted for in studies of plague virulence is the landscape of the human body itself, and its co-infections and co-morbidities. What was the disease burden,<sup>8</sup> chronic

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**8** “Disease burden” is the total cost to a community of a type or category of disease. It can be measured in a variety of ways: mortality, birth rate and infant mortality, life expectancy, economic trends, declining productivity, etc. Each study should define its

and infectious, borne by the communities devastated by these epidemics? Expanding aDNA work to include other pathogens not only yields a better understanding of the disease burden of these communities but also looks for potential synergistic effects, or syndemics, between pathogens affecting the same populations (Barrett and Armelagos 2013). New methods are making the identification of all microbial contributions in an aDNA sample better and more efficient (Devault et al. 2014). Considering co-infection by other unrelated pathogens, such as malaria, is also important in estimating the overall health of the population and its response to plague. But again, because archeological remains always represent only a subsection of the population, this data must be balanced by study of surviving documentary sources. All of our evidence will always be a fraction of what once existed, so we must use all available sources to assess the overall health of earlier populations and their susceptibility to disease.

Identifying other pathogens, like typhus, can also tell us more about the parasite burden of these same populations (Tran et al. 2011a and 2011b). For example, it has recently been shown (experimentally) that lice can transmit the plague (Houhamdi et al. 2006; Drancourt, Houhamdi, and Raoult 2006; Tran et al. 2011a; Ayyadurai et al. 2010). During the Thirty Years' War (1618–48), there was a clear epidemiological transition between a dominant typhus phase yielding to a plague phase (Price-Smith 2009). Could the same species of louse that transmitted typhus during the first half of the war have been transmitting the plague in the second half, throughout the lands of Central and Eastern Europe—which were already devastated by violence, forced migration, destroyed crops, and the other catastrophic side-effects of war?

## Conclusion

Interdisciplinary work is always a challenge, and it takes courage. It is daunting to confront another field with its own terminology and norms. But it is worth the effort. And happily, there are sources and people who can help to bridge the gap. In his *Evolutionary History: Uniting History and Biology to Understand Life on Earth* (2011), environmental historian Edmund Russell lays out a methodology for integrating biological information into historical studies and provides multiple examples of the difference that this makes. There are a variety of online forums for discussion, as well: these include the Medieval Medicine listserve (MEDMED-L)

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criteria and methods for measuring disease burden, as appropriate for the community (and time period).

moderated by Monica Green, blogs (like my own *Contagions*) that also reach out to a general audience, and the above-mentioned Environmental History Network for the Middle Ages.<sup>9</sup> All are very welcoming to people from a variety of backgrounds, with diverse levels of expertise.

As I hope to have shown, all kinds of plague studies are relevant to understanding the modern experience of plague and are crucial to the development of strategies for handling future pandemic threats. There are multiple opportunities for interdisciplinary work and the formation of multidisciplinary partnerships that can lower the barriers between the sciences and the humanities. Linking historical studies to our current plague concerns is further proof of the important vital place of the humanities in our academic curricula and in the public sphere. Confirmation that the East Smithfield cemetery in London was founded and used only for the burial of Black Death victims would have been impossible without the analysis of surviving documents and artifacts. Archeology alone, even with data from carbon dating, will not be able to date graves accurately enough to distinguish between plague epidemics separated by a twenty-year hiatus. We cannot discern the epidemiology of historic plagues without knowledge of the historical environment and human ecology. Only when the sciences and the humanities work together can we really begin to understand the medieval phenomenon of “the Black Death” and put that knowledge to work in our own world.

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<sup>9</sup> I also recommend *Infectious Thoughts*, by microbiologist Siouxsie Wiles <<http://sciblogs.co.nz/infectious-thoughts/>>; *Powered by Osteons*, by bioarcheologist Kristina Killgrove <<http://www.poweredbyosteons.org/>>; and *Bones Don't Lie*, by anthropology graduate student Katy Meyers <<http://www.bonesdontlie.com/>> [all accessed September 22, 2014].

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**Michelle Ziegler** (zieglerm@slu.edu) is a biologist with interests in the history of infectious disease and in science communication. She is particularly interested in the ways that science and history can inform each other, toward a greater understanding of plague. Her blog *Contagions* <<http://contagions.wordpress.com>> focuses on the intersection of science and history, and is intended to be a bridge between them, explaining scientific studies for people without a science background and exploring the historical contexts of infectious diseases under investigation today. She received an MS in Biological Science from Southern Illinois University at Edwardsville and an MS in Biosecurity and Disaster Preparedness from Saint Louis University. She is currently on the staff of the DNA Diagnostics Laboratory in the Department of Pathology at Saint Louis University.

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**Abstract** This essay summarizes what we know about the spread of *Yersinia pestis* today, assesses the potential risks of tomorrow, and suggests avenues for future collaboration among scientists and humanists. Plague is both a re-emerging infectious disease and a developed biological weapon, and it can be found in enzootic foci on every inhabited continent except Australia. Studies of the Black Death and successive epidemics can help us to prepare for and mitigate future outbreaks (and other pandemics) because analysis of medieval plagues provides a crucial context for modern scientific discoveries and theories. These studies prevent us from stopping at easy answers, and they force us to acknowledge that there is still much that we do not understand.

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**Keywords** Black Death, epidemiology, biosecurity, global history, public health, re-emerging infectious diseases.

