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Biocultural perspectives of infectious diseases and demographic evolution: Tuberculosis and its comorbidities through history

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Abstract

Anthropologists recognize the importance of conceptualizing health in the context of the mutually evolving nature of biology and culture through the biocultural approach, but biocultural anthropological perspectives of infectious diseases and their impacts on humans (and vice versa) through time are relatively underrepresented. Tuberculosis (TB) has been a constant companion of humans for thousands of years and has heavily influenced population health in almost every phase of cultural and demographic evolution. TB in human populations has been dramatically influenced by behavior, demographic and epidemiological shifts, and other comorbidities through history. This paper critically discusses TB and some of its major comorbidities through history within a biocultural framework to show how transitions in human demography and culture affected the disease-scape of TB. In doing so, I address the potential synthesis of biocultural and epidemiological transition theory to better comprehend the mutual evolution of infectious diseases and humans.

KEYWORDS
biocultural anthropology, comorbidities, demographic evolution, epidemiological transitions, tuberculosis

1 | INTRODUCTION

To fully understand health and disease means to deeply understand the cultural and ecological contexts in which they exist. Infectious diseases are critical actors in shaping the human condition and vice versa, but while there is some prominent anthropological scholarship dedicated to infectious disease research, it is a relatively underrepresented focus of biological anthropology despite its significant contributions to understanding human health. Some scholars have emphasized the need to study diseases, social conditions, behavior, culture, and ecology as nonmutually exclusive entities, citing the fact that health exists on a continuum.[1–4] To understand the contemporary relationship between human infectious diseases, we must consider the intersecting historical and evolutionary trajectories of disease comorbidities, demography, and culture.[5]

Tuberculosis (TB) has been a constant companion of humans for millennia and has been with us through—and has helped shape—every major demographic and cultural shift. Given the complex biological nature of the human TB disease processes and their coevolution with human culture, it is best understood via a reckoning of its common infectious comorbidities and the social, cultural, and political economic forces that perpetuate them. This understanding can be augmented by a deeper engagement with the long-term coevolution of biology, demography, and infectious pathogens through a biocultural evolutionary perspective.

The purpose of this paper is to argue for a stronger role of biocultural anthropology in the study of infectious diseases for a more comprehensive understanding of the mutually coevolving relationships of humans, culture, demography, and disease using human pulmonary TB and some, but not all, of its major comorbidities

as specific examples of this complex, long-term relationships. Below, I review two theoretical frameworks that biological anthropologists use to research and interpret human health: biocultural anthropology and epidemiological transition theory. In doing so, I discuss the synthesis of these two approaches to encourage more holistic inquiry of the evolution of population health while centering the role of TB. I then give a brief biological overview of TB disease and identify points of intervention of the anthropological approaches to the study of TB. Finally, I examine TB and its contemporaneous comorbidities within the biocultural and epidemiological transition frameworks to (1) discuss why some conditions were more prevalent at specific times than others and (2) illustrate the coevolution of humans and TB disease to contextualize modern comorbidities.

2 | THEORETICAL APPROACHES TO DISEASE STUDIES

2.1 | Biocultural anthropology

The *biocultural* perspective emphasizes that the biological elements of anthropology, such as evolution and human biological plasticity, and the cultural elements of anthropology, such as social structures, economics, and globalization, not only coexist but perpetually coevolve.[6,7] Culture can become embodied and manifested as "local biologies," or distinct characteristics of the physical body that are exclusively the consequences of macrosocial socioeconomic forces.[8,9] In other words, human biology and culture are fundamentally integrated. This approach is used in the modern context because of global socioeconomic inequalities, health inequities, resource insecurity, and anthropogenic climate change that require a more macro-level, holistic perspective on human livelihood.[6] This perspective recognizes that modern population health does not exist in isolation but is rather the product of continuous evolution that has been driven, in part, by the human relationship with infectious diseases.

The biocultural perspective has gained popularity among anthropologists recently and has proven useful in many realms, including but not limited to the intersections of health and the spectra of gender and sex,[10] the impact of rapid socioeconomic change on infants and children,[11] and linking periodontal disease expression to nutrition and food insecurity.[12] There has been some notable work that has applied a biocultural framework to infectious diseases studies such as early work linking biology and culture to disease patterns in ancient Nubia,[13] the biosocial integration in the anthropology of infectious diseases,[14] discussions of syphilis in antiquity,[15,16] application of the socioecological model to the AIDS pandemic,[1] and recent applications of biocultural theory to increased vulnerabilities to COVID-19 among gender and sexual minorities.[17] Recently, Dimka and colleagues have outlined many ways in which biological and biocultural anthropology can contribute to holistic pandemic studies, specifically.[18] One of the earliest and most compelling biocultural analyses was about an infectious disease. Allison discussed the genetic basis for the prevalence of the sickle cell traits in locations in which malaria is hyperendemic and concluded that the trait persisted because the heterozygous genotype conferred protection against infection with *Plasmodium falciparum*, and therefore malaria disease.[19] Livingstone expanded on this and pointed out that the malaria vector in West Africa, *Anopheles gambiae*, is particularly drawn to the material used for building roofs in African villages and is ubiquitous in the area. The intensification of agriculture and destruction of surrounding natural habitats in West Africa had three consequences: (1) increase in human population density, and therefore an increase in hosts for *A. gambiae*; (2) increase in mosquito population size due to more opportunities to breed in pools of still water; and (3) loss of other large mammal hosts as a result of habitat destruction, diverting the mosquitoes' attention to primarily humans.[3] Livingstone was therefore able to illustrate that the evolution of high prevalence of the sickle cell trait was biocultural in nature, that is, it was driven by consequences of human behavior and was an adaptation to the persistent threat of malaria infection. Biocultural theory can further be applied to acute infectious disease epidemics and pandemics because culture shapes behavior, behavior contributes to pathogen transmission, and ecological contexts in which transmission occurs directly impact pathogen evolution.[20]

Some areas of anthropology engage directly with infectious disease dynamics, such as cultural approaches that consider non-biomedical health systems,[21,22] studies of HIV/AIDS,[23,24] and critical medical anthropological approaches grounded in ethnographic methods to understand the political economic drivers of infectious diseases, suffering, and inequality.[25,26] One of the most important prominent anthropological frameworks for understanding infectious diseases is *syndemics*, or the interactions of two or more pathogens, diseases, or social conditions that result in acceleration of degradation of health.[4,27,28] The biocultural framework does not detract from these approaches, but as a fundamentally evolutionary approach, it rather adds the essential element of temporal depth to contemporary conceptualizations of infectious diseases and human health. Moving forward, the human experience with infectious diseases should be included as persistent stressors that impact human biological and cultural evolution. This is especially pertinent in the study of epidemic and pandemic events, for which a biocultural perspective can provide insights into how catastrophic mortality impacts demography, health, and culture in the intervening generations, decades, and even centuries.[5,29]

2.2 | Epidemiological transitions

Early work on biocultural applications to understanding infectious diseases of antiquity, such as syphilis and other treponemal diseases, TB, and leprosy, was produced by Armelagos and colleagues.[13,30–33] Such work was done within the context of the *epidemiological transitions*, a framework that conceptualizes the evolution of human demography and epidemiology as punctuated by fundamental, irreversible changes in human behavior and culture.[33]

Before any major population transitions occurred, in a period referred to as the *Paleolithic baseline*,[33] human populations were characterized by low population densities and affliction with chronic disease pathogens that were specific to certain environments. Vital processes such as fertility and mortality of Paleolithic populations are difficult to discern[34]; demographic processes of modern hunter-gatherers have been used as analogies to this time period, but they should not be assumed to be a perfect model for those of prehistory.[35] It is generally accepted that population size and density were low, and vital processes were volatile. The small sizes of Paleolithic groups would have made them unable to sustain what we refer to as modern crowd diseases such as measles, mumps, influenza, and smallpox.[31–33] These diseases are easily transmissible and require a large population of susceptible hosts; epidemics would have run their course quickly in small hunter-gatherer populations, which was the singular mode of subsistence for most of human existence.[1] Skeletal pathologies that pre-date the onset of agriculture are rarely, if ever, associated with infectious diseases, and there is no evidence of TB in the bioarchaeological record during this time period.

