How vector-borne disease shaped the course of human history

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Abstract

The extent to which vector-borne diseases (VBDs) have shaped human history remains under-recognized, even in the disease ecology community, despite several well-known examples. Although they represent a significant threat to global human health, accounting for more than one billion cases and one million deaths annually, VBDs have coexisted with humans since the advent of civilization and have migrated with humans around the world. Here, we synthesize historical, anthropological, and archaeological evidence and examine it through an ecological lens to illustrate how four major VBDs—plague, malaria, yellow fever, and trypanosomiasis—have shaped the course of human history through three main pathways: (1) outcomes of colonialism, imperialism, war, and conflict; (2) human interactions with the environment; and (3) intrasocietal human interactions. For example, malaria tipped the American Revolution toward the Continental Army; plague promoted reforestation in Europe; yellow fever entrenched African slavery in colonies in the Americas; trypanosomiasis impeded large settlements and central governments in pre-colonial sub-Saharan Africa. By drawing comparisons across diseases, time periods, and geographic locations, we show how VBDs have historically affected human populations, from the age of early *Homo sapiens* to the modern context, and how they continue to impact the world.

Introduction

When the British occupied Walcheren, a swampy island at the mouth of the Scheldt in the Netherlands, with forty thousand troops in July 1809, Napoleon fought the largest British force ever assembled with a bold and unconventional strategy. Recalling a disastrous French expedition to the island years earlier, Napoleon breached dikes on the Dutch countryside, flooding the area with brackish water that amplified suitable mosquito-breeding habitats, and declared: "We must oppose the English with nothing but fever, which will soon devour them all" (Winegard 2019). Within months, 40% of the British force were debilitated by a lethal combination of malaria, typhus, and other diseases, while the French, watching from afar, declared victory with minimal combat engagement (Howard 1999). This is just one example of the profound extent to which vector-borne diseases (VBDs) have shaped our world.

VBDs—illnesses caused by pathogens transmitted by biting arthropods—have played a fundamental role in human history and culture. Homer described seasonal cycles of malaria in 900–800 BCE in the *Iliad* (Lafferty 2009), but malaria records date back to Mesopotamian clay tablets and Egyptian mummies as ancient as 3200–1304 BCE (Miller *et al.* 1994; Arrow *et al.* 2004). Chaucer's *Canterbury Tales* took place against a backdrop of endemic malaria and the aftermath of the Black Death in medieval England (1385 CE) (Lafferty 2009). Today, VBDs account for more than one billion cases, one million deaths, and one-sixth of worldwide disability and illness annually (World Health Organization 2014). Although the effects of VBDs span the arc of human history, the extent of this influence, and its connection to disease ecologies uniquely situated in historical places and times, remains largely obscure.

Here, we draw on historical, anthropological, and archaeological evidence within a disease ecology context to understand the impacts of VBDs on the course of human history (Fig. 1). We focus on case studies of four major diseases that have had profound influence across history and geography: plague, malaria, yellow fever, and trypanosomiasis. Because of their reliance on arthropod vectors, these diseases are intimately linked to ecology, human behavior, settlement patterns, and agricultural practices (Fig. 2; Box 1). Each VBD is distinctly suited to its particular socio-ecological setting, which determines its historical impact.

VBDs have shaped human history through three main pathways, by affecting: (1) outcomes of colonialism, imperialism, war, and conflict; (2) human interactions with the environment; and (3) intrasocietal human interactions. After introducing these three mechanisms with brief examples, we examine each focal disease through its distinct ecology, and the resulting historical impacts across geography and time periods (Tables 1-2).

Pathways of Influence

(1) Colonialism, imperialism, war, and conflict

VBDs played significant roles in human conflicts through differential rates of acquired immunity or resistance (hereafter, differential immunity) and exposure (Box 2). Human movement has resulted in interactions among peoples and cultures that often included exposure to diseases. When people arrive in a new setting they can be exposed to new VBDs, introduce infectious disease to the indigenous population, or both. Differential immunity has been a critical factor in cases where people with acquired immunity against endemic pathogens interact with foreign

groups (McNeill 2010). For example, as discussed below, native Haitians' plan to engage in guerrilla warfare by luring French troops into the interior of Hispaniola, where the immunologically naïve French were vulnerable to yellow fever, was a successful battle strategy during the Haitian Revolution of 1791–1804 CE (Bell 2009; Girard 2011). In these cases, VBDs asymmetrically affected war as one side leveraged differential immunity as an advantage to outlast the enemy.

(2) Human interactions with the environment

Disease has mediated human interaction with the natural world, affecting where people settle and how they use natural resources. For example, malaria outbreaks indirectly protected the Amazon forest by impeding human settlement and led to changing agricultural practices (Sawyer 1993; Singer & de Castro 2001) trypanosomiasis altered the practice of pastoralism and migration routes in Africa (Lambrecht 1964; Ingold 1987; Alsan 2015). VBDs have indirectly promoted conservation; for instance, plague outbreaks in the Middle Ages promoted widespread land abandonment and subsequent reforestation in Europe (Poos 1991; Williams 2000; Stebich *et al.* 2005; Yeloff & Van Geel 2007). Human responses to VBDs caused both environmental degradation and reform in methods of water collection, pesticide usage, and biotechnology (Trigg & Kondrachine 1998; van der Hoek *et al.* 2001; Hoffmann *et al.* 2011).

(3) Intrasocietal human interactions

VBDs affect day-to-day interactions within human communities through differential disease exposure and immunity across race, social class, and gender groups, leading to empowerment of some and disenfranchisement of others. Power structures and social and racial hierarchies can

emerge from immunological and social factors involved with VBD transmission. Groups perceived to be superior (e.g., due to real or perceived immunity or reduced exposure) often receive social benefits, while those at the bottom of hierarchies are marginalized and exploited. VBDs have disrupted existing class boundaries in some settings and intensified inequality in others. For example, plague in Europe contributed to the downfall of feudalism and increased the economic power of peasants (Gelman 1979; Blockmans 1980; Clark 2016), while yellow fever solidified racial and socioeconomic hierarchies in the U.S. South by perpetuating racist stereotypes and consolidating power in the hands of White men (Olivarius 2019). VBD epidemics have also catalyzed changes in public health and governance through infrastructure development (e.g., roads, sewers, urban sanitation) and establishment of national and international organizations (e.g., CDC, U.S. EPA).

To illustrate the depth of VBD impacts on human history, we examine four VBDs—plague, malaria, yellow fever, and trypanosomiasis—through the lens of these three pathways of influence.

