

Monica H. Green, “The Globalisations of Disease,” in *Human Dispersal and Species Movement: From Prehistory to the Present*, ed. Nicole Boivin, Rémy Crassard, and Michael D. Petraglia (Cambridge: Cambridge University Press, 2017), pp. 494-520, ISBN 9781107164147

## CHAPTER 19

### THE GLOBALISATIONS OF DISEASE

*Monica H. Green*

#### **Abstract**

Several disciplines – including genetics, bioarchaeology, and documentary history – contribute to the stories we tell of humankind’s major infectious diseases over the past 100,000 years. In some cases, these diseases have dispersed globally because, as obligate pathogens, they have gone wherever their human hosts have gone. Thus, tuberculosis, leprosy, smallpox, syphilis, and HIV/AIDS have traveled along paths (and via technologies) that have moved human populations to all five inhabited continents and Oceania. In other cases, diseases have moved because humans transported micro-environments that brought pathogens along; this would describe the histories of malaria, plague, and cholera. However, many aspects of these narratives are still under debate, including their chronologies and geographic trajectories. This essay will not attempt to settle those debates, but, rather, suggest why the points of debate matter. How does the story change if we alter the chronology by several thousand years, or propose different geographical routes?

**Key words:** global health, bioarchaeology, historical method, phylogenetics, aDNA

#### GOING GLOBAL

What turns a handful of human-pathogen encounters (a small outbreak) into a global human disease, affecting millions of people around the world? Answering that question in the present day seems very simple: jet travel. Intercontinental airborne transmission has indeed been a critical component of the latest diseases posing global threats (see Tatem, this volume), including SARS, MERS, and, most dramatically, HIV/AIDS, whose recognition by the biomedical establishment in 1981 was due to its presentation in middle-class urban patients in the United States several decades after the disease had taken root in populations in West Central Africa (Pepin 2011; Faria et al. 2014). “Sexual tourism” facilitated by jet travel was an important part of the global spread of HIV/AIDS in the 1970s and ’80s. Yet of the global diseases to be examined in this essay, HIV/AIDS is the only one whose historical globalisation is a product of the jet age. All the others were globalized by the early twentieth century, if not hundreds of years before.

In asking what facilitates one disease to become global while others remain localized to specific environments, many factors must be assessed. The microbiologist will look at the level of the micro organism, assessing the virulence of the pathogen, or its relative success in transmission from host to host. But while dispersal of pathogens can be used, it has been suggested, as a proxy for human genetic data in studying the evolution and migrations of *Homo sapiens* (Gilbert and Wirth 2011), the historian normally looks at the human actors themselves. Humans are and have always been an inherently mobile species (see volume introduction and other chapters in this book; also Hoerder 2002), and the circulation of pathogens has been an inherent by-product of human movements. Even so, not all human diseases become globally distributed. For that to happen, for a disease to somehow create a biological connection among people dispersed onto all five inhabited continents, takes a particular set of circumstances.

HIV-1, whose global emergence has been studied in most extensive detail, serves as a “natural history experiment” of those circumstances that must fall into alignment to allow disease globalisation. There are four groups of HIV-1. All emerged over the course of the twentieth century, but only one established itself as a global disease. HIV-1 groups M, N, O, and P differ in their ability to replicate within the human body and find efficient routes of infection into other bodies. HIV-1 group M, which has infected an estimated 75 million people over the past 90 years, has different biological properties than, say, group P, which thus far has been documented in only two people (Pepin 2011; UNAIDS 2013). But the global story of HIV/AIDS is also a story of colonialism, shifting labor markets, changes in medical technologies and public health agendas, gendered poverty, and international politics (Pepin 2011). In addition, the most recent assessment of the early decades of the pandemic highlights the nineteenth-century technology of train transport, not jet travel, as a key factor in HIV-1’s amplification (Faria et al. 2014).

The eight globally dispersed diseases being surveyed for a larger project currently in preparation (see Table 19.1) have few commonalities. Of these eight – leprosy, malaria, tuberculosis, smallpox, plague, syphilis, cholera, and HIV/AIDS – one has been eradicated and several more have been radically reduced in incidence in the past half century. Several others, however, remain at or near the top of the list of leading causes of death worldwide. Several are bacterial, one is protozoan, two are viral. Several are zoonotic in one or the other sense of the term: either they originally came from animals and became established as exclusively human diseases (vivax and falciparum malaria, and smallpox), or they are repeatedly being transmitted from animals to humans (plague). The origins of leprosy, tuberculosis, and syphilis are still so imperfectly understood that it is unclear how to classify them; the pathogens causing the latter two have related species in other animal hosts, the circumstances and timing of transmission are as yet unclear. Only one of the eight pathogens – that

TABLE 19.1 *Eight paradigmatic infectious diseases (\* under debate; see text for discussion)*

Disease	Causative Organism	Geographic Origin	Zoonotic Origin	Earliest Impact on Humans	Current Global Prevalence (P) and Incidence (I) <sup>1</sup>
leprosy (Hansen's/ Lucio & Lapati's)	<i>Mycobacterium leprae</i>	*Africa	unknown	*4–5000 BP	180,618 (P) and 215,656 (I)
	<i>M. lepromatosis</i>	*Africa	unknown	*	unknown
malaria	<i>Plasmodium vivax</i>	Africa/Asia	various non-human primates	*late Pleistocene	627 million (I) (vivax = 9% of global total)
	<i>P. falciparum</i>	Africa	gorillas	*early Holocene	
tuberculosis (TB)	<i>Mycobacterium tuberculosis</i>	*Africa	unknown	*6000 BP	12 million (P) and 8.6 million (I)
	<i>M. africanum</i>	Africa	unknown	*4–5000 BP	unknown
smallpox	<i>Variola major</i> and <i>minor</i>	Horn of Africa	camels & gerbils	3–4000 BP	0
plague	<i>Yersinia pestis</i>	Tibet-Qinghai Plateau/C. Eurasia	intermittent transferal from multiple species	*5000 BP	2,173 <sup>2</sup>
syphilis	<i>Treponema pallidum pallidum</i>	*	unknown	*	unknown
cholera	<i>Vibrio cholerae</i>	Ganges Delta	none	* (1st pandemic began 1817)	129,064
HIV/AIDS	HIV-1	West Central Africa	western chimpanzee	1920s	35.3 million (P) and 2.1 million (I)
	HIV-2	West Africa	sooty mangabey	1940s	unknown

which causes cholera – normally lives in the open environment. Despite claims that tropical climates are particularly prone to generate disease (Guégan et al. 2008; Mitchell 2013), all the global diseases considered here have been found at one point in history or another at very high latitudes. There is thus no single geographic gradient or circumstance of emergence or mode of transmission they all share. Whatever their origins, all came to be globally distributed because some accident of the organism's character aligned with other accidents of circumstance to allow global dissemination.

This constellation of factors is what the historian calls “contingency” – the chance intersection of certain agents and circumstances. Contingency is not unique to humans, and global disease transmissions are known for more than just human pathogens (Keim and Wagner 2009). But as other chapters in this volume confirm, were it not for transport by humans, few organisms besides birds would have achieved global distribution in the late Pleistocene and Holocene. The same is true of the global diseases addressed here. And that, of course, is what puts the history of disease globalisation squarely in the province of the historian, whose task is to reconstruct the lives of human actors. Disease history is the point at which the evolutionary trajectory of the pathogen intersects with human history.

The histories of infectious pathogens are, by definition, great chains of being. Although convergent evolution of pathogenic organisms is a theoretical possibility – for example, prior to 2004, discussions about *Yersinia pestis* implied that it had arisen in both Africa and Asia, or at least that there was no basis to decide between the two possibilities (Green 2014) – the phenomenon of convergent evolution has not yet been documented with respect to human pathogens. Rather, research in molecular phylogenetics and palaeogenetics is making the lines of unique evolutionary development of pathogenic organisms ever clearer, with some pathogens even proving to be so “genetically monomorphic” that their distinct clonal genealogies allow routes of transmission to be reconstructed (Achtman 2012). With obligate human pathogens – such as smallpox, whose only host is the human body – that “chain of being” must necessarily involve one human body connecting to another. Even with pathogens that move through other animal species and impact humans in zoonotic transfers only occasionally, human movement and anthropogenic environmental change are parts of the chain. Tracing all those individual links in the chains of pathogen evolution will never be possible. But the human sections of those chains are more readily knowable, particularly when the forces of genetics, bioarchaeology, and documentary history are combined. That reconstructed chain is *narrative* – a story defined by the basic rules of logic that tie particular actors to particular locations in space and particular moments in time, and that define a forward trajectory of points in time and place.

At present, the narratives of global diseases have been constructed on the basis of the most exiguous data. Despite epidemiological inferences that millions of people have died of these diseases over the past decades, centuries, or millennia, with the exception of HIV/AIDS, current phylogenetic models of their evolutionary histories have been drawn from microbial samples numbering only in the dozens or hundreds at most. Nor are historical records much better. Nobody prior to the late nineteenth century saw bacteria, let alone viruses, meaning that historical texts referring to disease or its consequences prior to that period are usually incompatible with our categories of biomedical science. Thus, even when written records have survived, it will be exceptional that they provide the information disease historians would really like to have.

Both historians and evolutionary biologists, therefore, construct narratives – stories to connect the dots – because most of the links in the great chains of being are lost. But not all stories can be simultaneously true, or even plausible. If the beginning or intermediate point changes – whether in space or time – then all subsequent elements of the story must change as well. In what follows, I focus on the gaps in our narratives for five global diseases – malaria, tuberculosis, leprosy, smallpox, and plague – and particularly those points where the evidence is profoundly contradictory.