The beginning of the Neolithic period (~12–10 kya) was the first marked shift in human population dynamics and is considered the time of the *first epidemiological transition*. The rise of an agricultural mode of subsistence led to increasing population size and density, increasing fertility and mortality, sedentism, and emerging crowd diseases.[32,36] The agricultural revolution was originally considered a time of improved population health, but further research has shown that this transition was one of increased nutritional deficiencies and infectious diseases.[37,38] The transition from hunting and gathering to food production led to significant increases in dental disease,[39,40] decreased skeletal robusticity,[41,42] and malnutrition.[43] Juengst and colleagues challenge this generalization, however, by showing that the transition to agriculture in the Titicaca Basin (Andes Mountains of Peru) led to health consequences not as a result of malnutrition, but rather from an increased disease burden and sanitation issues.[44] Sedentism in general allowed for the rise of vector-borne diseases such as malaria, yellow fever, and dengue fever due to close contact with pools of still water that sustained mosquito populations and destruction of natural environments, leading to closer proximity with vectors.[3,33] Proximity to waste deposits, irrigation, and fertilizing agricultural soils with human waste likely increased prevalence of schistosomiasis and cholera.[45] Upon closer proximity with domesticated animals, zoonotic pathogens that caused smallpox and measles could persist in the much larger, more dense populations. These diseases, along with TB and leprosy, were the major causes of death for millennia.

The *second epidemiological transition* occurred alongside industrialization first in Europe and North America in the mid- to late-19th century. The transition is characterized by a decrease in infectious disease mortality and a proportionate increase in chronic disease mortality.[46] Critically, the second epidemiological transition intends to explain the mortality component of the *demographic transition*, which is a population shift from high mortality and high fertility to an initial decrease in mortality followed later by a decrease in fertility, resulting in increases in population size and life expectancy, as represented in Figure 1.[47,48] One explanation of the infectious disease mortality decline was that population increases and health shifts observed in the 18th and 19th centuries were driven more by advances in sanitation and improved nutrition than by most other medical advancements (aside from the highly successful smallpox vaccine).[49] The argument was that infectious mortality declines, specifically of TB, had already occurred by the time biomedical advancements (e.g., antibiotics) became widespread.[49] This has been hotly debated for decades, with critics suggesting that conclusions were reached in an unscientific manner and without substantial evidence.[50,51] In the decades since, others have pointed out that the progression—and initiation—of the second epidemiological transition worldwide is highly variable and dependent on many cultural, behavioral, and political economic factors.[52]

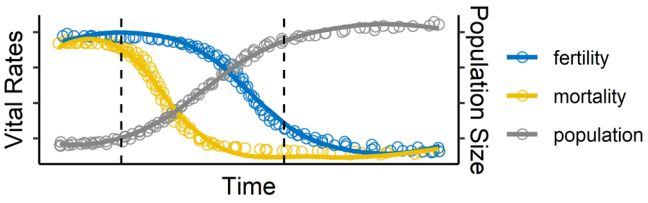

FIGURE 1 The demographic transition model.[47] The model shows (1) pretransition dynamics of high fertility and mortality with low population size; (2) a period of falling mortality followed by falling fertility coinciding with natural population increase; (3) a posttransition period of low fertility and mortality with larger population sizes. Axes indicate variable names but no specific quantities for "Time," "Vital Rates," or "Population Size."

In discussions of the demographic and epidemiological transitions, it is essential to highlight the fact that these models were developed and theorized with significant Western bias. In 1929, Thompson published the first discussion of the changing birth rates, death rates, and rates of natural population increase (the demographic transition, although he did not use this term) using data from Australia, India, New Zealand, Canada, the United States, Japan, and 16 European nations.[48] Notestein,[53] Davis,[54] and Kirk[47] all similarly made contributions to demographic transition theory but rarely, if ever, expanded the geographic or cross-cultural scope of the discussion. Additionally, Omran's classic paper from 1971 outlined the second epidemiological transition primarily with data from England and Wales and by superficially comparing observed trends to Japan, Ceylon (Sri Lanka), and Chile[46]; shortly after, he expanded the theory to the United States.[55]

In the 50 years since Omran's description of the second epidemiological transition, one of the primary critiques of the theory is that observations of decreasing infectious disease mortality and proportionately increasing chronic disease mortality are restricted to a particular set of historical circumstances, such as those faced by Western nations that were already industrialized.[32] Not all populations will experience a uniform transition in either timing or speed. In a review on how these concepts apply to the African continent,

Defo concludes that the fundamental components of both the demographic and epidemiological transitions are "*incomplete and irrelevant* for charting population health experiences… in the African context"[56] (emphasis added). Further, the implication that the linear march towards "modernity" is fundamentally good is highly flawed and, at its core, a colonial ideology. Populations are adapted to their specific ecological circumstances, and there may be myriad ways to model population health transitions.[57,58]

Finally, high-level discussions of population transitions overlook within-nation population heterogeneity, specifically, differences in morbidity and mortality experiences in urban and rural spaces, sex- and gender-based differences, and socioeconomic inequalities. For example, the focus on a rigid dichotomy of urban versus rural health overlooks the role of inequalities *within* urban spaces.[59,60] The lowest socioeconomic status groups within urban populations have been said to suffer a double burden of both old and new epidemiological profiles (infectious diseases, chronic diseases, and new and re-emerging diseases),[59] and on much higher levels than both affluent urban and rural populations.[60,61] These are important nuances to consider when discussing infectious disease dynamics in the biocultural context because they necessitate a deeper understanding of human social organization and the differential risks that exist not only between and among populations, but within them as well. By expanding the breadth of epidemiological transition inquiry to include the expansive variation in population adaptation, biocultural anthropologists may meaningfully apply the local biology framework to understand individual trajectories of demographic and cultural evolution—specifically as they apply to infectious diseases in health.