Plague

Disease Ecology

From ancient times to the present, plague, caused by the bacterium *Yersinia pestis* and maintained in enzootic cycles with rodents and fleas, has had a persistent influence on society throughout history. Although at least 31 flea species can transmit *Y. pestis*, the Oriental rat flea, *Xenopsylla cheopis,* is considered the primary vector in human pandemics (Perry & Fetherston 1997; Bitam *et al.* 2010). Over 300 mammal species can become infected with plague, with large

variation in susceptibility and reservoir competence (Pollitzer & Meyer 1961; Christie 1982; Biggins & Kosoy 2001). While *Y. pestis* typically causes low mortality in rodent hosts, it occasionally causes massive die-offs, putting humans at higher exposure risk as rodent fleas seek alternative hosts (Gage & Kosoy 2005). Plague is endemic to Africa, the Americas, and Asia; the disease is typically found in semi-arid forests and grasslands (Stenseth *et al.* 2008), but can also exist in densely-populated urban environments.

(i) Neolithic Revolution in Eurasia

Evidence suggests that plague contributed to the downfall of the Cucuteni-Trypillian society and other agricultural settlements, which originated over seven millennia ago in the Eurasian steppe (Rascovan *et al.* 2019). From around 5500 BCE, the Cucuteni-Trypillian culture inhabited megasettlements in Eastern Europe; populations in the tens of thousands lived in compact arrangements of houses and utilized novel technology (e.g., metallurgy, animal traction, pottery), division of labor, and trading (Kirleis & Dal Corso 2016). However, these settlements had poor sanitation, high density of animals, and accumulated food storage: ideal conditions for rodents and plague (Barrett *et al.* 1998). Around 3400 BCE, many buildings were abandoned and burned, residents perished or moved, and megasettlements collapsed. Phylogenetic and genomic analyses from prehistoric human remains have revealed that multiple independent lineages of *Y. pestis* spread across Eurasia during this decline (Rascovan *et al.* 2019). These strains likely spread through early trade routes and wheeled transport, fueling the downfall of these Neolithic megasettlements.

(ii) Middle Ages in Europe

The Plague of Justinian (541–544 CE) facilitated changing agricultural practices and socio-politics around Constantinople, the capital of the Byzantine Empire. One of the world's deadliest pandemics, the Justinian Plague was initiated by plague-infected rat fleas found aboard merchant grain ships from Egypt and caused over 100 million deaths (Haensch *et al.* 2010). After the disease arrived, farmers were unable to tend their crops, inflating grain prices in Constantinople marketplaces, decreasing tax revenues, and causing famine (Sabbatani *et al.* 2012). It soon spread to neighboring ports and critically weakened the Byzantine Empire, ushering in the invasion of the Kingdom of the Lombards (Evans 2005).

The Black Death in the mid-1300s CE, the most well-known plague pandemic, killed over 50 million people (30–45% of Europe's population) and illustrates how plague altered the outcome of war. In 1343, amid tensions between Mongols and Italian traders, the Mongolian ruler Jani Beg ordered his troops to besiege the trading post of Caffa (in modern-day Crimea) and the Italian enclave at Tana (Wheelis 2002). During the Siege of Caffa, the Mongols hurled plague-infected corpses into the city, infecting the Italians and forcing them to capitulate. The fleeing Italians carried the disease to Mediterranean ports, ultimately allowing plague to reach the heart of Europe (Wheelis 2002).

After spreading through Europe, the Black Death toppled the feudal system through demographic changes—an example of disease impacting intrasocietal dynamics. Between 1000–1200 CE, medieval European populations had grown, leading to increasing conflicts over land. In the feudal system, land-owning lords commissioned serfs to work in exchange for a small portion of earnings, heavy taxation, and caps on their surpluses (Moore 2002). By the 1300s,

feudalism was under threat due to its inefficiency and inability to keep up with rising demands for productivity (Moore 2002). When the Black Death caused rapid population declines, a labor shortage, and higher serf wages (Clark 2016), the economic power of serfs increased. Case studies in England, Belgium, the Netherlands, and Luxembourg demonstrate that the per capita economic conditions of surviving serfs drastically improved post-pandemic (Gelman 1979; Blockmans 1980), enabling them more economic freedom and rendering the feudal system unprofitable.

Population decline due to plague led to large-scale land abandonment and woodland regrowth and altered human-environment interactions (Williams 2000). High mortality of farmers and farm animals reduced agricultural activity and grazing pressure, allowing succession of woody tree species by the late 1300s (Yeloff & Van Geel 2007). Paleoecological evidence shows that arable land decreased and forest area increased in Southern England from 1307–1377 (Poos 1991). Analyses in France and Denmark show an increase in pollen cover beginning in 1375, indicating changing patterns of vegetation due to agricultural decline and reforestation (Stebich *et al.* 2005).

(iii) Qing Dynasty in China

Plague originating in the Yunnan Province affected the Panthay (Du Wenxiu) Rebellion, leading to demographic change in China. High population density and rapidly developing transportation brought people into close contact with plague-infected fleas. The Panthay Rebellion (1856–1873), where Muslim Hui miners rebelled against the Qing, resulted in large numbers of refugees. Plague killed many Imperial soldiers and was disseminated via refugee and troop

movements, resulting in the depopulation of Yunnan Province during the conflict (Peckham 2016). In Luoping county and others, villages were rapidly deserted following successive years of epidemics of plague and other infectious diseases (Benedict 1988). In Lufeng county, 70–80% of the population perished, and the spatial patterning of plague supports the idea that plague caused these demographic changes (Rocher 1879; Benedict 1988).

(iv) Modern India

Recent plague epidemics in India have catalyzed public health infrastructure development. An outbreak of nearly 700 cases in Surat in 1994—a city with irregular garbage collection, informal housing structures, and low access to piped water—prompted over half a million people (one-fourth of the population) to emigrate within two days, leading to a mass shutdown of businesses (Dutt *et al.* 2006). In the resulting panic, tourism plummeted and flights were cancelled. Following the outbreak, the city upgraded urban cleaning services, enforced new food hygiene standards, and paved streets (Chatterjee 2015). Surat became one of the cleanest cities in India, and today serves as a nation-wide model for sanitation. This example serves a modern outlier, since availability of antibiotics now deters contemporary plague outbreaks.

Malaria

Disease Ecology

Malaria is caused by protozoan *Plasmodium* parasites (primarily *P. falciparum, P. malariae, P. vivax,* and *P. ovale*) and transmitted to humans primarily by *Anopheles* mosquitoes (Dutta & Dutt 1978). Infection typically manifests as recurring fever and flu-like symptoms, but severe cases can progress to organ dysfunction, anemia, and death (Bartoloni & Zammarchi 2012).