#### ESTABLISHING THE CHRONOLOGIES AND GEOGRAPHIES OF DISEASE ORIGINS IN AFRICA

It is not likely that competing claims to be the “first” global disease will be resolved any time soon. Partly, this is a matter of definition. *Helicobacter pylori*, for example, is likely as old an organism as the oldest diseases discussed in the present chapter (see Achtman, this volume). But it is debated whether the organism has always been a pathogenic threat rather than, as it may initially have been, a beneficial part of the gut microbiome. Intestinal parasites, many of which are also globally distributed, are also likely to have a very ancient history with humans and, in some cases, our hominin ancestors (Mitchell 2013). As for the major globally distributed infectious diseases analyzed here, three – malaria, tuberculosis, and leprosy – have been assumed to have narratives that parallel the origins of anatomically modern humans in Africa. All three, however, have recently had their allegedly deep historical narratives troubled.

**Malaria.** Malaria’s African narrative is currently the strongest, having been buttressed by two landmark studies by Weimin Liu and colleagues in 2010 and 2014 (Liu et al. 2010, 2014). James L. A. Webb, Jr. provides a summary of this research in his chapter in this volume. Here, it merits noting how radically Liu and colleagues have changed the narrative of vivax (*Plasmodium vivax*) and falciparum (*P. falciparum*) malaria with these studies. Whereas the relative age of vivax vs. falciparum was debated even a few years ago, Liu and colleagues put vivax’s age unquestionably deeper than falciparum’s (Liu et al. 2014). Likewise, whereas it was still questioned a few years ago whether vivax originated in Africa or Asia, Liu and colleagues place its origin squarely in Africa, where it likely circulated amongst primate species, migrating only later to Asia where it finally established itself as a specifically human disease. Falciparum, in contrast, may have originated as a human disease in Africa through a sudden, unique species transference from gorillas, perhaps as recently as 10,000 years ago (Sundararaman et al. 2016).

Much of the data that have gone into these analyses come from non-human primates in sub-Saharan Africa, which still carry a very heavy burden of malarial infection and therefore provide a rich array of related species and strains for comparative analysis. Liu and colleagues’ work is particularly notable for having

pioneered use of a virtually inexhaustible supply of genetic material: fecal matter collected from primates' natural habitats, without any harm or disruption of the animals themselves. But by far the most important technological shift in disease history, one that permits a level of analysis hitherto impossible, is aDNA (ancient DNA): genetic fossils that can now be reconstructed through the painstaking work of archaeogenetics (see also discussion in Larson, this volume). Research using aDNA has transformed the narratives we can now tell about both tuberculosis and plague.

**Tuberculosis.** Until recently, the disease historian (Green 2012), the geneticist (Wirth et al. 2008; Galagan 2014), and the bioarchaeologist (Stone et al. 2009) would have all agreed that tuberculosis (TB) was among the oldest of the globally distributed diseases: “this disease originated at least 35,000 years ago and probably closer to 2.6 million years ago” (Stone et al. 2009: 66). Its narrative looked as follows: It took its origin in Africa in *Homo sapiens* populations, or even earlier hominins, well before small populations began to migrate into the Middle East and Asia around by 60,000–80,000 years before the present (Gutierrez et al. 2005; Comas et al. 2013). It was likely a disease acquired initially from the soil, an assumption based on the fact that most mycobacteria are saprophytes, water- or soil-dwelling organisms that draw nutrients from decaying matter. Still, an early zoonotic transfer cannot be ruled out. Whereas malaria's eastward out-of-Africa progression in the pre-Columbian period seems to have stopped before reaching Australia or other far eastern Pacific regions and malaria never reached the Americas (Buckley 2006; de Castro and Singer 2005), TB came to the New World with the First Peoples (Buikstra 1999), though that strain seems to have been replaced after the fifteenth century CE by the European lineage 4, which came into the Americas as part of the Columbian Exchange and achieved dominance due to its greater virulence in establishing active infection (Gagneux 2012). Tuberculosis was found in almost all human populations worldwide up until the mid-twentieth century, when segregation practices (aided by the tuberculin skin test and X-rays) and then antibiotics radically reduced its incidence in certain industrialized nations (Roberts and Buikstra 2003; Bynum 2012). Nevertheless, it remains a global disease today, with an estimated one-third of living human beings carrying the bacillus in their bodies (WHO 2013). It was declared a global health emergency in 1993, largely because it exhibits a pronounced progression toward active disease in those co-infected with HIV and has proved one of the most dangerous “opportunistic diseases” in full-blown AIDS (WHO 2013).

The beginning point of this TB narrative – the alleged early origin in the late or even middle Pleistocene – has now been challenged profoundly by Bos and colleagues, who suggest that the entire known spectrum of the *Mycobacterium tuberculosis* complex (MTBC) has evolved only in the past few thousand years (Bos et al. 2014; cf. Kay et al. 2015). The core of Bos and colleagues' study focuses on the retrieval and sequencing of TB aDNA from three Peruvian



mummies, which radiocarbon dating places between 1028 and 1280 CE (at not less than 98.5 percent probability). The strain of MTBC found in these mummies was not, contrary to expectations, closest to that documented from contemporary isolates in East or Southeast Asia (Lineages 1, 2, and 3), as would be expected if TB had been brought into the Americas via the Beringia passage. Rather, the strain in pre-Columbian Peru was closest to the organism now found in seals and sea lions (*Mycobacterium pinnipedii*). Moreover, not only do the Peruvian samples suggest a hitherto-unsuspected zoonotic transfer of the disease, but Bos and colleagues also suggest that the most recent common ancestor (MRCA) of the whole global MTBC (excluding *M. canettii*) should be placed at 4,449 years before present (2,990–6,062 yr BP 95% HPD). A second calculation they did from mummified remains of a woman who died in Hungary in 1797 produced a slightly deeper date for the MRCA, 5268.5 years before present (2689.6–8417.7 95% HPD), but still far more recent than previous estimates. Such drastic foreshortening of the pathogen's history (by a factor of 10) fundamentally disrupts whatever narratives of human migration we might have tied to the organism and the genesis of the seven lineages of obligate human TB that are now recognized by genetics. Subsequent studies have, to date, not yet decisively contradicted their claims (Comas et al. 2015; Kay et al. 2015).

Bos and colleagues posit that the zoonotic transfer of the seal-related strain could have occurred along the coasts of Peru, where southern fur seals are still found and where there is ample evidence for the slaughter of seals historically. Similarities between the three sequenced Peruvian TB genomes suggest that a sustained human chain of transmission had been going on for at least 100 years at the time of these individuals' deaths (Bos et al. 2014). What has yet to be established, however, is whether this seal-related strain also caused the tuberculosis disease that is well-documented in other pre-Columbian settings in both North and South America (Gómez i Prat et al. 2003). By itself, the presence of a seal-derived form of MTBC in pre-Columbian Peru would not nullify the possibility that an Asian-derived strain was brought through Beringia and became the exclusive or dominant strain of TB in North America. However, the drastically foreshortened timeframe for TB's entire history in humans definitively rules out a Beringia passage simply on the issue of dating: a pathogen whose age does not exceed 6,000 years cannot have been involved in a human migration that took place 17–20,000 years ago.

Bos and colleagues' discovery has implications not simply for the New World history of TB, but for the whole global history of MTBC, which, aside from the whole aDNA genomes that Bos and colleagues have sequenced, has thus far been understood only on the basis of aDNA fragments (Donoghue et al. 2004). Currently unexplained is how, precisely, MTBC could have moved into so many different human populations in the Old World *and established distinct genetic characteristics* – the seven geographically defined

human lineages documented thus far – during a period (the past 4–6000 years) when Old World populations were connecting regularly (as addressed in Boivin, this volume). Paleopathological evidence suggests the presence of TB in the early first or late second millennium BCE in Egypt (Bedeir 2004), the early second millennium in the Indus River Valley (Robbins Schug et al. 2013), the fifth millennium BCE in Hungary (Masson et al. 2013), the sixth millennium BCE in Italy (Canci et al. 1996; Rubini et al. 2014 provide a summary of evidence for Italy), and perhaps the seventh millennium BCE in the Eastern Mediterranean (Hershkovitz et al. 2008). Either these earliest palaeopathological assessments are misdiagnoses and/or misdatings, or Bos and colleagues' chronology is an underestimate. Apart from ongoing debates about methods and dating that are a standard feature of aDNA work, therefore, the simple demands of historical logic need to be addressed. Until Bos and colleagues' shortened chronological narrative is buttressed by a complementary and plausible narrative in human migration history, its logical holes will gnaw.

Interestingly, Bos and colleagues might have found just such buttressing had they explored one particular human dimension of their project. The phylogenetic trees posited for MTBC for some time have placed two lineages: *Mycobacterium africanum* 1 and 2, both situated deep near the tree's roots, in a clade separate from all other strains. These two human lineages of the MTBC are also the ones most closely related to the animal strains: those now associated with cows, sheep and goats, rock hyraxes, voles, seals and sea lions, mongooses, and meerkats (respectively, *M. bovis*, *M. caprae*, dassie bacillus, *M. microti*, *M. pinnipedii*, *M. mungi*, and *M. suricattae*). Currently confined to West African populations, *Mycobacterium africanum* 1 and 2 seem to have proven inefficient in establishing themselves outside of the continent, despite the massive out-migration of West Africans during the period of Atlantic slavery and subsequent smaller migrations since then (Bentley et al. 2012).