A *third epidemiological transition* was first characterized in the late-20th century by new and re-emerging infectious diseases.[32,33,36] The primary points of interest are (1) the recognition that new diseases are significant contributors to morbidity and mortality patterns and (2) diseases that were previously characterized as "receding," such as TB, are now re-emerging, this time with adaptations that make them less amendable to modern medical intervention.[33,36] Critiques of the description of this ongoing transition poignantly highlight the role of socioeconomic inequality and the conceptualization of health. For example, diseases characterized as "new" in the third transition may only be newly *described*.[33] Identification and description in recent years may be more dependent on the advancement of biomedical technology for isolation and identification. There are also consistently questions about categorizing diseases as "new" when some epidemics are truly novel, such as antibiotic-resistant TB and HIV, while some, such as Ebola, have been around for much longer but have only recently gained attention of high-income nations.[25] In some cases, this is an oversight of ethnobiological knowledge of pathogens and disease, particularly as it pertains to Indigenous conceptualizations of disease.[62] Despite these critiques, there is no doubt that new and re-emerging diseases are major threats to human health, and there are yet unknown demographic consequences for many modern pathogenic threats.

The epidemiological transition framework is ideal to investigate the relationships among behavior, demographic evolution, and infections because shifts in human demography and their sociocultural drivers are products of irreversible transformations in human behavior. Biocultural approaches are popular, but epidemiological transition theory, especially in applications to human nature and infectious diseases within the scope of anthropology, has not enjoyed mainstream attention despite its clear strengths as an evolutionary framework. As previously mentioned, there have been some prominent scholars and colleagues who have formally and compellingly integrated biocultural and epidemiological transition inquiry. Moving forward, I argue that anthropologists using biocultural perspectives should more broadly engage with the temporal depth and theoretical elements of the epidemiological transitions. Epidemiological transition theory unites human biological change with social, cultural, and environmental origins of diseases that have plagued humans for millennia; therefore, epidemiological transition theory and biocultural anthropology are essential to one another[63] and research within anthropology could be considerably strengthened with a more purposeful integrative perspective.

Because humans have long been afflicted with TB disease, this relationship has been influenced by the demographic and cultural shifts that form the basis of epidemiological transition theory. The rest of this paper critically discusses TB and some of its major infectious comorbidities (leprosy, influenza, HIV, malaria, and COVID-19) in the context of the three epidemiological transitions and biocultural anthropology. A full discussion of the many infectious and chronic comorbidities and social conditions that put populations at risk of TB extends beyond the scope of this paper, but some known risk factors are listed in Table 1. Other scholars have reviewed the coevolution of humans and TB,[65,66] as well as its comorbid communicable and noncommunicable diseases.[64] Some attention has been directed towards how the archaeological record can be used to inform current and future epidemics.[29,67] Comorbidities, however, are essential for a comprehensive understanding of epidemiological progressions and how they influence human demography through time. Additionally, this paper considers ways in which biocultural theory can improve our understanding of how humans and infectious diseases are persistent companions that push and pull at each other over the course of our mutual evolutionary trajectories.

3 | BIOLOGICAL OVERVIEW OF TB

Studying infectious diseases in any context requires a basic understanding of the biology of the pathogen and its disease etiology. Here, I give a brief overview of the biology of the causal pathogen, *Mycobacterium tuberculosis* (*M.tb*), and the disease processes of human TB. This paper focuses specifically on pulmonary TB as an illustrative example, but there are other extra-pulmonary forms that could be considered in other contexts.

The causal pathogen discussed primarily in this paper is *M.tb*, but this pathogen is only one of many that make up the *Mycobacterium tuberculosis* complex (MTBC), a group of bacteria that collectively make up the causative agents of TB in humans and other animals.[68]

TABLE 1 Tuberculosis comorbidities and risk factors

Infectious diseases	**Living conditions**
Plague	High population density
Leprosy	Alcohol misuse/abuse
Bovine TB	Substance misuse/abuse
Syphilis	Smoking
Influenza	Prison
Pneumonia	Homelessness
HIV	
Malaria	
COVID-19	**High-risk working environments**
Helminths & other parasites	Mining
Sexually transmitted infections	Front-line health care
	Prison staff
Chronic/noncommunicable diseases	Close contact with domesticated bovine
Diabetes mellitus	
Chronic lung disease (COPD)	
Congenital deficiencies	
Autoimmune disorders	
Cancer	
Cardiovascular disease	

Note: Adapted from table 4 of Bates and colleagues.[66]

There are five human-adapted species (*M.tb sensu stricto*), several others that are found primarily in domesticated animals (e.g., *Mycobacterium bovis*, *Mycobacterium caprae*), and one that causes only opportunistic infections in humans but is likely an environmental microbe (*Mycobacterium canettii*).[69–71] *M.tb* has nine recognized lineages, which are specific in their geographic distributions and their close associations with humans.[72–74]

TB disease is one of the most prolific infectious diseases in the world, and one of the top infectious killers. In 2020, the WHO estimated that 10 million people fell ill with TB; of the 1.5 million people who died from TB, 214,000 were HIV-positive.[75] Antibiotic-resistant strains of *M.tb* have also emerged: multi-drug resistant TB (MDR-TB) is resistant to the first-line drugs rifampin and isoniazid, and extensively-drug resistant TB (XDR-TB) meets the criteria for MDR-TB but is additionally resistant to any fluroquinolone and a second-line chemotherapeutic drug.[76] Despite the critical need for drug innovation to combat the increasingly resistant strains of the bacterium, there have only been a few new promising drugs in the last half century.[77–79] While the global burden of and deaths due to TB have been falling throughout the last decade, the burden of MDR- and XDR-TB forms of the disease has remained stable.[75] The overall decline is encouraging, but the persistence of drug resistant forms is one of the primary health threats of the 21st century, and their evolution is strongly driven by human behaviors, specifically those surrounding treatment surveillance, antibiotic regimens, and systemic social inequalities.

The disease process of human pulmonary TB is complex and occurs in several stages, summarized in Figure 2. In the primary stage, infection occurs via inhalation of aerosolized droplet nuclei containing *M.tb*. When these droplets reach the lungs, the cell-mediated immune response includes phagocytosis of the bacteria by macrophages, after which either the causal organism may be destroyed or it may necrotize the macrophage.[80] For TB disease to be considered primary and progressive, the bacteria must survive the immune response and continue to replicate.

The immune response will continue throughout this process, and the macrophages, epithelioid cells, multinucleated cells (e.g., Langerhans cells), and lymphocytes that accumulate around the replicating bacteria to mitigate their growth and spread develop the primary defining characteristic of clinical TB disease: the granuloma.[81–83] The goal of the adaptive immune response is to reduce, and eventually halt, the rate of bacterial growth, leading to the eventual modification of the granuloma into a lesion with no bacterial activity. Most commonly, the adaptive immune response will result in a containment of the active bacteria; in a small percentage of cases, the disease will progress beyond this latent state into the active, symptomatic stage.[83]

Most individuals infected with latent TB never show symptoms or exhibit cause for suspicion that they are infected with *M.tb*. Up to 10% of these latent infections, however, can progress into the active disease state when the host's immune system is compromised by age, malnutrition, or coinfection with another pathogen.[84,85] Because the immune response depends on the body's ability to apprehend the infection, this is a natural entry point for biocultural questions: what are the behavioral, cultural, and ecological factors that would cause a latent infection to become reactivated? Further, over time, how do these extra-somatic factors drive the human experience with TB, intergenerational health, comorbid conditions, and ultimately inequalities in mortality from the disease? Biocultural perspectives of TB can help answer these questions in light of the local biology framework. While it is estimated that one-third of the human population is infected with *M.tb*, there is substantial heterogeneity in risk for developing acute TB disease, reactivated latent disease, or the fully latent form that could persist for decades. A holistic conceptualization of the local contexts in which clusters of diseases exist is paramount to the anthropological approach to infectious disease research.