Although historically distributed throughout temperate and tropical zones in 140 countries, malaria is currently restricted to 88 countries in the tropics and subtropics, and in some regions centered on agricultural areas undergoing land conversion (Martens *et al.* 1995; Hay *et al.* 2004; Zahouli *et al.* 2017). Climate is a key driver of the distribution and seasonality of malaria, with moderate temperatures required for parasite transmission and sufficient rainfall needed for larval mosquito habitat (Thomson *et al.* 2006; Béguin *et al.* 2011; Mordecai *et al.* 2013; Yamana & Eltahir 2013). Malaria migrated out of Africa with humans and into prehistoric Europe, then to Asia, and eventually to the Americas during the transatlantic slave trade (Carter & Mendis 2002). Because of its widespread distribution in Africa, the Americas, Europe, and Asia during pre-colonial and colonial periods and beyond (Hay *et al.* 2004) and its high virulence, malaria fundamentally influenced the course of human history.

(i) Ancient Rome to Modern Italy

Most historians and archaeologists agree that malaria increased mortality and morbidity in Roman Italy starting in the Imperial period (ca. 100 CE), if not earlier. Evidence includes biomarkers of the disease detected within Roman-era skeletal remains from Apulia, Umbria, and Campania, a child cemetery from the Late Antique period, and Roman author Cicero's letters to his friend Atticus detailing quartan fevers between 50–49 BCE (Sallares 2002; Soren 2003; Marciniak *et al.* 2016). While the Romans did not know the etiology of the disease, they recognized its major symptom (recurrent fever), and understood that it was tied to environments like marshlands (Sallares 2002). Malaria in Roman Italy likely emerged from the interplay of pan-Mediterranean trade and latifundia (large estates that practiced extensive agriculture and livestock rearing): trade facilitated the spread of both the disease and its vector from the East

where it had long been present, and latifundia increased the availability of suitable vector breeding habitat (Sallares *et al.* 2004; Yasuoka & Levins 2007; Harper 2017). In turn, this interaction likely depressed the agrarian economy of the Roman Empire and affected demography across the peninsula (Sallares 2002). Hot-spots of malaria probably occurred near coastal marshes, low-lying flood plains, and in Rome, due to wet and warm conditions (Di Luca *et al.* 2009).

Malaria likely reinforced socio-economic and gender inequities in ancient Roman Italy, as it often does today (Heggenhougen *et al.* 2003; Shah 2010; WHO 2018). Many enslaved and poor men had little choice but to work in low-lying agricultural fields and reside in unsanitary conditions—like animal pens and temporary shelters—during peak malaria seasons, increasing their risk of exposure to vectors that bite humans and livestock at dusk (Joshel 2010). By contrast, wealthy elite Romans had greater mobility and access to sanitary spaces, and were able to avoid the regular epidemics that overtook urban areas in the summer and fall by fleeing to higher-altitude (cooler) rural estates (Sallares 2002). Further, both free and enslaved women in the ancient Roman world were mostly confined indoors and away from swampy, countryside environments (Knapp 2011), which, while oppressive, likely decreased women's exposure to malaria relative to those enslaved and non-elite men, the majority of whom were compelled to live and work in high-risk spaces.

Malarious environments influenced human settlement patterns and infrastructure development. The Bronze Age Nuragic civilization (1700–238 BCE) on the island of Sardinia adapted their housing and agricultural practices to deal with malaria (Brown 1986; Setzer 2010). While most

pastoralist cultures reside in lowlands near the most productive grazing grounds, the Sardinian pastoralists instead practiced inverse transhumance, in which settlements and summer grazing occurred in high-elevation areas, and lowlands were grazed only during winter months with lower malaria risk (Brown 1981, 1986). Moreover, rules restricting women, especially pregnant women, to the home and away from the more malarious countryside may have represented a cultural adaptation to avoid the most severe morbidity and mortality from malaria (Brown 1986).

(ii) Post-Columbian South America

Malaria likely altered settlement patterns throughout the Americas, particularly in the Amazon basin (Sawyer 1993). Malaria vectors in the Americas thrive in recently deforested areas and forest edges on the fringes of rural settlements (de Castro *et al.* 2006; Vittor *et al.* 2006, 2009; Sallum *et al.* 2019). By reducing the health and productivity of subsistence farmers in the Amazon (Sawyer 1986, 1993; Singer & de Castro 2001), malaria may have prevented successful establishment and consolidation of large, permanent settlements. These impacts on the success of colonization projects in the Amazon may have indirectly protected much of the interior of the Amazon from development during the colonial period. Even today, evidence from Brazil suggests that, particularly in the interior of the Amazon, malaria continues to be strongly associated with deforestation and reduces rates of forest clearing where incidence is highest (MacDonald & Mordecai 2019).

(iii) American Colonial Period, Revolution, and Civil War

During the Atlantic Slave Trade, malaria played a crucial role in entrenching social and racial hierarchies between White slaveowners and enslaved African people. In the American colonies, the cost of African slaves depended on the perceived strength, physical fitness, age, and sex of the individual (Kotlikoff 1979; Littlefield 1991). Those who were resistant to malaria due to previous exposure in their homeland were viewed as more valuable in malaria-infested U.S. states than those with no resistance (Esposito 2015). Thus, acquired resistance was commodified, and malaria-exposed African individuals commanded higher prices on the slave market (Esposito 2015; "Louisiana, Slave Records, 1719-1820").

Differential resistance to malaria impacted the outcome of the American Revolution (1765–1783). While most British troops had no previous malaria exposure, many American militiamen of the Continental Army had acquired resistance through repeated exposure growing up in the South (McNeill 2010). The susceptibility of British soldiers to malaria contributed to the failure of Southern campaigns and defeat at Yorktown, a key turning point in the war (McNeill 2010). In the Carolinas, the Lowcountry landscapes of irrigated rice plantations created an ideal environment for *Anopheles* mosquitoes (McCandless 2007). After besieging Charleston early in 1780, British general Charles Cornwallis found his troops in a hostile, unfamiliar environment, with less than half of his troops healthy and able to fight, leading to his eventual surrender at Yorktown (McNeill 2010). With this defeat, the scales of the Revolutionary War tipped in favor of the Americans.