Aside from its inclusion in their phylogenetic tree, Bos and colleagues never mention *M. africanum*, perhaps because they do not think it likely that humans transferred what became *M. pinnipedii* to seals on the argument that “humans did not herd or farm seals” (Bos et al. 2014: 497). In fact, however, just as there is ample evidence for humans hunting seals in South America up to 4400 BCE (Zanfrando et al. 2014), so there is evidence for both the hunting and systematic slaughter of seals at Kasteelberg, on the Vredenburg Peninsula northwest of Cape Town, South Africa, which was near a prime nesting spot for Cape fur seals (*Arctocephalus pusillus*), one of several seal species of the circum-Antarctic ocean (Smith 2005, 2006). Kasteelberg is a site used by a herding group, possibly the Khoekhoen, for a period of at least 1,000 years starting in the first century CE. It lies 4 km inland and archaeological remains give ample evidence of the systematic harvesting of seals, as much for their fat as for their meat. Whether this can properly be called “herding” could be questioned, though archaeologists increasingly question the firm divisions between



foraging and plant/animal management that were once envisioned (see, e.g., Denham, this volume). Either way, sustained inter-species contact it surely was, especially since it seems that the local herders took advantage of the seals' breeding season to target the animals while in a vulnerable position on land (Smith 2006).

Moreover, the chronology fits. Bos and colleagues have put the evolution of the pathogen *M. pinnipedii* within the past 2,500 years, which agrees with the arrival in South Africa of the seal "herders" nearly 2,000 years ago (Smith 2005, 2008). Missing as yet is any evidence that TB was present in either the hunter or herder populations of the area in this period (Alan Morris, personal communication). As noted above, the obligate human *M. africanum* lineages, which are closest to the animal strains of MTBC, are now found in West Africa, but only as far south as Cameroon (de Jong et al. 2010). Yet a study of the history of TB in South Africa (drawing solely on documentary sources dating from the seventeenth century and later) found suggestive evidence that TB may have been present prior to European colonization (Packard 1989). Moreover, modern genetics studies show that the European lineage 4 now predominates there, raising the possibility that that strain, known for its relative virulence, swamped weaker pre-existing strains of TB just as it seems to have done in the Americas (Gagneux 2012).

Much research would need to be done to substantiate this suggestion that South Africa may have been the site of anthroponotic transfer of TB to seals. That the seals should have then transferred it to other human populations on a different continent seems too fantastic to imagine, yet that is what Bos and colleagues' sophisticated aDNA study has already suggested. The developing *narrative* for at least this clade in the MTBC, therefore, is – on genetics and on historical grounds – plausible. Indeed, given that most of the other animal MTBC strains come out of the same or a similar southern African environment (Alexander et al. 2010; van Ingen et al. 2012; Parsons et al. 2013), it is possible to ask whether their genesis might also be due to similar human–animal interactions. Even the evolutionary origin of *M. bovis* might be worth investigation in this context, since we know now that cattle were introduced to the region by at least the middle of the first millennium CE (Orton et al. 2013). By looking for a coherent narrative that joins pathogen and human history, a new research question comes to light – an opening for a history that satisfies both microbiology and known human settlement patterns and cultural practices.

**Leprosy.** Leprosy's narrative is truly contentious. Is leprosy a human disease of fairly recent origin (c. 4–5000 years old, according to Schuenemann et al. 2013) or "the oldest disease," going back many hundreds of thousand years and carving its effects permanently into the human immune system (Han and Silva 2014)? Ever since the Norwegian leprologist Armauer Hansen claimed his discovery of the leprosy bacillus in 1873, it has been assumed that the many ways in which leprosy manifests itself in the human body – from whitish, numb

skin patches to necrotizing digits, from collapsed facial features to hairless skin nodules – were all due to the many ways the obligate pathogen, *Mycobacterium leprae*, could manifest in the body's tissues. Those assumptions have been overturned since 2008, when it was announced that a second leprosy bacillus, *Mycobacterium lepromatosis*, had been identified on the basis of genetic analysis (Han et al. 2008; Han et al. 2009; Vera-Cabrera et al. 2011). That the two species are “cousins” has already been demonstrated by Han and colleagues (Han et al. 2009; Han and Silva 2014), and was confirmed by the complete sequencing of *M. lepromatosis* in 2015 (Singh et al. 2015), which allowed full comparison of the two species' common features and estimation of their divergence about 13.9 million years ago. That both species have African origins seems possible, given how deep their evolutionary histories seem to be. But have they always been parallel in their geographical trajectories, as might be suggested by the fact that some individuals are infected with both organisms (Han et al. 2012b, 2014)? If not, when did their trajectories diverge?

Initially, the new leprosy species seemed to be tied to the characteristic symptomatology of “Lucio's phenomenon” (diffuse lepromatous leprosy), a condition characterized by endothelial proliferation of the bacilli with necrotizing lesions of the skin. This leprosy manifestation has been reported from all continents save Australia and Oceania (Sehgal 2005). Further research on *M. lepromatosis* in archived biopsy samples, however, has thus far confirmed its presence only in Mexico and Brazil (the two countries reporting the highest number of cases to date), Singapore and Myanmar, and Canada (Han et al. 2012; Jessamine et al. 2012; Han et al. 2014). How much more broadly this organism will be documented is unclear: thanks to a multi-drug therapy that has been made available for free since the 1990s, leprosy incidence is declining worldwide (WHO 2014). Nevertheless, although *M. lepromatosis* cannot be said to have true “global” distribution, its documented presence in both the Americas and Southeast Asia makes this something other than a “local” disease. The question now is: how do we construct the narratives of *M. lepromatosis* and its better known “cousin,” *M. leprae*?

At the moment, bioarchaeology cannot resolve this question. It has been accepted since the 1950s that *M. leprae* can leave lesions in the skeleton distinctive enough to suggest leprosy infection. The oldest currently known sample of human skeletal remains showing characteristic infection with *M. leprae* is about 2000 BCE (Robbins et al. 2009). For *M. lepromatosis*, on the other hand, we currently know of no distinctive signs in the hard tissues of the body that would indicate infection with this organism. Nor can the documentary records of the historian settle this: although references to “leprosy” have been claimed to date back to about 600 BCE, no persuasively comprehensive clinical description of the disease can be found before the first centuries BCE and CE.

Genetics, in contrast, has been making elaborate claims about leprosy's history. In 2005, Monot and colleagues, working from modern clinical samples of *M. leprae* (*M. lepromatosis* having not yet been discovered), proposed two scenarios of origin and migration, both of which were deemed "equally plausible evolutionary scenarios." In both scenarios, leprosy had an Old World origin, and Europeans were responsible for transmitting it to West Africa and the Americas within the last 500 years (Monot et al. 2005). In 2009, Monot and colleagues further confirmed that *M. leprae* as it is found in the world today is clonal (99.995 percent identical) and likely reflects a "recent" (date unspecified) evolutionary bottleneck (Monot et al. 2009). Importantly, this study brings in data from aDNA isolates, thus allowing some time depth to be added to the analysis. Monot and colleagues' 2009 findings were further supported in 2013 by Schuenemann and colleagues, who were able to reconstruct the whole genome of five of their medieval samples, thus allowing time depth to be assessed for every part of the genome. They now argued decisively that all of *M. leprae*'s documented genetic variance occurred within the past 3,000–4,000 years (Schuenemann et al. 2013). Further studies from one of the same cemeteries produced comparable results (Mendum et al. 2014).

Thus, the narratives of tuberculosis and leprosy now look remarkably similar, at least as far as their relative youth as human diseases goes. The problem arises in the fact that, aside from these studies, we have no reason to think that leprosy is a young disease; its two species are certainly not "young" as organisms. Moreover, certain genetic characteristics widely shared among human populations suggest long adaptation to this pathogen (Han and Silva 2014). A number of questions, therefore, must be raised:

- If *M. leprae* is only about 3,000–4,000 years old as a human disease, where was it before ca. 2000 BCE? Its high percentage of pseudogenes (the highest, in fact, of any pathogen known to affect humans), which probably reflects long adaptation to a single host environment (Gomez-Valero et al. 2007), suggests that it has been in humans or a species very similar to modern *H. sapiens* for a very long time (Han and Silva 2014). In other words, if *M. leprae* and its current demographic spread are evidence for a bottleneck, what came before the bottleneck? And if the bottleneck itself reflects a period when *M. leprae* was residing in some non-human species, what caused it to move into human populations?
- An additional question is *where* did that zoonotic transfer (if it happened) occur? As noted, in 2013 Bos and colleagues added a fifth lineage to the four already posited by Monot and colleagues in the 2000s. That fifth lineage is, according to several analyses, basal to all other extant strains (Schuenemann et al. 2013; Mendum et al. 2014; Singh et al. 2015). "Lineage o" is currently known only from samples from China, Japan,

and the Pacific island of New Caledonia, which received a considerable influx of Chinese immigrants in the nineteenth century. The currently known African lineage (“Lineage 4”) is in a clade separate from all the other three lineages, but is more related to them than to Lineage o. Thus, in the current state of research, it is entirely uncertain whether leprosy, as a human disease, presents a “within-and-out-of-Africa” narrative, or an Asian origin narrative.