4 | COMORBIDITIES IN EPIDEMIOLOGICAL TRANSITION CONTEXT

4.1 | Origins and expansion of human TB

The current consensus on the antiquity of *M.tb* as the causal pathogen of TB disease in humans has changed dramatically in the

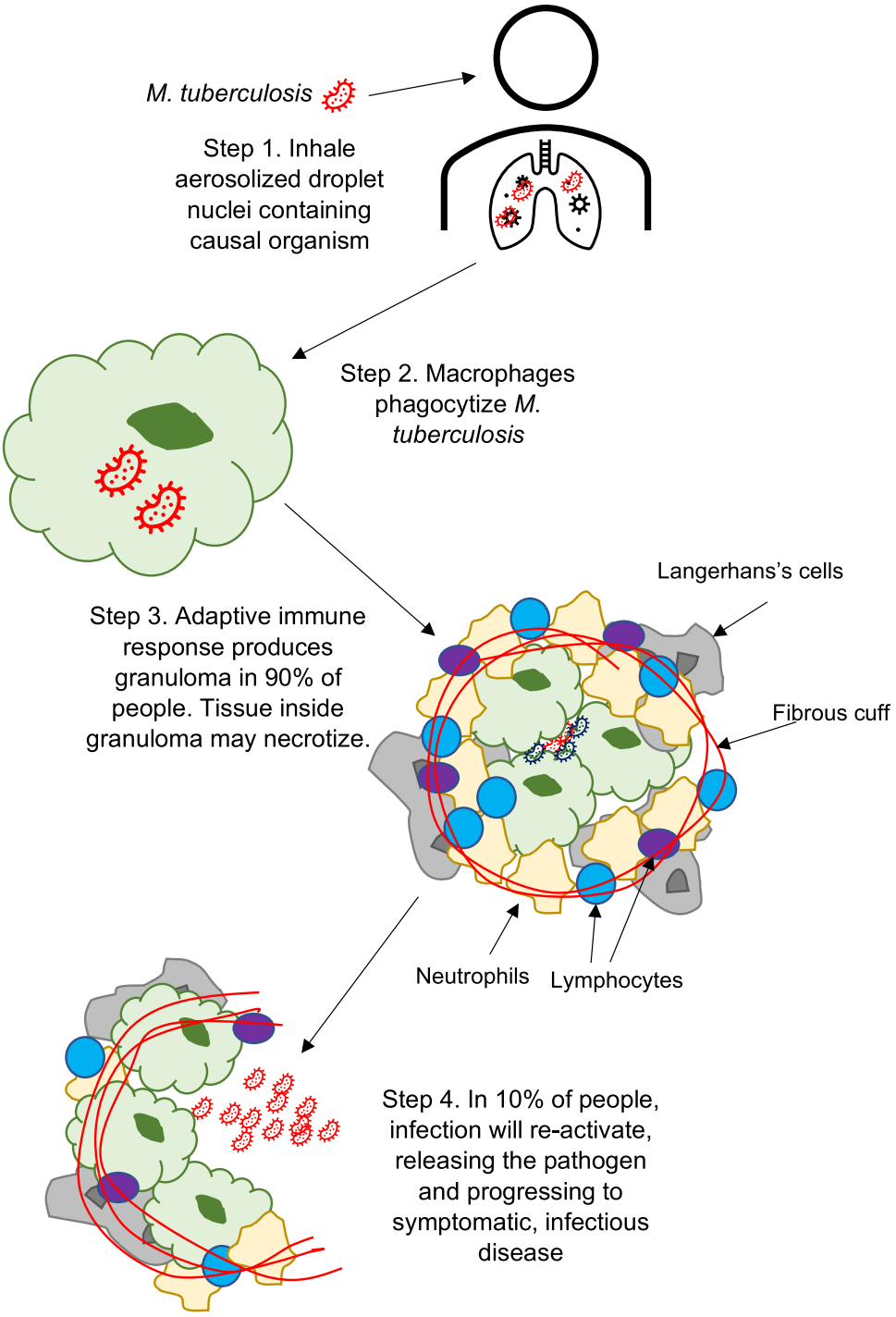

FIGURE 2 Visualization of TB disease process. Author's own. TB, tuberculosis.

last decade. Previously, polymerase chain reaction (PCR)-based analyses suggested that *M.tb* first afflicted humans up to 40,000–70,000 years ago.[86] Recently, with the publication of whole genome sequences of *M.tb* lineages, researchers have begun to use molecular clock dating calibrated with ancient DNA (aDNA) to more reliably locate the coalescence of modern lineages to determine their most recent common ancestors (MRCA).[87] In doing so, it has been shown that the MRCA for *M.tb* in the MTBC is less than 6000 years old.[88–90] In this sense, the origins of the disease that causes TB in humans do not lie within the realm of the Paleolithic at all, and much of the concrete evidence we can use to synthesize paleopathological, paleodemographic, bioarchaeological, and cultural knowledge does not appear until well into the Neolithic.

This much shorter time frame has given rise to hypotheses and explanations that support the relationship between the expansion and evolution of human-adapted lineages of *M.tb* to the expansion of

trade, connectivity, and exploration in the "Old World" and beyond.[91–95] Figure 3 illustrates patterns of *M.tb* dispersal in Africa and Asia using evolutionary rates inferred from whole genome aDNA calibration.[94] This has interesting implications for our understanding of human–pathogen coevolution with *M.tb* because it requires that we reframe our understanding of our relationship with the modern pathogen versus the progenitors of that pathogen, which were likely producing tubercle bacilli infections long before this specific MRCA.[96] The fact that research has closely linked the dispersal of *M.tb* with human movement tied to cultural purposes helps substantiate the claim that TB disease can, and should, be studied through a biocultural anthropological lens.

Beyond molecular evidence of *M.tb* in skeletal samples, identification of TB in skeletal lesions is a complex, difficult process, riddled with questions about diagnostic criteria and accuracy.[97] For example, there is a mismatch between clinical presentation of TB and skeletal lesions in the bioarchaeological record: clinical advanced TB typically presents with rib lesions, but not *all* cases of TB manifest rib lesions and not all rib lesions can be attributed to TB.[98,99] More recently, Dangvard Pedersen and colleagues[100] showed that sensitivity and specificity estimates of skeletal lesions attributable to TB—specifically those of thoracic and lumbar vertebral bodies—can help glean insights into disease prevalence, which is epidemiologically more meaningful than lesion frequency.

The relationship between the prevalence of skeletal pathologies and the overall health of the population has been a major topic within paleoepidemiology and paleodemography for the last few decades. Wood and colleagues'[101] classic osteological paradox research makes the salient point that the presence of skeletal pathologies does not indicate a generally frail population, but rather that individuals with lesions lived long enough with their afflictions for pathologies to appear in the skeletal tissue despite progressed disease or adverse health conditions. It is difficult to understand the level at which TB existed in a population solely based on the frequency of skeletal lesions, because only up to 10% of individuals who are infected with the pathogen will eventually develop lesions. Even fewer of these individuals will make it into the bioarchaeological record. However, the presence of lesions attributable to TB likely point towards community spread in the once-living population, and this allows anthropologists to ask and answer paleoepidemiological questions. We can align our bioarchaeological and paleoepidemiological knowledge of TB lesions in a population with critical moments of cultural evolution to provide insight into how infectious diseases were part of, and likely helped shape, human biology and demography through time.