In the bloodiest American conflict in history—the American Civil War (1861–1865)—two-thirds of the 488,000 soldiers who perished died of disease, most of which was vector-borne

(Lockwood 2012). Malaria negatively impacted both sides in the Civil War, forced campaigns to be abandoned, and prolonged the conflict (Bell 2010). For example, during the campaign to take Vicksburg in 1862, Union General Winfield Scott encouraged waiting until November, after the "return of frosts," which would reduce fevers in latitudes below Memphis (Lockwood 2009). When his advice was ignored and the campaign began in the summer, malaria decimated Union regiments, and the campaign failed. For their part, Confederate troops attempted to recapture Baton Rouge in August 1862 following Union retreat from Vicksburg, but unexpectedly lost two-thirds of their troops while en-route, largely to malaria, allowing Union troops to narrowly escape defeat (Steiner 1968). Malaria incapacitated a large number of soldiers such that campaigns were postponed, lengthening the war and resulting in more battles, deaths, and time as a nation in turmoil (Sartin 1993).

(iv) Modern Global Conflict

Malaria similarly prolonged World War II and the Vietnam War. World War II had the largest number of military and civilian casualties in human history, between 65–75 million deaths (Leitenberg 2006). Malaria contributed to this mortality by lengthening the war and affecting both Allied and Axis Powers. The intensity of malaria in the Pacific resulted in forced surrenders of U.S. troops in Bataan, Philippines and evacuations of Japanese forces from the island of Guadalcanal (Joy 1999). Similarly, malaria prolonged the Vietnam War (1955–1975) by delaying missions on both sides. U.S. troops reported over 24,000 individual cases and took nearly 400,000 sick-days due to the disease (Beadle & Hoffman 1993). The prevalence of malaria among Viet Cong units was around 50–75%, and some sources posited that troops raided plantations and dispensaries for drugs to treat symptoms (Bruce-Chwatt 1985).

406

407 Responses to war-related malaria outbreaks domestically in the United States had a major impact
408 on public health policy. The Malaria Control in War Areas (MCWA) program was established to
409 manage malaria around military bases in the Southern U.S. to minimize lost productivity.
410 MCWA trained local and state health department officials on control techniques. This led to the
411 creation of what has become the Centers for Disease Control and Prevention (CDC) in 1946,
412 with the primary mission of preventing malaria spread across the nation (Parascandola 1996).
413 Throughout the 20th century and today, the CDC has focused on disease prevention and
414 surveillance—a fundamental component of U.S. public health.

415

416 **(v) Modern Environmental Management**

417 Malaria played a major role in redesigning water management and environmental practices. In
418 the 1930s, the Tennessee Valley Authority practiced mosquito control by storing winter
419 rainwater in upstream tributaries and releasing it as the mosquito breeding season arrived to
420 reduce the effect of dams on malaria transmission (Kitchens 2013). Similarly, managers of
421 Ethiopia's Koka Reservoir lower water levels quickly at the end of the wet season to dry out
422 mosquito breeding habitats, reducing malaria incidence with minimal effects on hydropower
423 generation (Endo & Eltahir 2018). Such water management techniques have spread to agriculture
424 (e.g., rice cultivation), with the alternate wet/dry irrigation method now common in Asia to lower
425 VBD spread and save on water costs (van der Hoek *et al.* 2001).

426

427 The widespread misuse and ecological damage wrought by dichlorodiphenyltrichloroethane
428 (DDT) and other compounds for malaria control led to increased environmental awareness and

protection laws. Annual DDT use soared above 70 million tons by the late 1950s due to global malaria eradication efforts (Trigg & Kondrachine 1998), causing serious ecological damage that galvanized Americans to take pro-environmental action (e.g., Rachel Carson's 1962 book *Silent Spring*) and shifted cultural attitudes toward the environment (Stapleton 2004; Maguire & Hardy 2009). As a result, nongovernmental organizations such as the Environmental Defense Fund and federal organizations like the U.S. Environmental Protection Agency were founded in the 1960s to enact environmental legislation, culminating in the ban of DDT usage in the United States in 1972 (Wurster 1973). In this way, early environmentally destructive vector control efforts ushered in a wave of pro-environmental action at both grass-roots and institutional levels.

Yellow Fever

Disease Ecology

Yellow fever is an acute viral disease with symptoms including hemorrhaging, jaundice, vomiting, muscle pain, and often death (McGuinness *et al.* 2017). The causative agent is yellow fever virus (YFV), an RNA flavivirus (Barnett 2007). The disease is endemic in tropical regions of the Americas and Africa and is maintained in a sylvatic cycle of transmission between non-human primates and tree-hole breeding mosquitoes (Barrett & Monath 2003). Spillover from the sylvatic cycle can result in urban outbreaks of yellow fever with transmission primarily between humans and *Aedes aegypti* mosquitoes (although *Ae. albopictus* have been demonstrated as a competent vector) (Miller *et al.* 1989). In Africa, an intermediate or savannah cycle has been identified with mixed transmission between mosquitoes, humans, and non-human primates (Barrett & Monath 2003). Historically, *Ae. aegypti* thrived in sugar and other monoculture plantations that provided ample storage containers for mosquito breeding and had fewer

452 insectivorous birds compared to forests (Fig. 2) (McNeill 2010). Children are more likely than
453 adults to survive infection, which confers long-term immunity. As a result, differential immunity
454 to yellow fever played a major role in human culture and conflict, particularly before the
455 discovery of the mosquito transmission cycle and a highly effective vaccine in the early 20th
456 century (McNeill 2010).
457
458 **(i) Colonization and Empire in the Americas**
459 Yellow fever was a key driver of socio-demographic change and institutionalization of Black
460 slavery in the Caribbean in the 17th century. During this time, yellow fever arrived in the
461 Americas from Africa with the rise of transatlantic shipping, trade, and travel. When English
462 settlers arrived in Barbados in 1627 to establish a colony (Gragg *et al.* 2003), they initially relied
463 on White indentured servant labor, until a 1642 treaty allowed access to Portuguese slave
464 dungeons on the African coast (Great Britain & Chalmers 1790). Soon, slave vessels—along
465 with *Ae. aegypti* mosquitoes and YFV—arrived and colonized the hospitable tropical island,
466 causing a major yellow fever epidemic by 1647 (Cray 2015). While European servants died by
467 the thousands, enslaved people of African origin remained largely unaffected, probably due to
468 immunity from previous exposure (Opal & Opal 2019). Planters replaced lost labor from
469 European servants by enslaving more African people, and White British emigrants became
470 hesitant to move to Barbados. YFV thus positioned African slavery as the island's primary labor
471 system and rendered Barbados the first fully-fledged slave society in the British Empire. The
472 Barbados Slave Code of 1661 provided the legal framework for slavery and was extended to
473 other British Caribbean islands (e.g., Jamaica) and Southern colonies that would become U.S.

states (e.g., Virginia and South Carolina) (Nicholson 1994). YFV spread to other Caribbean islands through commerce.