- Once released from its bottleneck, wherever that was, how did *M. leprae*, a slow-moving, slowly progressing organism, come to be transmitted so widely in such a relatively short period of time? Given that prolonged domestic intimacy seems to be key to transmission, should we be looking at the particular practices of slavery (which has usually involved sexual as well as labor exploitation) rather than more casual kinds of trade (Mark 2002; Ferragud 2013)?
- Most importantly, what are we to make of the geographical puzzle that *M. lepromatosis* currently presents? Myanmar and Mexico? Canada and Brazil? There is nothing currently known about Mexico’s relations with East or Southeast Asia in the post-Columbian period to suggest a migratory path connecting these two regions of the world (Bennett 2005; Buchenau 2001). There is simply not enough evidence yet to postulate a Beringian crossing of *M. lepromatosis* around the time of the Last Glacial Maximum (c. 20,000 BP). But since *M. lepromatosis* appears to be a human obligate pathogen, if we are to connect those dots, it will likely be through the bodies of human beings.

At the moment, therefore, the globalisation narratives of *M. lepromatosis* and *M. leprae* seem to be completely different, even if the processes that moved them around the world have now placed them in some cases in the same bodies (Han et al. 2012b, 2015). Given that leprosy raises major questions about its effects on human immune response (Han and Silva 2014; Degang et al. 2014), and given the continued entrenchment of the disease(s) in human populations today, these puzzles about its global history are not without consequence.

#### LONG-DISTANCE TRADE AND URBANIZATION: SMALLPOX AND PLAGUE

The notion that “crowd diseases” are a distinct epidemiological category tied to the origins of agriculture has long been accepted; Wolfe and colleagues make them central to their search for the origins of human disease (Wolfe et al. 2007). However, what constitutes a “crowd” might not be the same for epidemiology as it is for social or labor relations. It is generally believed that hunter-gatherer societies, being small and continually mobile, would have had little disease

burden beyond parasites. A disease such as malaria, particularly falciparum malaria, which does not have the same kind of latent period in the body that vivax does, needs a higher concentration of individuals to sustain it. But as Webb explains in this volume, even temporary gatherings around water sources or oil palm groves may have been sufficient to facilitate the spread of malaria long before established agriculture.

Full sedentism brought closer quarters, to be sure, facilitating the more regular transmission of respiratory diseases and others that needed close and/or prolonged contact. But there were likely health effects arising from the transition to sedentism beyond an increased infectious disease burden. The rise of agriculture in particular brought a more limited range of nutrients by decreasing the range of foodstuffs available, and what is now called the Neolithic Demographic Transition saw increased female fecundity and so a higher burden of obstetric stress and mortality (Bocquet-Appel and Bar-Yosef 2008). The transition to agriculture, at least in Old World settings, may not have signaled as much change in infectious disease as previously thought, for the simple reason that human settlements in most parts of the world continued to rarely exceed more than a few hundred people. Those are not yet “crowds” large enough to sustain new kinds of diseases.

Rather, true crowd diseases, and then pandemics, came with the rise of not simply settled but urbanized and networked populations in the millennia just before and after the beginning of the Common Era. These large, networked urban centers, amassing populations of many thousands and connecting them to other urban centers of similar size, facilitated the spread of diseases the likes of which humans had probably never seen before. This connectivity, in fact, is why plague is included in this section. Unlike smallpox (or the organisms that cause leprosy or TB), *Yersinia pestis* is not an obligate human pathogen. Humans are irrelevant to the evolutionary history of the disease, except in one respect. It is likely human activity that facilitated the long-distance spread of the causative organism, *Yersinia pestis*, to geographies and ecological niches so very different from its place of origin. That human factor – the way human networks facilitate the transmission of disease – unites the global histories of smallpox and plague. Fortuitously, these are also the diseases for which we begin to have historical records – written documents and works of art – that can help in the reconstruction of their histories.

**Smallpox.** The narrative for smallpox remains among the weakest of the diseases considered here, not because there is doubt about its historical impact, but rather because its viral nature and its limited osteological impact have thus far made it difficult to trace by either palaeogenetic or palaeopathological methods. Although the mummy of the Egyptian pharaoh Ramses V (died 1157 BCE) has long been understood to have skin lesions characteristic of smallpox (Strouhal 1996), no viral material amenable to DNA analysis has been found earlier than what was recovered from a late eighteenth-century gravesite

in Siberia (Biagini et al. 2012; McCollum et al. 2014). Older historical accounts that have relied primarily on documentary sources have rarely shown full command of the necessary languages and tend to repeat anecdotes drawn from prior Anglophone literature without verifying information in the original sources (Hopkins 1983/2002; Fenner et al. 1988).

Particularly lacking for the pre-modern history of smallpox are any studies with ambitions to construct an epidemiologically rich account of its global spread. Smallpox's biological character is key to its history. A combination of an acute infection (lasting just a month, from initial infection to resolution in death or survival), followed by long-lasting immunity for survivors, plus the absence of any non-human reservoirs, means that it can only survive with suitably sized host populations who continue to provide new non-immunes in the form of immigrants or new births. Therefore, smallpox must be a disease that, whatever its context of origin, quickly found and took advantage of the networked, urbanized societies that it needed to flourish.

The gaps in our narrative of smallpox thus demand attention in their own right. Unlike plague, where we can assume continuing enzootic transmission and explain away a lack of historical documentation because non-domesticated animals are often invisible in the historical record, periods where smallpox "disappears" are very problematic for its overall narrative. Where *was* smallpox between its (first?) major appearance in ancient Egypt (Strouhal 1996), its alleged epidemic role in the Antonine Plague in Rome (165–180 CE with another wave in 185 CE; Lo Cascio 2012), and al-Razi's famous tenth-century account of it as an endemic disease of children in Baghdad (Rhazes 1848)? Presumably, smallpox carried on a double life for several millennia: settling in as an endemic disease in large urban areas where, as in Baghdad, it would have been seen largely as an affliction of children (the main non-immunes in a population already exposed to the disease), yet flaring up as a lethal epidemic disease in smaller communities not previously (or recently) exposed to it as it traveled along epidemic corridors that connected them to major population hubs.

The relationship of smallpox to camelpox was recognized in 2002, the latter being identified as the closest known extant relative to the now eradicated variola virus (Gubser and Smith 2002). More recent studies have suggested connected histories of the taterapox (gerbilpox), camelpox, and variola viruses, which are thought to have started to evolve separately about 3,500 years ago. That grounding in time is now accompanied by a postulated origin in geographic space. Previously, in 2007, Li and colleagues placed smallpox's origin in Asia, referring to it there as an *endemic* disease and interpreting the Egyptian cases as isolated infections brought about by war (Li et al. 2007); they do not factor camels into their narrative, and suggest that the gerbil pox is a later development. A more plausible suggestion – because it postulates a historical juxtaposition of all three affected hosts – is that of Babkin and Babkina, who



suggest that all three viruses emerged from a MRCA “in the region of the Horn of Africa, and that the introduction of camels to East Africa induced their divergent evolution” (Babkin and Babkina 2012: 1597–2015). This thesis is intriguing not simply because the unique immunological character of camels makes them a plausible candidate as “incubators” of a new viral entity, but because it situates the camels in the specific context of their domestication and introduction into East Africa (cf. Marshall et al. 2014) and correlates that biological circumstance with the beginnings of great urban civilizations in the Old World, which occurred barely two millennia before this suggested disease emergence. In other words, the right biological ingredients (an adaptive virus and new hosts) meet the kind of environment necessary to sustain long-term circulation of this new obligate human pathogen among new susceptible individuals.

Descriptions of a smallpox-like condition have been reported from documents from 1500 BCE in India and 1122 BCE in China (Hopkins 1983/2002). If the first description in particular, which uncannily falls around Ramses V’s date of death, can be trusted, this would be a rare circumstance of virtually coeval sources documenting what must have been a widespread transmission event. The narrative for smallpox’s emergence, therefore, would be that it arose *as an epidemic disease* in the Horn of Africa, spread to Egypt (the closest large population center), and then took advantage of the sustained interconnected urbanism and long-distance trade of ancient and medieval Eurasia to reach India and China, and, in the latter area, establish itself as an *endemic disease* of long duration. This narrative may not be true (it may yet be invalidated), but for the moment it is plausible. As such, it shows the principal reason that the variola virus, an extraordinary immunological fluke, turned into a major global disease: because human-made environments facilitated its survival.

In constructing a narrative for smallpox beyond that moment of origin, we must think of both the endemic reservoirs of the disease and epidemic corridors that linked them. Al-Razi (ca. 854–925 or 935), working in hospitals in Rayy (near modern-day Tehran) and Baghdad when he wrote his classic description of the disease, clearly sees smallpox as an endemic disease that mostly afflicts children (Rhazes 1848). Baghdad had at the time a population of about 1 million, a rich demographic pool that would offer an endless supply of children and immigrants who had not yet survived a prior exposure to the disease and so lacked the acquired immunity that protected others in adulthood.