4.2 | TB alongside agriculture

The Neolithic was the first marked shift in human population dynamics and is defined by major changes in human culture (intensification of agriculture), demography (rapid population growth), and health. This was when skeletal lesions attributable to TB disease generally began to appear. Reviews of the timeline of evidence of skeletal TB show early loci of prevalence in Northern Europe and the Mediterranean, followed by Asia and other parts of Europe, and finally in South America around 700 AD.[102]

Paleoepidemiologists recognize the difficulties and nuances of studying the physical manifestations of diseases in skeletal remains and are careful not to apply modern epidemiology of diseases to their historical expressions.[103] As Boldsen and Milner state: "…the skeletons are not really what are of most interest… we are instead concerned with the lives they led before they died."[104] One of the fundamental tenets of paleoepidemiology is that analyses of prevalence of pathological conditions in once-living populations must be embedded within their appropriate cultural contexts.[105] This idea

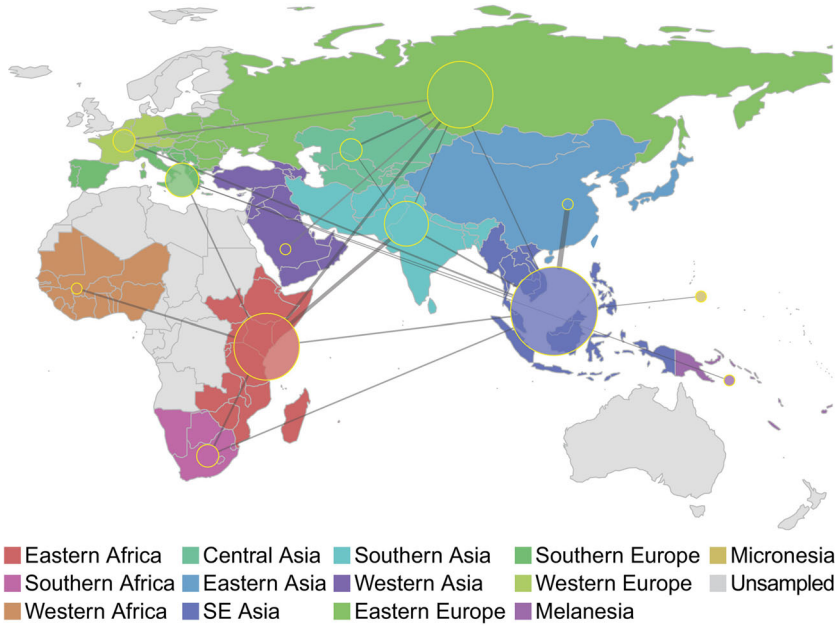

FIGURE 3 Connectivity of Asian and African regions based on United Nations criteria to identify and quantify dispersal patterns of *M.tb*. Node size refers to the number of migration events from the area, and line thickness illustrates estimated relative rate of migration. Directionality is not included. Previously published by O'Neill et al.[94] (figure 6) under Open Access Creative Commons Attribution license (CC BY 4.0).

has been operationalized broadly, for example, in studies including but not limited to the gradient of socioeconomic inequality and TB in medieval and early modern Denmark,[106] how the emergence of urbanization affected TB and leprosy prevalence,[107,108] and holistic determinants of vitamin D deficiency leading to numerous health problems, including TB.[109] Additionally, paleopathological research on TB skeletal lesions in Peru specifically operationalizes the colonial period as biocultural context.[110] It could be said that paleoepidemiological inquiry has long been engaging with ideas akin to the local biology framework that is prominent in biocultural anthropology, whether explicitly stated or not.

4.2.1 | Selective mortality and leprosy

Leprosy (Hansen's disease) is an ancient disease that causes chronic inflammation of the skin and peripheral nerves.[111] The primary causal pathogen is *Mycobacterium leprae*, but Han and colleagues recently identified a new *Mycobacterium* species that causes a form of lepromatous leprosy, *Mycobacterium lepromatosis*.[112] The two causal organisms have slightly different pathogeneses, and they are remarkably conserved despite a distant estimated MRCA (13.9 mya).[113] Not much more is known about *M. lepromatosis* currently, and the remainder of this discussion focuses on research published on leprosy likely caused by *M. leprae*. Due to the known high prevalence of TB and leprosy within the millennium before the Industrial Revolution, and the ample paleoepidemiological research done therein, the following discussion focuses primarily on this period. This is not to suggest there was a negligible presence of both diseases before this time, but rather to emphasize its elevated, persistent presence during this period and to glean insights about how urbanization and other demographic processes (e.g., mobility and fertility) affect infectious disease dynamics. *M.tb* and *M. leprae* can be cocirculating pathogens that both lead to diseases that are associated with similar determinants such as poverty, poor healthcare access, malnutrition, crowding in urban spaces, and compromised immune systems.[114] Skeletal lesions attributed to leprosy in India have been described and dated to 2000 BC,[115] and skeletal material dated to the Swedish medieval period (10–14th century) has been shown to contain aDNA of a strain of *M. leprae* transmitted from the Asian continent.[116] Plentiful evidence for leprosy emerges in Europe between the 5th and 11th centuries AD.[117] There is neither skeletal nor biomolecular evidence of leprosy or its causative agent west of the Atlantic before the 16th century.[117,118]

The rise in prevalence and distribution of *M. leprae* during the last millennium rather than any time before was most likely due to the pathogen's dependence on close human contact for transmission. Reasons for this conclusion include the lack of paleopathological evidence of leprotic material before urbanization in many places worldwide (aside from, for example, the aforementioned evidence in India[115] and osteoarchaeological evidence in the 1st millennium AD in Uzbekistan[119]). Although humans have been considered the primary hosts for *M. leprae* in the past,[120,121] recent research has shown that the pathogen does have nonhuman hosts such as chimpanzees, who have been shown to acquire the infection in the wild,[122] armadillos,[123,124] and red squirrels[125] that have the potential for or have contributed to zoonotic spillover. Further, the rise in prevalence and transmission of *M. leprae* is often associated with the rise in urbanization, specifically high population densities,[121,126] but this relationship is complex. Urban environments do not necessarily always have higher leprosy *or* TB rates; Kelmelis and colleagues[107] described patterns in medieval Denmark (1050–1536 AD) in which higher rates of leprosy were found in rural settlements and there were no significant urban versus rural differences in TB rates.[108] This difference was likely because one of the urban settings had a long-established leprosarium (probably since 1280 AD), while the other had a leprosarium first mentioned only in 1492 AD.[108] This discrepancy would have resulted in a much lower frequency of individuals with skeletal lesions—primarily facial lesions—in the region with the much older leprosarium due to social exclusion of leprotic individuals from burial there; conversely, there were many more individuals with skeletal lesions through the Danish Medieval period where this stigmatic exclusion did not begin until relatively late.[108] Ultimately, the primary conclusion is that TB-leprosy dynamics cannot be attributed exclusively to urbanization.[107]