Differential immunity to yellow fever aided native Haitians in their fight for independence from France in the turn of the 19th century. The economy of Saint-Domingue—the French colony on the western half of the island of Hispaniola—was based on sugar and coffee plantations that depended on African slave labor, making it the richest colony in the world (Perry 2008). Toussaint L'ouverture, a former slave who governed in the name of the French Republic, led slave revolts between 1791 and 1804, drawing French troops into guerrilla battles away from the safety of their coastal enclaves and resupply ships, where they were vulnerable to yellow fever (Bell 2009). Emperor Napoleon Bonaparte attempted to quash the revolution by deploying 23,000 soldiers to Haiti in 1801 (Bollet & Jay 2004). Yellow fever disproportionately killed and debilitated the immunologically naïve French, and by 1803 had also killed an estimated 10,000 replacement soldiers. Haiti gained independence in 1804, which was followed by the massacre of the remaining White colonizers (Girard 2011). Haiti created a "terrified consciousness" among slave-owners in the Americas and was the first successful slave uprising that led to the establishment of a new country ruled by former captives and free from slavery (Maingot 1996). Realizing major defeat in the Americas and fearing further losses, Napoleon sold the Louisiana territory to the United States and withdrew from the continent. Ironically, just five years later Napoleon would use VBD (primarily malaria) as a weapon against the British in the invasion of Walcheren, Netherlands, as described in the Introduction.

(ii) Industrial Revolution in North America

Yellow fever played an integral role in shaping urban and sanitation systems. In 1793, Philadelphia was a cosmopolitan city with high population density (50,000 residents), but it had few safeguards to handle a deadly yellow fever outbreak that originated from French colonizers fleeing the Haitian rebellion and claimed over 5,000 lives (Foster *et al.* 1998). Dock Creek, a tributary of the Delaware River, had been converted to an open sewer and citizens believed that dirty well water caused yellow fever (Gum 2010). Seeking a solution, the city government's Watering Committee commissioned Philadelphia's first municipal water system in 1800, which resulted in the installation of public hydrants, wide availability of potable drinking water, and an end to unhygienic water collection practices (Donaldson 1987). Philadelphia replaced granite and asphalt streets with cobblestone, constructed storm sewers, installed hundreds of miles of sewage pipes, instituted trash collection, and implemented regular house inspections across the city and state (Higgins 2016). The newly-created Board of Health became equipped to handle complex tasks like enforcing vaccination of children against diseases like smallpox, chlorinating the city's water supply, and producing diphtheria antitoxin, setting the foundation for parts of the modern-day U.S. healthcare system (Higgins 2016).

Yellow fever immunity uniquely affected social hierarchies, as illustrated in New Orleans during the 19th century. During this period, roughly half of all individuals who contracted yellow fever died. As a result, the concept of immunocapital—a socially acknowledged lifelong immunity to this highly lethal virus—took hold (a term coined by Olivarius 2019). In contrast to how plague reduced inequality by undermining the feudal system, yellow fever reinforced inequalities. White men with demonstrable immunity were deemed worthy of investment and granted access to previously inaccessible realms of economic, political, and social power (Olivarius 2019).

However, immunocapital was not racially consistent. Physicians monitoring yellow fever cases noted lower death rates of Black individuals as compared to White individuals (Olivarius 2016). White proponents of slavery twisted these statistics to argue that Black people had a duty to be enslaved into strenuous labor because of their alleged natural resistance to yellow fever, and impeded the upward social mobility of Black individuals. Immunity therefore translated into immunocapital for the White population, but not for the Black population.

In the American South more broadly, yellow fever was a substantial burden on economic development between 1840 and 1905 (Humphreys 1999). A large proportion of the South's foreign commerce consisted of agricultural products grown in tropical regions with high yellow fever rates, such as fruit and coffee (Sterns 1900). The prevailing debate centered on balancing the protective public health effects of shipping quarantine versus the negative economic effects of halting trade. Business in the South was a risky endeavor, as the stringency of quarantines fluctuated with public anxiety. These circumstances discouraged northern investment, paralyzed productivity of ports, and inhibited distribution of goods from urban to rural regions (Humphreys 1999). Further, an 1878 yellow fever epidemic caused mass emigration from urban centers like Memphis, Tennessee, halting economic activity almost entirely (Evans 2012).

(iii) Expansionism in Central America

Creating a water passage across the isthmus of Panama to link the Atlantic and Pacific Oceans held strong economic and political appeal. When the French first undertook the Panama Canal project in 1880–1888, they lost 22,000 lives to yellow fever and ultimately abandoned the effort (Jeffs 2014). After a significant delay from the devastating mortality of yellow fever, the United

States spearheaded a new campaign to build the canal in 1904, equipped with the new knowledge that mosquitoes transmit the disease. Colonel William Gorgas of the Canal Commission led an effort to eliminate mosquito populations in Panama through mosquito brigades that removed objects that collected stagnant water, sprayed houses with insecticide, and treated stagnant pools with oil and larvicide (Heitmann 1991; Cope 2005). The local elimination of yellow fever in November 1906 enabled the United States to complete the Panama Canal in 1914, providing control over the most efficient trading route between the Pacific and Atlantic oceans (Jeffs 2014).

Trypanosomiasis

Disease Ecology

Two different diseases caused by parasitic trypanosomes have had significant impacts on human history: African sleeping sickness and Chagas disease. We primarily focus on African sleeping sickness, due to the abundance of available evidence, followed by a brief discussion of Chagas disease and its potential impacts in South America.