Reconstructing the epidemic corridors of smallpox’s penetration into less densely populated areas, however, is more of a challenge. The kinds of historical sources often cited for the early history of smallpox rarely have the clinical specificity of al-Razi’s in describing symptoms, a problem compounded by the need for linguistic and cultural command of pre-modern sources in order to properly contextualize and interpret them. There are,

however, some possible points on which historical and biological interpretations can be brought together. Here, at the moment, palaeopathology is more of an aid than aDNA. Although we usually think of smallpox as a disease of the skin, it also affected other organ systems. Al-Razi, in his incisive case notes written in the ninth/tenth century, reported acute leg pain as a common symptom of the disease when death was impending (Álvarez Millán 2010). Modern clinicians and paleopathologists have recognized that in children who survive acute smallpox infections, a bone infection known as osteomyelitis variolosa occurs in 2–5% of patients (Aufderheide and Rodríguez-Martín 1998); one study in Rhodesia (modern Zimbabwe) from 1961 found a 20 percent incidence (Davidson and Palmer 1963). The elbows are involved in about 80 percent of cases. This level of skeletal damage is distinctive enough in victims who survive an infection to allow diagnosis in historical remains even without evidence of skin blistered by smallpox's most characteristic symptom, the pustules.

Darton and colleagues have documented what they believe is a case of osteomyelitis variolosa in remains from Pont-sur-Seine (Aube, north-eastern France) dating from the eleventh or twelfth century CE. The individual in question was an adolescent male, probably between the ages of 15 and 17 (Darton et al. 2013); no isotopic studies seem to have been done to determine whether he was a native to this rather small community or a recent immigrant. Pont-sur-Seine, though small, was not “out of the way.” As its name suggests, it lies on the Seine River and likely served as a way station for river traffic moving between the larger cities of Troyes and Paris; it also connected those cities via an old Roman road. In other words, this seemingly insignificant discovery of a single smallpox case in a small town may signal how new patterns of disease transmission occur in changing economic circumstances, such as the rapidly urbanizing and demographically expanding situation of western Europe in the eleventh and twelfth centuries.

Descriptions of what might be smallpox are not common in western European sources before the late Middle Ages (Carmichael and Silverstein 1987), which may indicate that this young man (assuming his lesions are indeed indicative of smallpox) was the victim of an isolated importation of the disease that soon burnt itself out. It seems that smallpox became an *endemic* disease in Europe only in the early modern period, as most parts of it began to recover from the demographic assault of the Black Death (Carmichael and Silverstein 1987).

Jumping ahead several centuries and across an ocean, Fenn paints a similar scenario of a new economic regime as she reconstructs from documentary sources the spread of smallpox among First Peoples in the North American West in the late eighteenth century (Fenn 2006; cf. Fenn 2015). Although smallpox arrived episodically in North America before that (Jackes 1983), the first *continent-wide* outbreak of the disease was in 1775–1782. This great *pox*

*Americana* is usually described in the context of the American Revolutionary War on the East Coast, but a more important story, Fenn argues, is how the disease spread through the still sparsely populated territories of the West. Here there were no major urban centers; it was all just “corridor.” This smallpox story involves Comanches who embraced horse culture from the Spanish, Shoshones who got horses from the Comanches, slaves whom the Shoshones traded for the horses, and firearms that the Shoshones’ enemies acquired to protect themselves. Among the few groups to escape devastating losses were the Lakota, who still lived a nomadic existence.

The cases of smallpox in a small town on the Seine in the eleventh or twelfth century and in the North American West in the late eighteenth century suggest some ways that thinking about the mechanics of spreading epidemic disease at a smaller scale than dramatic outbreaks may enable better understanding of disease globalisation. The story of smallpox’s role in the Conquest of Mexico in the sixteenth century is often told (McCaa 1995; Riley 2010); less dramatic, but probably equally important for the introduction of smallpox into the Americas, were the many independent introductions of smallpox from slave ships arriving from West Africa (Alden and Miller 1987). Fenn stresses that it was changes in communications – in connections – facilitated by the introduction of the horse and firearms, that allowed the spread of smallpox throughout so many of the western tribes in the later eighteenth century. And all these narratives need to be complicated by new work both by historians and others (including climate scientists) that complicate the sometimes naïve notions of “virgin populations” that have thus far dominated accounts of the impact of smallpox on indigenous communities throughout the world. While there is no question that major depopulations occurred, their various causes are far from certain (Cameron et al. 2015; cf. Liebmann et al. 2016). At least in the sixteenth century, the impact of smallpox in Native American communities does not seem all that different from its explosive impact in other parts of the world at the same time. In other words, Native Americans may have just been part of a global pandemic.

**Plague.** Plague is not usually considered a “crowd disease”: except in cases of pneumonic plague or iatrogenic septicemic transmission, it is not transmitted directly from human to human. Nevertheless, the pathogen *Yersinia pestis* has caused three of the greatest pandemics in human history. Those sixth-, fourteenth-, and nineteenth-century outbreaks must also now be placed alongside evidence for plague’s effects on human populations of Eurasia in the Bronze Age (Rasmussen et al. 2015). Although the mode of transmission of the Bronze Age outbreaks is yet to be determined, plague’s semi-global (first and second Pandemics) and then fully global (third Pandemic) dissemination very much depended, like the virus variola, on the active interconnectivity of human societies and cultural networks. Unlike TB, malaria, or leprosy, plague has no biological “twin” with which it can readily be compared. Its evolutionary origin as a clone of *Yersinia pseudotuberculosis* is now well established

(Achtman 1999, and this volume). But the two organisms are now so unlike in terms of mode of transmission, genetic structure, and virulence as to make any further comparison meaningless. *Y. pseudotuberculosis* is a telluric (soil-based) pathogen that presents as a gastro intestinal disease with usually mild symptoms. *Y. pestis* circulates in mammalian hosts through the lymphatic and blood systems, is transmitted normally by insect vectors (fleas and ticks, and possibly also lice), and is usually quite lethal. It may have an ability to survive a telluric stage (for example, in rodent burrows), but this has not yet been securely documented.

Plague's narratives have had changing fortunes in the past several decades. A combination of phylogenetics work and aDNA has succeeded in bringing the history of the causative organism, *Yersinia pestis*, into evolutionary time, resolving long-term confusion over whether the organism evolved in Africa or central Asia. The balance of evidence now argues for an Asian origin, likely within the past 20,000 years BP (Cui et al. 2013; Rasmussen et al. 2015; Achtman, this volume). aDNA has now confirmed not simply that *Y. pestis* is present in the remains of humans who died at the time of the Black Death (1347–1351 CE) in western Europe (see the narrative of discovery summarized by Little 2011), but also in skeletal remains from the time of the Justinianic Plague (ca. 541–ca. 750 CE) (Harbeck et al. 2013; Wagner et al. 2014) and, most recently, Bronze Age Eurasia (Rasmussen et al. 2015).

The very presence in human remains of this organism *which does not make humans its normal host* means that we have to explain historically how the flea-rodent micro-environments that gave rise to *Y. pestis*'s particular ecology, likely in or near the Tibet-Qinghai Plateau, came to be replicated thousands of miles and many climate zones away to cause mass mortality in Europe, North Africa, and the Middle East, and perhaps in other areas of Afroeurasia and the Indian Ocean basin that have not yet been investigated (Green 2014). The Justinianic Plague, for example, is fairly well documented in written sources coming from around the Mediterranean, where it broke out starting in 541 CE (Little 2006; Mitchell 2014). But it has always been known that the plague was first sighted by Byzantine observers at the port town of Pelusium at the western edge of the Nile Delta, which indirectly implicates the Red Sea as the route of introduction into the Mediterranean. The new genetics narrative, which posits an origin in (and, likely, continued extrusions from) the Tibet-Qinghai Plateau or central Eurasia, demands that any narrative of plague “connect the dots” back to that source. This has not yet been done for the Justinianic Plague, though every indication from a widening world of archaeological and historical scholarship on the Indian Ocean basin (Seland 2014) suggests that it is there that we should look for the activities of trade that would have allowed the plague bacillus to travel so far, so quickly, from its home in the Central Asian highlands.

Migration, pastoralism, trade, and slavery have all been invoked thus far to explain disease globalisations. An additional human activity to consider is war.

This, it has been suggested, may be the spark that ignited the thirteenth-century polytomy (sudden evolutionary divergence) of *Yersinia pestis* postulated by Cui and colleagues in 2013. Historian Robert Hymes has proposed that the timing and general location of the postulated polytomy coincides uncannily with what we know about the military campaigns of the Mongols through the Gansu corridor in the early thirteenth century (Hymes 2014). War by itself does not cause plague, of course. But disrupted ecosystems – when those ecosystems include sylvan rodents that are natural reservoirs of plague – can. And when those same rodents are also exploited as sources of food and furs, then we can see the ingredients of longer-distance transmission of a pathogen by humans, even though humans are never technically “carriers” of the disease. Connect those practices of animal husbandry with networks of grain and textile distribution (which facilitate transfer of commensal rodents and their fleas), and we begin to see how plague, as it manifests itself epidemically in human populations, is a disease of trade and human-rodent commensalism.

True, all three pandemics must have involved stages of pathogen transfer that occurred well outside the ambit of human activities. The repeated habit of *Y. pestis* rising to higher altitudes when it invades new territories is surely a function of migrations of and flea exchanges between different rodent and lagomorph species. The establishment of new enzootic foci and their persistence is what the three plague pandemics really are. But it was human warriors and traders, herders and sailors who facilitated the long-distance spread of disease “packages” of rodents and fleas and bacilli (Green 2014; Carmichael 2014; Varlık 2014). In this respect, plague’s history parallels what has been argued for the introduction of malaria to the New World, having been brought there not simply because of the forced migrations of the Atlantic slavery system from the sixteenth century on, but because the specific technologies used in sugar and cotton plantation farming allowed the re-creation of micro-environments that in turn allowed malaria (and that other major mosquito-borne disease, yellow fever) to establish itself permanently in new colonial habitats (McNeill 2010).