The cocirculating nature of *M. leprae* and *M.tb* in populations in Europe likely led to the decline and ultimate disappearance of leprosy, but how this happened continues to be debated. One of the earliest hypotheses was that latent TB infection provided protection against leprosy, referred to as cross-immunity.[127] Roberts and Buikstra suggest that the close relationship between the two pathogens results in a competitive exclusion of one or the other over the time.[97] Alternatively, there may have been a deleterious effect, such that individuals infected with *M. leprae* were more likely to suffer an activation of latent *M.tb* infection and be at risk for a strong selective effect against dual sufferers due to a cell-mediated immune response.[120] Crespo and colleagues[128] discuss moving towards a multifactorial model of explaining the TB-leprosy cross-immunity hypothesis, arguing that cultural and social landscapes in the past were not homogenous, therefore immunological landscapes were not homogeneous either. Thus, the cross-immunity hypothesis does not fully explain leprosy declines in all localities. Even though leprosy declined in the following centuries, it maintained a presence in some parts of urban and industrial Europe through the 20th century, leading Hansen and Looft[129] to make the classic observation that patients dually infected with TB and leprosy suffered significantly higher mortality than those with only leprosy.

Evidence of pathogenic comorbidities with TB leading up to the second millennium AD is sparse, but there are important human behavioral patterns and historical records that support a selective effect between *M.tb* and *M. leprae*. In populations for which they are available, the historical record should be qualitatively analyzed and integrated with results gleaned from quantitative paleodemographic and paleoepidemiological analyses. Scholars have successfully drawn connections between economic history (pieced together using primary historical documents) and increased life expectancy due to

improved standards of living, housing, and economic opportunities—direct consequences of depopulation due to catastrophic Black Death mortality[130,131] (although, I will not argue that the Black Death and other pandemics are ultimately good).

The urban spaces that arose with the agricultural revolution are highly complex and heterogeneous between and among groups. Local contexts of TB epidemiology and susceptibility will likewise differ for comparable urban spaces. This cultural layer is critical to understanding how lifestyle, diet, trade, social structure, and inequality all may have contributed to heterogeneous human biology, demography, selective forces of TB and leprosy specifically, and infectious diseases more broadly.[108] In lieu of the historical record, which is not extensively available for most populations, DeWitte[29] suggests the integration of bioarchaeology, paleomicrobiology, and stable isotope analyses to get better insights into how socioeconomic status and dietary stress manifest in the body. As the agricultural revolution was one of the turning points in human health for populations that adopted this mode of subsistence, biocultural perspectives on how human behavior drove transmission and severity of pathogens and vice versa are important for understanding health during the next major phase of population transition.

4.3 | The second epidemiological transition: Alongside industrialization

TB held a constant presence in populations until this time, and its decline throughout the second epidemiological transition punctuates major shifts in public health, infrastructure, and eventually, medical advancement. The first populations to undergo this transition (Western Europe and parts of North America) saw a decline in infectious disease mortality, proportionate increase in chronic disease mortality, and an overall increase in life expectancy.[46] Infectious diseases that killed primarily children (e.g., pneumonia, smallpox, measles, gastrointestinal infections) and young adults (e.g., TB), were replaced with diseases that manifest in aging bodies (e.g., cardiovascular disease, cancer, respiratory and/or kidney failure). The decline of TB throughout this period greatly contributed to the overall decrease in infectious disease mortality, but the exact mechanism is debated.[50] Not all populations experienced, or will experience, a uniform transition in either timing or speed (see Santosa and colleagues'[58] systematic review of the variation in nature and timing of mortality shifts in low- and middle-income nations, as well as departures from Omran's original model). Populations are adapted to their specific ecological circumstances and there may be myriad ways to model population health transitions.[57,58] It is important for anthropologists to engage with these debates to better understand how changes in infectious disease mortality contribute to demographic evolution specifically *because* of immense cross-cultural heterogeneity. The biocultural concept of local biologies can illuminate the ways populations underwent, or had a relatively delayed, second epidemiological transition.

4.3.1 | Selective mortality during the 1918 influenza pandemic

One important observation of 19th century mortality shifts was the relationship between TB and other respiratory infectious diseases.[49] Although these conclusions are contested on the grounds of imprecise recording of cause of death, it has since been shown that there is a significant comorbid relationship among TB and respiratory diseases.[132,133] This is best highlighted by the 1918 influenza pandemic, a global mortality event that was highly variable in its determinants, impacts, and consequences. Such an event must be conceptualized more broadly than simply influenza, however, and the relationship between influenza and TB may have been critical to not only epidemiological patterns of the 1918 influenza pandemic, but for epidemiological consequences of TB for decades afterwards.

Selective mortality of TB with influenza is characterized by a high frequency of TB deaths in pandemic years due to co-infections of TB and pandemic influenza/pneumonia, leading to increased TB mortality followed by a postpandemic decrease in prevalence and mortality of TB, ultimately resulting in an overall healthier postpandemic population.[134–137] The 1918 influenza pandemic, therefore, is considered the turning point in TB epidemiology in the United States.[135] Critically, TB mortality rates were already on the decline, most likely due to the successful TB sanatoria system across the country,[138,139] but the acceleration of the decline immediately after the pandemic raises questions about the specific role of the pandemic diseases.[140]

This comorbidity has been investigated in other populations, as well. In Norway, female patients in two sanatoria, especially those in the 20–29 age group, had significantly higher case fatality rates when simultaneously infected with TB and influenza.[141] Oei and Nishiura sought to formalize the relationship between the age-based mortality signature of the 1918 influenza pandemic and TB,[142] that is, the pandemic phenomenon that the highest excess mortality occurred in otherwise healthy adults aged 20–44.[143] They found a significant association between TB and pandemic influenza deaths in younger adult age classes and no significant increase in mortality in non-TB control populations in the United States, Japan, and the Netherlands.[142] An increased risk of mortality in those infected with both TB and influenza was also identified in Switzerland.[144]

This selective relationship was also investigated for the preindustrial population of Newfoundland. There was no significant postpandemic decline in TB mortality observed, which was attributed to consistently high prevalence of the disease on the island, in addition to poor availability of nutritious diets and intergenerational propagation of poor health.[140] Analyses of sex-based differences in mortality during the 1918 pandemic, however, identified significantly higher female mortality where TB mortality was also the highest for females during the early 20th century.[145] Newfoundland had a relatively delayed second epidemiological transition,[146] and the persistent burden of TB may have been one of the reasons.[140] The historical record suggests that anti-TB campaigns were underway in Newfoundland from the beginning of the 20th century, which raises

questions about the ways public health infrastructure advanced throughout the next several decades to finally reach a point that resembled "control" of TB on the island. This would make Newfoundland an interesting case study for illuminating how a selective mortality event like the 1918 influenza pandemic led to dramatically different postpandemic epidemiological and demographic outcomes compared to the United States. Regrettably, despite the highly unique age-based pattern of mortality during the 1918 influenza pandemic and clear selective effects with TB in some populations, there are few studies that closely investigate the pandemic's long-term demographic effects. In a recent review, DeWitte and Wissler discuss the substantial untapped potential of this line of inquiry.[67]

Biocultural anthropologists are uniquely equipped with many complementary research skills that can be turned toward recent historical events such as the 1918 influenza pandemic and its interactions with TB. Much of the anthropological research that exists on infectious diseases either focuses on prehistoric or modern threats; recent history (i.e., the 20th century) has remained a puzzling outlier as a study period for many anthropologists, especially work that does not involve skeletal material or other explicit biomarkers. Biological anthropologists can engage with the written historical record to better understand the cultural contexts in which such an acute infectious pandemic spread, the general health of the population (through public health reports or yearly reports on health and hospitals), or living conditions in urban versus rural spaces (see Herring and Swedlund's edited volume, *Human Biologists in the Archives*[147]). A biocultural anthropological perspective can go beyond observed epidemiological patterns to develop ultimate explanations as to how and why some populations experience cocirculating infectious diseases, or how the impacts of severe mortality events linger for decades afterwards.