African trypanosomiasis is caused by three *Trypanosoma brucei* subspecies and transmitted by tsetse flies (*Glossina palpalis* and *G. morsitans*) to both humans and ruminants. Symptoms include fever and joint pain, which can progress to behavioral changes, poor coordination, and death. Historically, it occurred in the tsetse fly-belt of tropical Africa, with *T. b. rhodesiense* in East Africa and *T. b. gambiense* in coastal West Africa and drainages of the Congo and Niger Rivers. *T. b. brucei* causes animal trypanosomiasis ("nagana"), which lowers productivity and increases livestock mortality. The primary historical impacts of trypanosomiasis are via effects

566 on livestock rather than on humans. Further, the tsetse fly's relatively low reproduction rate and
567 breeding site preference for loose soil prevented it from migrating out of Africa—unlike many
568 disease-vectoring mosquitoes—and resulted in profound effects on human history that were
569 constrained to Africa (Alsan 2015).
570
571 American trypanosomiasis, or Chagas disease, is caused by *Trypanosoma cruzi* and is spread by
572 Triatominae insects. Chagas disease is endemic to South America, Central America, and Mexico
573 and currently infects an estimated 7–8 million people (Steverding 2014). Chagas manifests in
574 both acute and chronic forms; while the acute phase is often asymptomatic and constitutes a
575 small (3%) proportion of Chagas-related deaths (Martins-Melo *et al.* 2012), many of the 15–30%
576 of infected people who develop chronic symptoms will suffer organ damage and heart failure
577 10–25 years after their first infection (Barrett *et al.* 2003).
578
579 **(i) Paleolithic Africa**
580 The evolutionary history of African trypanosomes, tsetse flies, and their mammalian hosts is
581 long and has influenced human history throughout sub-Saharan Africa. The trypanosomes
582 responsible for nagana and African sleeping sickness evolved around 380 million years ago.
583 Their transmission to mammals arose as early as 35 million years ago, when the tsetse fly vector
584 evolved. Due to this long shared evolutionary history, many native African wildlife are
585 "trypanotolerant," (i.e., can be infected but show no signs of disease), and serve as reservoir
586 hosts that can infect vulnerable non-native, domesticated cattle (Lambrecht 1985; Steverding
587 2008). During the Paleolithic Era in Africa, trypanosomiasis likely influenced where people
588 settled, creating geographical barriers to movement. Early savannah-dwelling humans may have

589 recognized that biting tsetse flies congregate in certain patches of vegetation, and avoided areas
590 with high concentrations of flies (Lambrecht 1964). High density fly-belts could have effectively
591 functioned as a barricade for human occupation.
592
593 **(ii) Ancient Egypt**
594 Evidence of African trypanosomiasis arises from the Veterinary Papyrus of the Kahun Papyri
595 from around 2000 BCE, where text describes cattle with nagana-like symptoms and ointments
596 used as treatment against biting tsetse flies (Griffith 1898; Ebel 1937; Steverding 2008).
597 Pastoralists in ancient Egypt may have been able to transition from raising native purebred and
598 trypanotolerant cattle (*Bos primigenius*) to imported Indian zebu cattle (*Bos indicus*) only after
599 the course of the Nile River was physically altered, destroying the habitat of the tsetse fly vector
600 (Steverding 2008).
601
602 **(iii) Pre-Colonial Africa**
603 The effects of tsetse-transmitted trypanosomes on agriculture and society shaped the pre-colonial
604 history of Africa and set the stage for future colonization. Nagana limited the use of
605 domesticated animals as sources of draft power, and ethnic groups who inhabited tsetse-suitable
606 land were less likely to use plows (Alsan 2015). This exclusion of livestock precluded intensive
607 farming, large agricultural surpluses, and the ability to readily transport goods across land (Nash
608 & Others 1969; Diamond 1999). Together, these factors influenced human settlement structure,
609 altered labor specialization, and decreased fiscal capacity in Africa (Alsan 2015). Without
610 surplus crops to support a ruling class and a tax base to support central authority, people in
611 tsetse-suitable areas with higher burdens of trypanosomiasis were less likely to form politically

centralized states (Alsan 2015). Given that pre-colonial African political centralization is positively correlated with modern economic development (Gennaioli & Rainer 2007; Michalopoulos & Papaioannou 2013), studies have argued that these areas remain less developed today due to historical effects of nagana (Alsan 2015).

One hypothesis for why early colonization of Africa by Arabic peoples did not spread more widely is the difficulty of travelling through, developing agriculture in, and establishing settlements within the tsetse fly-belt. Documents from 1373–1374 reveal that King Mari Diate II, ruler of the Mali Kingdom, was overtaken by "illat an-nawm," or sleeping sickness (Lambrecht 1964). Trypanosomiasis also determined the geographic range of the Great Zimbabwe civilization (1000–1400 CE). Located on a plateau between the Limpopo and Zambezi rivers, the settlement is a "peninsula in a sea of tsetse" according to archaeologist Tim Connah (Connah 1987). Analyzing the climatic range of the tsetse fly, other archaeologists have suggested that these limits align with the boundaries of the pastoral civilization (Garlake 1978; Rogers & Randolph 1988). These qualitative writings, along with econometric analyses, provide evidence that African development of cities and centralized governments would have advanced more without the effects of trypanosomiasis (Alsan 2015).

African trypanosomiasis affected the routes of migrating pastoralists throughout the 1500s CE. In the Rift Valley, the main route of travel was on either side of the valley, down the high ridge country (Lambrecht 1964), probably because this path was tsetse-free and preferred by livestock-owning pastoralists. Resting places and water-holes along commonly used migration lines likely became permanent settlements and marketplaces for trade. Entomologists and antiquarians, such

as Claude Fuller and B.H. Dicke, have given accounts of struggles in South African fly-belts (Fuller & Others 1923; Dicke & Others 1932). Similarly, migratory patterns of pastoral groups in the Sahel edge were heavily affected by seasonal shifts of tsetse fly-belts (Ingold 1987). The tsetse fly probably impeded the spread of pastoralism in Africa (Alsan 2015). Archaeological evidence highlights stalled diffusion of domestic animals as compared to ceramics, probably due to trypanosomiasis (Gifford-Gonzalez 2000). The survival advantage of wild game over domesticated animals might have encouraged hunting and gathering over food production reliant on animal husbandry.

(iv) Colonial and Imperial Africa

During the 1400s and 1500s CE, Portuguese explorers launched expeditions into East Africa's interior, but trypanosomiasis acted as a barrier to colonization. The Portuguese were forced back due to deaths of their horses and camels from trypanosomiasis and malaria. Paleoecological literature suggest that the history of Africa would look quite different if, from the 1400s onwards, western explorations were not confined to coastal areas by trypanosomiasis and other disease hazards in the continental interior (Lambrecht 1964). In 1742, the British naval surgeon and colonialist John Atkins described a disease likely to be African sleeping sickness in enslaved people on the Guinea Coast taken from the forest interior (Lambrecht 1968).