#### THE LESSONS OF DEEP HISTORY: LOOKING FOR HOLES IN OUR NARRATIVES

The early narratives of malaria, TB, leprosy, smallpox, and plague that I have recounted here would be carried forward, with new trajectories, into early modern European colonialism and trans-Atlantic slavery, modern industrialization and present-day hyper-urbanization. Mapping disease narratives onto standard human migration narratives produces both overlaps and discrepancies, and aDNA work on more recent periods may likely trouble some of our narratives as much as the seals have troubled TB’s early history (Müller et al. 2014; Devault et al. 2014). With TB, it makes sense that the European lineage (Lineage 4) would be spreading in colonial contexts, since we know from so

much historical work how dominant the disease was in the eighteenth and nineteenth centuries in Europe's growing metropolises (Bynum 2012; Kay et al. 2015). But for leprosy, our dominant narrative has various holes in it. Whether it was due to co-infection with TB, the Malthusian effects of the Black Death, or the success of several centuries of segregationist practices in leprosaria, a late medieval European decline in leprosy has been a standard part of the narrative about this disease. So how could Europe be exporting the disease to West Africa and the New World (Monot et al. 2009) right when it was supposedly disappearing from its own shores?

"Global" is something of a euphemism. It captures the widest possible spatial distribution and has clear rhetorical purchase in garnering the attention of politicians, funding bodies, and the general public. We are indeed moving toward a "microbial unification of the world" in terms of our scientific knowledge of the types and distribution of various strains of infectious diseases that have afflicted humankind, a desideratum particularly for those parts of the world that neither have deep traditions of writing nor have yet benefited significantly from an infrastructure of genetics laboratory capacity or bioarchaeological fieldwork. But "global" can also serve as an agenda to craft truly capacious stories of human experiences with disease. Narratives that tell the stories of global diseases show that they are rarely uniform in their spread across the human landscape. Beyond sheer accidents in biology, we must also factor in gradients of habitation and transportation, political structures and social class, sexual identities and practices. These all belong on the list of potential contingencies that eventually add up to global dissemination. And most of them belong squarely in the historian's domain: the reconstruction of human lives. Telling the histories of global diseases, therefore, can never be the province of genetics alone. As the tentative histories of HIV/AIDS, malaria, TB, leprosy, smallpox, and plague presented above indicate, human actions – in migrating, love-making, trading, herding, or warring – have always played a role in making disease global.

## NOTES

1. "Prevalence" refers to the number of people currently suffering from the disease. "Incidence" is the number of people who are newly infected with the disease each year. For acute diseases which resolve quickly in either death or survival, there will be only incidence rates, not prevalence. All information in this column comes from WHO reports, unless otherwise indicated. Syphilis is not currently a reportable disease.
2. The WHO no longer collects regular data on plague. The figure cited here is derived from Butler 2013, who from his own tally of country data counted 21,725 cases worldwide in the first decade of the twenty-first century. I have cited 10% of that figure.



## REFERENCES

- Achtman, M. 2012. Insights from genomic comparisons of genetically monomorphic bacterial pathogens. *Philosophical Transactions of the Royal Society B* 2012 367: 860–867.
- Achtman, M. et al. 1999. *Yersinia pestis*, the cause of plague, is a recently emerged clone of *Yersinia pseudotuberculosis*. *Proceedings of the National Academy of Sciences* 96: 14043–14048.
- Alden, D. and Miller, J. C. 1987. Out of Africa: the slave trade and the transmission of smallpox to Brazil, 1560–1831. *Journal of Interdisciplinary History* 18: 195–224.
- Alexander, K. A., Laver, P. N., Michel, A. L., Williams, M., van Helden, P. D., et al. 2010. Novel *Mycobacterium tuberculosis* complex pathogen, *M. mungi*. *Emerging Infectious Diseases* 16(8): 1296–1299.
- Álvarez Millán, C. 2010. The case history in medieval Islamic medical literature: *tajarib* and *mujarrabat* as source. *Medical History* 54: 195–214.
- Aufderheide, A. C. and Rodríguez-Martín, C. 1998. Tuberculosis. In: *The Cambridge Encyclopedia of Human Paleopathology*, ed. A. C. Aufderheide and C. Rodríguez-Martín, pp. 118–141. Cambridge: Cambridge University Press.
- Babkin, I. V. and Babkina, I. N. 2012. A retrospective study of the Orthopoxvirus molecular evolution. *Infection, Genetics and Evolution* 12(8): 1597–1604.
- Babkin, I. V. and Babkina, I. N. 2015. The origin of the variola virus. *Viruses* 7(3): 1100–1112.
- Bedeir, S. A. 2004. Tuberculosis in ancient Egypt. In: M. M. Madkour (ed.). *Tuberculosis*, pp. 3–13. Berlin: Springer-Verlag.
- Bennett, H. 2005. *Africans in Colonial Mexico: Absolutism, Christianity, and Afro-Creole Consciousness, 1570–1640*. Bloomington: Indiana University Press.
- Bentley S. D., Comas I., Bryant J. M., Walker D., Smith, N. H., Harris, S. R., Thurston, S., et al. 2012. The genome of *Mycobacterium Africanum* West African 2 reveals a lineage-specific locus and genome erosion common to the *M. tuberculosis* Complex. *PLoS Neglected Tropical Diseases* 6(2): e1552.
- Biagini, P., Thèves, C., Balaesque, P., Géraut, A., Cannet, C., Keyser, C., Nikolaeva, D., et al. 2012. Variola virus in a 300-Year-Old Siberian Mummy. *New England Journal of Medicine* 367(21): 2057–2059, plus Supplementary Appendix.
- Bocquet-Appel, J. P. and Bar-Yosef, O., eds. 2008. *The Neolithic Demographic Transition and Its Consequences*. London: Springer.
- Bos, K. I., Harkins, K. M., Herbig, A., Coscolla, M., Weber, N., Comas, I., Forrest, S. A., et al. 2014. Pre-Columbian mycobacterial genomes reveal seals as a source of New World human tuberculosis. *Nature* 514: 494–497.
- Buchenau, J. 2001. Small numbers, great impact: Mexico and its immigrants, 1821–1973. *Journal of American Ethnic History* 20(3): 23–49.
- Buckley, H. R. 2006. “The predators within”: investigating the relationship between malaria and health in the prehistoric Pacific Islands. In: *Bioarchaeology of Southeast Asia*, M. Oxenham and N. Tayles, pp. 309–332. Cambridge: Cambridge University Press.
- Buikstra, J. E. 1999. Paleoepidemiology of tuberculosis in the Americas. In: *Tuberculosis: Past and Present*, ed. G. Pálfi et al., pp. 479–494. Budapest, Szeged: Golden Book Publishers and Tuberculosis Foundation.

- Butler, T. 2013. Plague gives surprises in the first decade of the 21st century in the United States and worldwide. *American Journal of Tropical Medicine and Hygiene* 89: 788–793.
- Bynum, H. 2012. *Spitting Blood: The History of Tuberculosis*. Oxford: Oxford University Press.
- Cameron, C., Kelton, P., and Swedlund, A. C., eds. 2015. *Beyond Germs: Native Depopulation in North America*. Tucson: University of Arizona Press.
- Canci, A., Minozzi, S., Borgognini Tarli, S. M. 1996. New evidence of tuberculous spondylitis from Neolithic Liguria (Italy). *International Journal of Osteoarchaeology* 6(5): 497–501.
- Carmichael, A. G. 2014. Plague persistence in western Europe: a hypothesis. *The Medieval Globe. Special issue: Pandemic Disease in the Medieval World: Rethinking the Black Death* 1(1): 107–129.
- Carmichael, A. G. and Silverstein, A. M. 1987. Smallpox in Europe before the seventeenth century: virulent killer or benign disease? *Journal of the History of Medicine and Allied Sciences* 42: 147–168.
- Comas, I., Coscolla, M., Luo, T., Borrell, S., Holt, K. E., Kato-Maeda, M., Parkhill, J., et al. 2013. Out-of-Africa migration and Neolithic coexpansion of *Mycobacterium tuberculosis* with modern humans. *Nature Genetics* 45: 1176–1182.
- Comas, I., Hailu, E., Kiros, T., Bekele, S., Mekonnen, W., Gumi, B., Tschopp, R., Ameni, G., Hewinson, R. G., Robertson, B. D., and Goig, G. A. 2015. Population genomics of *Mycobacterium tuberculosis* in Ethiopia contradicts the Virgin Soil Hypothesis for human tuberculosis in Sub-Saharan Africa. *Current Biology* 25(24): 3260–3266.
- Cui, Y., Yu, C., Yan, Y., Li, D., Li, Y., Jombart, T., Weinert, L. A., et al. 2013. Historical variations in mutation rate in an epidemic pathogen, *Yersinia pestis*. *Proceedings of the National Academy of Sciences* 110(2): 577–582.
- Darton, Y., Richard, I., and Truc, M.-C. 2013. *Osteomyelitis variolosa*: a probable mediaeval case combined with unilateral sacroiliitis. *International Journal of Paleopathology* 3(4): 288–293.
- Davidson, J. C. and Palmer, P. E. S. 1963. *Osteomyelitis variolosa*. *Journal of Bone and Joint Surgery* 45: 687–693.
- de Castro, M. and Singer, B. H. 2005. Was malaria present in the Amazon before the European conquest? Available evidence and future research agenda. *Journal of Archaeological Science* 32: 337–340.
- de Jong B. C., Antonio M., and Gagneux S. 2010. *Mycobacterium africanum* – review of an important cause of human tuberculosis in West Africa. *PLoS Neglected Tropical Diseases* 4: e744.
- Degang, Y., Nakamura, K., Akama, T., Ishido, Y., Luo, Y., Ishii, N., and Suzuki, K. 2014. Leprosy as a model of immunity. *Future Microbiology* 9(1): 43–54.
- Devault, A. M., Golding, G. B., Waglechner, N., Enk, J. M., Kuch, M., Tien, J. H., Shi, M., et al. 2014. Second-pandemic strain of *Vibrio cholerae* from the Philadelphia cholera outbreak of 1849. *New England Journal of Medicine* 370: 334–340.
- Donoghue, H. D., Spigelman, M., Greenblatt, C. L., Lev-Maor, G., Bar-Gal, G. K., Matheson, C., Vernon, K., Nerlich, A. G., and Zink, A. R. 2004. Tuberculosis: from prehistory to Robert Koch, as revealed by ancient DNA. *Lancet Infectious Diseases* 4: 584–592.
- Faria, N. R., Rambaut, A., Suchard, M. A., Baele, G., Bedford, T., Ward, M. J., et al. 2014. The early spread and epidemic ignition of HIV-1 in human populations. *Science* 346: 56–61.