4.4 | The third epidemiological transition: Ongoing modernity

In a short period of time, we have seen the rise of not only urbanization, but globalization. This period of cultural evolution is characterized by advances in transportation and communication technologies, accelerated population growth, and new and re-emerging infectious diseases. The beginnings of globalization can be traced back a couple of centuries,[148] but its intensification in the late 20th century has given rise to the globalization of pathogens as well.[149] Demographic changes are important determinants of how diseases (re-)emerge: rapid population growth, along with an increase in the proportion of the total human population now living in cities (over half), provide more opportunities for infectious pathogens to take hold, adapt, and spread beyond their origins.[150] Human behaviors like international travel, increases in contact with new environments, anthropogenic climate change, and interpersonal social interactions have given rise to the hallmark emerging diseases of this transitional period (e.g., HIV, Ebola, Zika virus, and COVID-19).[33] Antibiotic resistance, additionally, is an adaptation driven by humans' use of antibiotics. The consequences of the emergence of antibiotic-resistant pathogens, namely MDR- and XDR-TB, are deeply rooted in socioeconomic inequality, the availability of biomedical resources, and a lack of social and medical infrastructure to sustain improvements in population health. The highest burdens of antibiotic-resistant TB exist in low-income nations that are also plagued with high burdens of other diseases, like HIV and malaria. Human behavior and demography are inextricable from the global patterns of TB burdens and its common modern comorbidities. The synergies between and among these diseases are the primary adversaries in public health programs that are looking for ways to improve health as the human population continues to grow. Throughout this section, I will highlight the ways that human infectious disease experiences are embedded in the macrosocial political economic forces that contribute to social inequalities, echoing the concept of health as a product of local biologies,[9] and therefore unequal disease afflictions.

4.4.1 | TB, HIV, and malaria

One of the deadliest comorbidities worldwide that has emerged during the third epidemiological transition is that of TB and HIV. TB is one of humankind's oldest plagues, HIV is one of its newest, and at their intersection they are the "synergy from hell"[151]: (1) they are both clustered in areas of poverty, and individuals afflicted with one or both of these diseases have little access to resources for diagnoses, therapy, or control; (2) both diseases are public health failures in the sense that incorrect use of antibiotics and antivirals has led to antibiotic and antiviral drug resistance, along with the compounded stigma, marginalization, and blame cast on gay and bisexual men in the early 1990s for their perceived moral shortcomings and supposed role in spreading HIV[152,153]; and (3) these diseases are not only overlapping clusters in social spaces, but they also interact on the pathological level, accelerating their respective disease processes and hastening physical deterioration.[27,154,155] It is estimated that HIV infection increases the risk of activation of a latent TB infection by almost 20-fold.[154] Amplifying these medical concerns are the evident gradients of social vulnerability to these diseases, which includes overcrowding, lack of basic hygiene, and difficulty accessing necessary antibiotics and antiviral treatments.[26]

There has been a continued increase in TB-HIV comorbidity, especially in MDR- and XDR-TB cases, in resource-poor countries where the prevalence of TB disease was already widespread.[151] This is contingent on the availability of biomedical resources to treat those already infected with HIV and to prevent infection of *both* diseases in at-risk populations. The breakthrough that tipped the scales in treatment and prevention was with the development of an antiretroviral therapy cocktail that drastically reduced viral load of HIV to the point where it was undetectable.[156,157] This advancement in biomedical knowledge and technology will be critical to reducing risk of infection with HIV in vulnerable populations, and therefore will

help mitigate the risk of mortality and other adverse health consequences of TB-HIV.

TB and HIV can each also be comorbid with malaria, and these three diseases comprise the top three most deadly infectious diseases in the world. Malaria itself caused one million deaths in 2010 and has been steadily declining for a decade, but almost all of these deaths were concentrated in tropical areas in which both *M.tb* and HIV are cocirculating endemic pathogens.[158,159] Over one billion people living in abject poverty are vulnerable to all three, and this number will likely grow due to the expanding range of the *Anopheles* mosquito, the vector of the parasite that causes malaria (including, but not limited to *Plasmodium falciparum* and *Plasmodium vivax*), due to anthropogenic climate change.[160] Despite the overlap of geographic space in which these three pathogens are endemic, high levels of coinfections in South America show that the TB-malaria comorbidity occurs regardless of HIV status.[161]

Further, there is an immunological response to malarial infection that directly impacts the immune response to TB. On one level, repeated infection with malaria can cause immune exhaustion and unresponsiveness to *Mycobacterium* infections, especially in children.[162] Additionally, the immune response to a malaria parasite directly impairs host resistance to *M.tb* by compromising the ability of the immune system to either develop or maintain the immune protection that prevents active TB disease.[158] In this way, malarial infection not only increases susceptibility to newly acquired *M.tb* infection but can also reactivate latent infections.[163] Perhaps one of the most at-risk demographics is pregnant women, from whom the babies who are exposed in utero to malaria and TB and/or HIV are more likely to be born at a low birth weight, die as infants, or later develop chronic health problems like hypertension.[162,164] Low birth weight and poor health in childhood are two strong determinants for predicting health in later life[165,166]; therefore, the persistent TB-HIV-malaria comorbidities in endemic regions lead to poor health that propagates through generations, creating serious difficulties for public health programs to address the ultimate determinants of poor intergenerational health borne of these infectious diseases. The fact that social conditions can directly affect gestational health, birth weight, and the intergenerational propagation of health conditions all within the context of TB, HIV, and malaria clearly illustrates how infectious diseases are part of the local biologies that determine health and can contribute to the embodiment of social inequalities.

4.4.2 | COVID-19: The most recent public health threat

The final major TB comorbidity that must be acknowledged in ongoing modernity is that of TB and the COVID-19 pandemic, the disease caused by the novel coronavirus SARS-CoV-2. At the time of this writing, there have been 630 million confirmed cases of COVID-19 and nearly 6.6 million deaths worldwide, but the unequal distribution of cases and deaths exposed gradients of risk, resource access, and preparedness. TB and COVID-19 share similar social determinants (e.g., poverty, crowding, and diabetes).[167] Given the novelty of the SARS-CoV-2 pathogen and the disease COVID-19, only a few studies have emerged since the start of the pandemic to provide hints about the relationship between COVID-19 and TB.