Signs of human trypanosomiasis were documented and used to select people for enslavement for centuries by the first Arabic colonizers. This approach was formalized following British physician Thomas Winterbottom's medical reports in 1803 on enlarged glands and nodules on the back of the neck, used to discriminate among people to be enslaved in Sierra Leone

(Steverding 2008). Those identified as infected were not taken as slaves because they were unlikely to survive the Atlantic crossing and were seen as less healthy and productive for labor. Slave dealers also helped spread human trypanosomiasis by disintegrating large settlements into smaller, dispersed communities either directly from raiding or indirectly from inciting fear (Fage & Oliver 1970). Additionally, caravans of enslaved people infected with trypanosomiasis were led through coastal markets and introduced the disease to naïve areas (Lambrecht 1964).

(v) Chagas Disease in South and Central America

While less is known about the impacts of American trypanosomiasis on human history, evidence suggests that Chagas disease affected civilizations for nearly 10,000 years (Steverding 2014). Tissue analyses show that 40% of human mummies from northern Chile and southern Peru were infected by *T. cruzi*, spanning eleven cultural groups over 9000 years (7050 BCE until 1500 CE) (Aufderheide *et al.* 2004). The widespread distribution and high prevalence suggests that Chagas disease had large impacts on these societies. Moreover, its potential cultural significance is demonstrated by 13th–16th century Peruvian ceramics that appear to depict sufferers of the disease (Diaz *et al.* 2011; Steverding 2014). Chagas disease in the Americas is closely linked to anthropogenic change, as deforestation and settlement brought humans and vectors into closer contact (Steverding 2014). This has led to a societal dichotomy over time, whereby settled societies exhibited relatively high disease burden, while Amazonian indigenous groups that used different types of dwellings without domesticated animals were able to avoid Chagas disease throughout much of their history (Aufderheide *et al.* 2004; Briceño-León & Méndez Galván 2007).

Discussion

Vector-borne diseases have shaped the course of human history and continue to impact society today through their effects on (1) outcomes of colonialism, imperialism, war, and conflict; (2) human interactions with the environment; and (3) intrasocietal human interactions. Distributions of VBDs, and their resulting impacts on human history, depend on the interplay between ecological conditions, vectors, and human interactions with the environment. Plantation ecology in the Americas promoted yellow fever, which in turn canalized slavery and inequality and played a central role in colonial power struggles. Lowland habitats in North America and Europe as well as in tropical regions of Africa, Asia, and the Americas supported a devastating burden of malaria that shaped war, pastoral traditions, environmental degradation, and conservation movements. Trypanosomiasis constrained the economic and developmental trajectory of sub-Saharan Africa by preventing use of domestic animals, thereby favoring decentralization, inhibiting industrialization, and leaving societies more vulnerable to colonization. Plague pandemics repeatedly cropped up in and decimated large, urbanized societies, upending civilizations from 5500 BCE through the Middle Ages. These profound impacts are not restricted to the past: VBDs continue to impose a major burden ("Lancet Global Burden of Disease" 2020), even as increased human population growth, demand for natural resources and land conversion, and climate change fuel VBD transmission and emergence (Patz *et al.* 2004).

Predicted climate-driven expansion of suitable areas for disease could further alter human settlement patterns by shrinking or eliminating disease refugia. Within the tropics, VBDs may

704 have historically driven humans to settle in highland regions that are too cool for optimal
705 transmission. While we lack direct evidence that malaria determined elevational settlement
706 patterns, it is notable that many major cities in Africa and the Americas are located at or above
707 the upper range of the malaria epidemic zone (1500-2500m), including Addis Ababa, Ethiopia
708 (2362m), Nairobi, Kenya (1728m), Kigali, Rwanda (1567m), Bogota, Colombia (2619m), Quito,
709 Ecuador (2850m), Guatemala City, Guatemala (1529m), and Mexico City, Mexico (2216m).
710 Climate warming is projected to increase suitability for malaria and other VBDs in these regions
711 (Ryan *et al.* 2015, 2019); evidence already supports the projected increase in malaria burden in
712 highland regions of Colombia and Ethiopia (Siraj *et al.* 2014). Therefore, the locations of major
713 cities, which may represent historical adaptation to disease, pose a modern problem as
714 anthropogenic pressures change the landscape of infectious disease.
715
716 Several VBDs are becoming more widespread, causing more human suffering but also sparking
717 new ideas to fight disease in environmentally friendly ways. Global trade and travel combined
718 with increased climate suitability has promoted the worldwide emergence of dengue,
719 chikungunya, and Zika, transmitted by the globally invasive (peri)urban mosquitoes *Aedes*
720 *aegypti* and *Ae. albopictus* that continue to shape history (Gubler 1998; Ali *et al.* 2017). The
721 2016 Zika pandemic, which caused over 200,000 confirmed cases (PAHO/WAHO 2017),
722 dramatically affected reproductive rights and contraceptive access due to the connection between
723 infection during pregnancy and congenital Zika syndrome (Sherwood 2016; Romero *et al.* 2018),
724 decimated tourism and economies in Latin America and the Caribbean (Gallivan *et al.* 2019),
725 and prompted renewed public interest in addressing the societal effects of infectious diseases
726 (Ali *et al.* 2017). Dengue fever affects an estimated 96 million people a year (Bhatt *et al.* 2013),

727 primarily those living in poverty (Torres & Castro 2007; Bonds *et al.* 2010). Dengue has led to
728 major developments in biotechnology with efforts to use genetic modification and *Wolbachia*
729 infection in mosquitoes to prevent virus transmission (Hoffmann *et al.* 2011). Whereas past
730 vector control methods like DDT would affect whole ecosystems, these new developments are
731 more targeted, leaving the rest of the ecosystem intact. At the same time, to the extent that VBDs
732 like malaria and yellow fever previously impeded encroachment into wildland areas, biomedical
733 and technological solutions could cause unanticipated environmental harm by opening them to
734 development.
735
736 The effects of VBDs also apply to other types of infectious disease, including directly-
737 transmitted pathogens like SARS-CoV-2, the viral agent of COVID-19. The ongoing pandemic
738 has altered human interactions with the environment by drastically reducing travel and carbon
739 emissions, improving air quality (Chen *et al.* 2020; Sharma *et al.* 2020). Responses to the
740 pandemic have impacted daily lives and social interactions through unemployment, working
741 from home, avoiding handshakes, wearing masks, and reducing in-person activities. As with
742 yellow fever, COVID-19 has reinforced social and racial hierarchies, as many salaried workers
743 safely work from home and maintain their income, while blue collar, service, and gig workers
744 have been laid off in unprecedented numbers or must risk exposure to the virus to earn a living
745 (Marshall & Barber 2020). Overwhelmingly, the highest COVID-19 death tolls have occurred in
746 predominantly Black and Hispanic communities, largely as a result of preexisting socioeconomic
747 and health disparities (Villarosa & Kasimu Harris 2020). The society that emerges from the
748 COVID-19 pandemic will be one unequivocally altered by infectious disease.
749