- Fenn, E. A. 2006. A revolutionary contagion: smallpox and the reshaping of the American West, 1779–82. In: *When Disease Makes History: Epidemics and Great Historical Turning Points*, ed. P. Hämäläinen, pp. 45–80. Helsinki: Helsinki University Press.
- Fenn, E. A. 2015. *Encounters at the Heart of the World: A History of the Mandan People*. New York: Hill and Wang.
- Fenner, F., Henderson, D. A., Arita, I., Ježek, Z., and Ladnyi, I. D. 1988. *Smallpox and Its Eradication*. Geneva: World Health Organization.
- Ferragud, C. 2013. The Role of Doctors in the Slave Trade during the Fourteenth and Fifteenth Centuries within the Kingdom of Valencia (Crown of Aragon). *Bulletin of the History of Medicine* 87: 143–169.
- Gagneux, S. 2012. Host–pathogen coevolution in human tuberculosis. *Philosophical Transactions of the Royal Society. B. Biological Sciences* 367: 850–859.
- Galagan, J. E. 2014. Genomic insights into tuberculosis. *Nature Reviews: Genetics* 15: 307–320.
- Gilabert, A. and Wirth, T. 2011. Elucidating human migrations by means of their pathogens. In: *Genetics and Evolution of Infectious Diseases*, ed. M. Tibayrenc, pp. 173–202. Amsterdam: Elsevier.
- Gómez i Prat, J., and Mendonça de Souza, S. M. F. 2003. Prehistoric tuberculosis in America: adding comments to a literature review. *Memórias do Instituto Oswaldo Cruz* 98(suppl.1): 151–159.
- Gomez-Valero, L., Rocha, E. P. C., Latorre, A., Silva, F. J. 2007. Reconstructing the ancestor of *Mycobacterium leprae*: The dynamics of gene loss and genome reduction. *Genome Research* 17: 1178–1185.
- Green, M. H. 2012. The value of historical perspective. In: *The Ashgate Research Companion to the Globalization of Health*, ed. T. Schrecker, pp. 17–37. Aldershot: Ashgate.
- Green, M. H. 2014. Taking “pandemic” seriously: Making the Black Death global. *The Medieval Globe, Special issue: Pandemic Disease in the Medieval World: Rethinking the Black Death* 1(1): 21–43.
- Gubser, C. and Smith, G. L. 2002. The sequence of camelpox virus shows it is most closely related to variola virus, the cause of smallpox. *Journal of General Virology* 83(4): 855–872.
- Guégan, J., Prugnolle, F., and Thomas, F. 2008. Global spatial patterns of infectious diseases and human evolution. In *Evolution in Health and Disease*, ed. S. Stearns and J. Koella, pp. 19–29. Oxford and New York: Oxford University Press.
- Gutierrez, M. C., Brisse, S., Brosch, R., Fabre, M., Omaïs, B., Marmiesse, M., Supply, P., et al. 2005. Ancient origin and gene mosaicism of the progenitor of *Mycobacterium tuberculosis*. *PLoS Pathogens* 1(1): e5.
- Han, X. Y., Aung, F. M., Choon, S. E., and Werner, B. 2014. Analysis of the leprosy agents *Mycobacterium leprae* and *Mycobacterium lepromatosis* in four countries. *AJCP* 142: 524–532.
- Han, X. Y., Seo, Y. H., Sizer, K. C., Schoberle, T., May, G. S., Spencer, J. S., Li, W., et al. 2008. A new *Mycobacterium* species causing diffuse lepromatous leprosy. *American Journal of Clinical Pathology* 130: 856–864.
- Han, X. Y. and Silva, F. J. 2014. On the age of leprosy. *PLoS Neglected Tropical Diseases* 8(2): e2544.

- Han, X. Y., Sizer, K. C., and Tan, H. H. 2012a. Identification of the leprosy agent *Mycobacterium lepromatosis* in Singapore. *Journal of Drugs in Dermatology* 11(2): 168–172.
- Han, X. Y., Sizer, K. C., Thompson, E. J., Kabanja, J., Li, J., Hu, P., Gómez-Valero, L., et al. 2009. Comparative sequence analysis of *Mycobacterium leprae* and the new leprosy-causing *Mycobacterium lepromatosis*. *Journal of Bacteriology* 191(19): 6067–6074.
- Han, X. Y., Sizer, K. C., Velarde-Félix, J. S., Frias-Castro, L. O., and Vargas-Ocampo, F. 2012b. The leprosy agents *Mycobacterium lepromatosis* and *Mycobacterium leprae* in Mexico. *International Journal of Dermatology* 51: 952–959.
- Han, X. Y., Zhang, J., and Li, L. 2015. Leprosy agents *Mycobacterium lepromatosis* and *Mycobacterium leprae* in Mexico: a clarification. *Journal of Clinical Microbiology* 53(10): 3387–3388.
- Harbeck, M., Seifert, L., Hänsch, S., Wagner D. M., Birdsellk, D., Parise, K. L., Wiechmann, I., et al. 2013. *Yersinia pestis* DNA from skeletal remains from the 6th century AD reveals insights into Justinianic Plague. *PLoS Pathogens* 9(5): e1003349.
- Hershkovitz, I., Donoghue, H. D., Minnikin, D. E., Besra, G. S., Lee, O. Y. C., Germaey, A. M., Galili, E., et al. 2008. Detection and molecular characterization of 9000-year-old *Mycobacterium tuberculosis* from a Neolithic settlement in the Eastern Mediterranean. *PLoS ONE* 3(10): e3426.
- Hoerder, D. 2002. *Cultures in Contact: World Migrations in the Second Millennium*. Durham: Duke University Press.
- Hopkins, D. R. 1983/2002. *Princes and Peasants: Smallpox in History*, reissued in 2002 as: *The Greatest Killer: Smallpox in History*. Chicago: University of Chicago.
- Hymes, R. P. F. 2014. Epilogue: A hypothesis on the East Asian beginnings of the *Yersinia pestis* polytomy. *The Medieval Globe* 1(1): 200–215.
- Jackes, M. K. 1983. Osteological evidence for smallpox: a possible case from seventeenth century Ontario. *American Journal of Physical Anthropology* 60: 75–81.
- Jessamine, P. G., Desjardins, M., Gillis, T., Scollard, D., Jamieson, F., Broukhanski, G., Chedore, P., et al. 2012. Leprosy-like illness in a patient with *Mycobacterium lepromatosis* from Ontario, Canada. *Journal of Drugs in Dermatology* 11(2): 229–233.
- Kay, G. L., Sergeant, M. J., Zhou, Z., Chan, J. Z. M., Millard, A., Quick, J., Szikossy, I., Pap, I., Spigelman, M., Loman, N. J., and Achtman, M. 2015. Eighteenth-century genomes show that mixed infections were common at time of peak tuberculosis in Europe. *Nature Communications* 6(6717).
- Keim, P. S. and Wagner, D. M. 2009. Humans and evolutionary and ecological forces shaped the phylogeography of recently emerged diseases. *Nature Reviews: Microbiology* 7(11): 813–821.
- Li, Y., Carroll, D. S., Gardner, S. N., Walsh, M. C., Vitalis, E. A., and Damon, I. K. 2007. On the origin of smallpox: Correlating variola phylogenics with historical smallpox records. *Proceedings of the National Academy of Sciences USA* 104(40): 15787–15792.
- Liebmann, M. J., Farrell, J., Roos, C. I., Stack, A., Martini, S., and Swetnam, T. W. 2016. Native American depopulation, reforestation, and fire regimes in the Southwest United States, 1492–1900 CE. *Proceedings of the National Academy of Sciences USA* 113(6): E696–704.
- Little, L. K. ed. 2006. *Plague and the End of Antiquity: The Pandemic of 541–750*. Cambridge: Cambridge University Press.

- Little, L. K. 2011. Plague historians in lab coats. *Past and Present* 213: 267–290.
- Liu, W., Li, Y., Learn, G. H., Rudicell, R. S., Robertson, J. D., et al. 2010. Origin of the human malaria parasite *Plasmodium falciparum* in gorillas. *Nature* 467: 420–425.
- Liu, W., Li, Y., Shaw, K. S., Learn, G. H., Plenderleith, L. J., Malenke, J. A., Sundararaman, S. A., et al. 2014. African origin of the malaria parasite *Plasmodium vivax*. *Nature Communications* 5(3346).
- Lo Cascio, E., ed. 2012. *L'Impatto della "Peste Antonina"*. Santo Spirito [Bari]: Edipuglia.
- Mark, S. 2002. Alexander the Great, seafaring, and the spread of leprosy. *Journal of the History of Medicine and the Allied Sciences* 57: 285–311.
- Marshall, F. B., Dobney, K., Denham, T., and Capriles, J. M. 2014. Evaluating the roles of directed breeding and gene flow in animal domestication. *Proceedings of the National Academy of Sciences USA* 111(17): 6153–6158.
- Masson, M., Molnár, E., Donoghue, H. D., Besra, G. S., Minnikin, D. E., Wu, H. H. T., Lee, O. Y.-C., et al. 2013. Osteological and biomolecular evidence of a 7000-year old case of hypertrophic pulmonary osteopathy secondary to tuberculosis from Neolithic Hungary. *PLoS ONE* 8(10): e78252.
- McCaa, R. 1995. Spanish and Nahuatl views on smallpox and demographic catastrophe in Mexico. *Journal of Interdisciplinary History* 25(3): 397–431.
- McCollum, A. M., Li, Y., Wilkins, K., Karem, K. L., Davidson, W. B., Paddock, C. D., Reynolds, M. G., Damon, I. K. 2014. Poxvirus viability and signatures in historical relics. *Emerging Infectious Diseases* 20(2): 177–184.
- McNeill, J. R. 2010. *Mosquito Empires: Ecology and War in the Greater Caribbean, 1640–1914*. Cambridge: Cambridge University Press.
- Mendum, T. A., Schuenemann, V. J., Roffey, S., Taylor, G., Wu, H., et al. 2014. *Mycobacterium leprae* genomes from a British medieval leprosy hospital: towards understanding an ancient epidemic. *BMC Genomics* 15: 270.
- Mitchell, P. D. 2013. The origins of human parasites: exploring the evidence for endoparasitism throughout human evolution. *International Journal of Palaeopathology* 3: 191–198.
- Mitchell, S. 2014. *A History of the Later Roman Empire, AD 284–641*, 2nd ed. New York: Wiley-Blackwell.
- Monot, M., Honoré, N., Garnier, T., Araoz, R., Coppée, J.-Y., Lacroix, C., Sow, S., et al. 2005. On the origin of leprosy. *Science* 308: 1140–42.
- Monot, M., Honoré, N., Garnier, T., Zidane, N., Sherafi, D., Paniz-Mondolfi, A., Matsuoka, M. et al. 2009. Comparative genomic and phylogeographic analysis of *Mycobacterium leprae*. *Nature Genetics* 41: 1282–1289.
- Müller, R., Roberts, C. A., and Brown, T. A. 2014. Genotyping of ancient *Mycobacterium tuberculosis* strains reveals historic genetic diversity. *Proceedings of the Royal Society B* 281: 20133236.
- Orton, J., Mitchell, P., Klein, R., Steele, T., and Horsburgh, K. A. 2013. An early date for cattle from Namaqualand, South Africa: implications for the origins of herding in southern Africa. *Antiquity* 87: 108–120.
- Packard, R. 1989. *White Plague, Black Labor: Tuberculosis and the Political Economy of Health and Disease in South Africa*. Berkeley: University of California Press.
- Parsons, S. D. C., Drewe, J. A., Gey van Pittius, N. C., Warren, R. M., and van Helden, Paul D. 2013. Novel cause of tuberculosis in meerkats, South Africa. *Emerging Infectious Diseases* 19 (12), 2004–2007.
- Pepin, J. 2011. *The Origin of AIDS*. Cambridge: Cambridge University Press.

- Rasmussen, S., Allentoft, M. E., Nielsen, K., Orlando, L., Sikora, M., Sjögren, K. G., Pedersen, A. G., Schubert, M., Van Dam, A., Kapel, C. M. O., and Nielsen, H. B. 2015. Early divergent strains of *Yersinia pestis* in Eurasia 5,000 years ago. *Cell* 163(3): 571–582.
- Rhazes [al-Razi, ca. 854–925 or 935]. 1848. *A Treatise on the Smallpox and Measles*, trans. William Alexander Greenhill. London: Sydenham Society.
- Riley, J. C. 2010. Smallpox and American Indians revisited. *Journal of the History of Medicine and Allied Sciences* 65(4): 445–477.
- Robbins, G., Tripathy, V. M., Misra, V. N., Mohanty, R. K., Shinde, V. S., Gray, K. M., Schug, M. D. 2009. Ancient skeletal evidence for leprosy in India (2000 B.C.). *PLoS ONE* 4: e5669.
- Robbins Schug, G., Blevins, K. E., Cox, B., Gray, K., and Mushrif-Tripathy, V. 2013. Infection, disease, and biosocial processes at the end of the Indus civilization. *PLoS ONE* 8(12): e84814.
- Roberts, C. A. and Buikstra, J. E. 2003. *The Bioarchaeology of Tuberculosis: A Global View on a Reemerging Disease*. Gainesville: University Press of Florida.
- Rubini, M., Zaio, P., and Roberts, C. A. 2014. Tuberculosis and leprosy in Italy. New skeletal evidence. *Homo – Journal of Comparative Human Biology* 65: 13–32.
- Schuenemann, V. J., Singh, P., Mendum, T. A., Krause-Kyora, B., Jäger, G., Bos, K. I., Herbig, A., et al. 2013. Genome-wide comparison of medieval and modern *Mycobacterium leprae*. *Science* 341(6142): 179–183.
- Sehgal, V. N. 2005. Lucio's phenomenon/erythema necroticans. *International Journal of Dermatology* 44(7): 602–605.
- Seland, E. H. 2014. Archaeology of trade in the Western Indian Ocean, 300 BC–AD 700. *Journal of Archaeological Research* 22: 367–402.
- Singh, P., Benjak, A., Schuenemann, V. J., Herbig, A., and Avanzia, C., et al. 2015. Insight into the evolution and origin of leprosy bacilli from the genome sequence of *Mycobacterium lepromatosis*. *Proceedings of the National Academy of Sciences USA* 112 (14): 4459–4464.
- Smith, A. B. 2005. *African Herders: Emergence of Pastoral Traditions*. Walnut Creek: Altamira.
- Smith, A. B. 2006. Kasteelberg: A pastoralist sealing camp in Western Cape Province, South Africa. *Journal of Island and Coastal Archaeology* 1: 109–122.
- Smith, A. B. 2008. Pastoral origins at the Cape, South Africa: influences and arguments. *Southern African Humanities* 20: 49–60.
- Stone, A. C., Wilbur, A. K., Buikstra, J. E., and Roberts, C. A. 2009. Tuberculosis and leprosy in perspective. *Yearbook of Physical Anthropology* 52: 66–94.
- Strouhal, E. 1996. Traces of a smallpox epidemic in the family of Ramses V of the Egyptian 20th Dynasty. *Anthropologie* 34: 315–319.
- Sundararaman, S. A., Plenderleith, L. J., Liu, W., Loy, D. E., Learn, G. H., Li, Y. et al. 2016. Genomes of cryptic chimpanzee *Plasmodium* species reveal key evolutionary events leading to human malaria. *Nature Communications* 7:11078.
- UNAIDS. 2013. *Global report: UNAIDS report on the global AIDS epidemic 2013*. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS).
- van Ingen, J., Rahim, Z., Mulder, A., Boeree, M. J., Simeone, R., Brosch, R., and van Soolingen, D. 2012. Characterization of *Mycobacterium orygis* as *M. tuberculosis* Complex subspecies. *Emerging Infectious Diseases* 18(4): 653–655.
- Varlık, N. 2014. New science and old sources: Why the Ottoman experience of plague matters. *The Medieval Globe* 1(1): 130–153.



- Vera-Cabrera L., Escalante-Fuentes, W. G., Gomez-Flores, M., Ocampo-Candiani, J., Busso, P., Singh, P., and Cole, S. T. 2011. Case of diffuse lepromatous leprosy associated with *Mycobacterium lepromatosis*. *Journal of Clinical Microbiology* 49(12): 4366–4368.
- Wagner, D. M., Klunk, J., Harbeck, M., Devault, A., Waglechner, N., Sahl, J. W., Enk, J., et al. 2014. *Yersinia pestis* and the Plague of Justinian 541–543 AD: a genomic analysis. *The Lancet Infectious Diseases* 14: 319–326.
- WHO [World Health Organization]. 2013. Global tuberculosis report 2013. Geneva: World Health Organization.
- WHO [World Health Organization]. 2014. Global leprosy update, 2013: reducing disease burden. *Weekly epidemiological record/Relevé épidémiologique hebdomadaire* 89 (36): 389–400.
- Wirth T., Hildebrand F., Allix-Béguec C., Wölbeling F., Kubica T., et al. 2008. Origin, Spread and Demography of the *Mycobacterium tuberculosis* Complex. *PLoS Pathog* 4(9): e1000160.
- Wolfe, N. D., Dunavan, C. P., and Diamond, J. 2007. Origins of major human infectious diseases. *Nature* 447: 279–283.
- Zangrando, A. F., Panarello, H., and Piana, E. L. 2014. Zooarchaeological and stable isotopic assessments on pinniped–human relations in the Beagle Channel (Tierra del Fuego, Southern South America). *International Journal of Osteoarchaeology* 24(2): 231–244.