750 The impacts of VBD on human society continue to shape our world. Since the chikungunya and
751 Zika epidemics of 2013–2017 took the global health community by surprise, discussion has
752 centered on anticipating the next waves of VBD, which include *Ae. aegypti*-vectored viruses like
753 Ross River and Mayaro viruses, pathogens exported from war zones such as leishmaniasis in
754 Syria, or even more obscure "unknown unknowns." The unexpected nature of these outbreaks,
755 combined with their inequitable effects, makes future social, economic, and cultural impacts of
756 (re)emerging and expanding diseases almost inevitable. Major public health surveillance and
757 control efforts are warranted for mitigating the worst health, social, and environmental
758 consequences of these epidemics.
759
760

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Boxes

Box 1. Mechanisms of VBD transmission

Transmission of VBDs to humans results from interactions among arthropod vectors, pathogens, human and/or non-human hosts, and the environment. For pathogens to be transmitted, vectors must be abundant, come in contact with infected human or non-human hosts to acquire the pathogen, and bite uninfected human hosts, who either continue the chain of transmission or end the cycle as dead-end hosts (Baum 2008). Vector population size, physiology, behavior, and competence to transmit pathogens are influenced by abiotic and biotic factors, such as habitat type, climate, predation, and competition (Moore *et al.* 2010; Couret *et al.* 2014; Ferraguti *et al.* 2016; Mordecai *et al.* 2019; Shocket *et al.* 2020). In particular, because of the partially aquatic life cycle of mosquitoes and many other vectors, vector abundance often depends on freshwater availability and water storage practices (Poh *et al.* 2019).

Human behavior interacts with environmental factors to affect disease transmission. For example, human modification of the physical environment can drive vector breeding habitat availability. Some vector species (e.g., *Anopheles* spp. mosquitoes) thrive in agricultural contexts and breed in ditches, canals, irrigated fields, and lowland freshwater swamps, while other species (e.g., *Aedes aegypti* mosquitoes) breed in abandoned containers (e.g., bottles, jugs, toilets, tires) and in contaminated aquatic systems (Zahouli *et al.* 2017; Du *et al.* 2019). Dense human populations in built environments such as urban centers, army barracks, and ships can facilitate contact between vectors and human hosts (Willoughby 2017). In turn, people may respond to real or perceived disease risk in the environment by distancing themselves, emigrating, or abandoning settlements in regions with high burdens of disease ("disease avoidance").

Finally, VBD dynamics depend on human disease susceptibility. Many pathogens induce some degree of immunity or resistance following infection, resulting in periodic epidemic cycles within populations as susceptibility waxes and wanes. When populations with differing disease histories come into contact, differential immunity to shared pathogens may cause asymmetric effects within and between populations (McNeill 2010). Together, these processes—abiotic factors, human behavior, and host susceptibility—combine to determine transmission and VBD burden in a given location (Bayoh & Lindsay 2004; Alto & Bettinardi 2013; Paaijmans *et al.* 2013).

Box 2. Glossary of relevant disease ecology terms

Vector: Organism that functions as a carrier of pathogens between organisms of a different species, including mosquitoes, ticks, fleas, and tsetse flies

Pathogen: A disease-causing agent, including bacteria, viruses, fungi, protozoa, and other infectious organisms

Host: An organism that harbors a pathogen, often with some energetic or fitness cost; in the context of this paper, hosts may include humans or other animals

Vector ecology: Study of arthropods that transmit pathogens, the interaction between such arthropods and disease-causing organisms, the impacts of the environment on their physiology and behavior, and their contact with humans

Vector competence: Ability of vectors to acquire, maintain, and transmit pathogens to hosts

Vector breeding habitat: Areas that are suitable for vectors to reproduce; stagnant water is often an optimal habitat for mosquito vectors

Reservoir host: Non-human organisms that can harbor pathogens without a fitness cost and can contribute to pathogen spillover into human transmission cycles

Reservoir competence: Ability of an infected reservoir host to make the pathogen available to a

vector

Disease avoidance: Organisms tend to avoid infectious agents (including vectors), when feasible, since the biological benefits of remaining disease-free may outweigh the temporary costs of avoidance

Acquired immunity: Upon exposure to a pathogen, the host starts to develop immunologic memory to recognize the pathogen and to activate the immune system; reliant on highly specific antibodies that can prevent reinfection or limit disease symptoms upon reinfection

Innate immunity: Intrinsic resistance possessed by a host prior to exposure to a pathogen; the general, nonspecific immune response and defense mounted by the host

Differential immunity: State in which particular classes or groups of people are more susceptible to diseases than others

Built environments: Human-made structures and spaces in which people live, work, and recreate

Infrastructure: Basic organizational structures, facilities, and programs which are needed for the successful operation of a human society

Human-environment interactions: Ways in which humans and their social systems, decision-

making, and behavioral processes interact with the natural world

Land use change: Process of human activities transforming ecological landscapes

Social and racial hierarchies: Systems of social stratification that arise from the belief that certain social classes or racial groups are superior to others

Figures and Tables

Note: Actual figures and tables are in the attached PDF and Word files. Below are the titles and captions.

Figure 1. Timeline of vector-borne disease impacts across history. Plague, malaria, yellow fever, and trypanosomiasis have affected human history from the Paleolithic era to the modern age; case studies highlighted for Africa (orange), Asia (yellow), South America (red), North America (blue), Europe (green), and Australia (purple).

Figure 2. Sugar plantation ecology promoted *Aedes aegypti* mosquito life cycle and yellow fever virus transmission. Plantations in settlements in the Americas provided ample vector breeding habitat containers, and indoor resting and biting adult mosquitoes came in frequent contact with humans. Blood-fed female mosquitoes would lay their eggs in water containers, which over time would develop into larvae, and later pupae. Finally, adult mosquitoes emerge from the pupae and close the life cycle. *Ae. aegypti* primarily bite at dawn and dusk and usually indoors where humans are still sleeping.

Table 1. Diseases by categories of influence. Examples in which plague, malaria, yellow fever, and trypanosomiasis affected the outcome of colonialism and war, human interactions with the environment, and intrasocietal interactions across geographic regions and historical time periods.

Table 2. Historical time periods, associated ecological characteristics, and VBDs. The unique ecological and human social context of the time period set the stage for each focal disease.