In a study from the first epicenter of the pandemic in Wuhan, China, *M.tb* infection was identified as the most common comorbidity with COVID-19.[167] Further, in the first published report of a cohort of active COVID-19 and TB comorbidity cases, 53% had TB before COVID-19, 28.5% had COVID-19 first, and 18.3% had both diagnosed in the same week.[168] This diagnostic categorization is questionable because individuals in the cohort likely had TB long beforehand and the COVID-19 pandemic merely activated many latent cases.[169] There is, however, a bidirectional relationship between the diseases; immunosuppression due to TB may increase susceptibility to COVID-19 and vice versa.[167] The social determinants of these diseases overlap in a concerning way: an increase in the global population living in poverty to half a billion people[170] and the ease of transmission in overcrowded urban spaces could exacerbate the prevalence of both diseases.

There is an obvious gradient of inequality of COVID-19 pandemic outcomes, with most of the newly impoverished victims residing in the global south.[170] Further, social disruption due to the pandemic has had a palpable impact on TB treatment programs, which also disproportionately impacts disadvantaged and high-burden populations.[171,172] The disruption of services in high-burden and high-risk populations will potentially facilitate higher rates of TB morbidity and mortality.[173] There has been specific concern about the case of COVID-19 comorbidities in South Africa, not just with TB but also with HIV (there is little knowledge yet about the synergies between COVID-19 and HIV), and there could be negative consequences on TB surveillance and treatment through deprioritization of TB in health systems overrun by COVID-19 patients.[174] This is an ideal space in which biocultural approaches in infectious disease studies with considerable temporal depth can coalesce with public health theory and efforts.[29,175] Specifically, biocultural knowledge within the context of the epidemiological transitions can help illuminate the prescient threat of new and re-emerging infectious threats in spaces that lack the public health, social, and medical infrastructure to combat these threats, especially those that are simultaneously experiencing the double burden of old and new epidemiological profiles.[59] This double burden must be critically assessed in the context of specific local biologies, especially in how it can widen the gradient of health and social inequalities both between and *within* populations.

A prominent public health framework, the social determinants of health (SDoH), provides a basis for understanding the ways the environments in which people are born, live, work, and age affect a wide range of health outcomes, and risks, visualized in Figure 4.[177] The SDoH is a popular context for modern health inequalities, but it lacks an explicit acknowledgement of how modern inequalities are the products of history; that is, how demographic and cultural evolution have contributed to the development of social structures

FIGURE 4 The SDoH and the five integral components, as defined by the Office of Disease Prevention and Health Promotion.[176] SDoH, social determinants of health.

that determine health. Other anthropologists have also noted the value of using past pandemics as points of reference for improving public health inquiry, namely through resilience management.[178] Anthropological studies of infectious diseases can connect the COVID-19 pandemic to past pandemic events, and possibly suggest ways to move forward into more thorough pandemic preparedness plans that are catered to heterogeneous populations' needs. More broadly, biocultural approaches that consider the long-term relationship between humans and infectious diseases may provide context for the highly variable outcomes of modern outbreaks.

The long-term impacts of the COVID-19 pandemic on human population dynamics, epidemiology of other infectious and non-infectious diseases, and society are unknown, and any hypotheses put forward are merely speculative. The COVID-19 pandemic will likely be the defining event of the decade, especially because we are aware from studies of past pandemics that consequences of pandemic events persist long beyond the end of the epidemic curve.[137,179,180] It is difficult to conceive of a way the consequences of the COVID-19 pandemic will not substantially interfere with WHO's End TB Strategy targets to end the epidemics of AIDS, TB, malaria, and neglected tropical diseases by 2030.[75] This ultimately highlights the pressing need for more comprehensive pandemic preparedness plans. Optimistically, we need not start from the beginning; there are consistencies in ultimate determinants of pandemics through time, so we must engage with knowledge of historical pandemics to better understand the role of humans in their origins, transmission, and consequences.[175]

BOX 1 Glossary

Biocultural anthropology: A theoretical framework/approach to anthropology that emphasizes the coevolutionary nature of human biology and culture.

Local biologies: Distinct characteristics of the physical body that are the consequences of macrosocial socioeconomic and ecological forces.

Syndemics: The synergistic interactions of two or more pathogens, diseases, or health conditions that result in accelerated degradation of health; the syndemic framework emphasizes the *clustering* of adverse co-circulating pathogens and health conditions.

Epidemiological transition theory: A theoretical framework that conceptualizes the evolution of human demography and epidemiology as punctuated by fundamental, irreversible changes in human behavior and culture.

Paleolithic baseline: The state of human health and culture before the agricultural revolution, characterized by low population density and affliction with chronic disease pathogens of their idiosyncratic environments.

First epidemiological transition: A period of increasing population size, population density, fertility, mortality, sedentism, and novel crowd diseases that roughly aligns with the agricultural revolution.

Second epidemiological transition: A period of a decrease in infectious disease mortality and proportionate increase in chronic disease mortality that roughly aligns with the industrial revolution. This change in mortality dynamics was intended as an explanation for the decrease in mortality discussed in the demographic transition model.

Third epidemiological transition: A period characterized by new and re-emerging disease that emphasizes that new diseases are significant contributors to morbidity and mortality, and that diseases previously characterized as receding are now re-emerging with adaptations that make them less amenable to modern medical intervention.

Demographic transition: The population shift from high mortality and high fertility to an initial decrease in mortality followed later by a decrease in fertility, resulting in an increase in population size and life expectancy.

Tuberculosis (TB): A disease commonly caused by *Mycobacterium tuberculosis* (although there are other causal pathogens that can cause TB disease, e.g., *Mycobacterium bovis*), that primarily infects the lungs. Active TB disease can produce symptoms of shortness of breath, bloody sputum, weakness, and weight loss; long-term active disease can impact extra-pulmonary organs.

Mycobacterium tuberculosis: The causal pathogen of human TB disease; typically infects the lungs upon inhalation and can be either suppressed by the immune response or can cause active, symptomatic pulmonary disease; long-term

active disease can impact extra-pulmonary organs such as bones, meninges, and the digestive tract.

Social determinants of health: A public health framework that provides a basis for understanding the ways environments in which people are born, live, work, and age affect a wide range of health outcomes and risks.

5 | CONCLUSIONS

With the accelerating popularity of biocultural perspectives in anthropology, there has been a disproportionate lack of engagement with infectious diseases from this perspective despite the many opportunities available to better understand human demographic and cultural evolution using knowledge of infectious disease dynamics. Some lines of inquiry within biological anthropology, specifically paleoepidemiology and paleodemography, have clearly engaged with the broader environment in which populations lived as context for biological manifestations of disease, but biological anthropology could improve by more specifically adopting the biocultural perspective within the epidemiological transition framework to increase crosstalk between and among subdisciplines. TB is a particularly good disease to track through history through this lens because of its constant companionship with humans throughout each of the punctuated transitional periods.

Humans' experiences with and burdens of infectious diseases are ultimately linked in their determinants and consequences. Proximate determinants of TB disease may simply include the high prevalence cocirculating pathogens that lead to the degradation of health, but ultimate determinants encompass the contexts of human disease and social conditions that create risk such as poor intergenerational health, malnutrition, immune competence, poverty, crowding, and other political economic forces. The changing disease-scape of TB, a serious and long-time human affliction, is punctuated by different social, cultural, and simultaneously emerging infectious threats at different times throughout our mutual evolutionary history, but these moments do not exist in isolation. This paper has shown how major demographic shifts in human populations that are characterized by human behaviors such as agriculture, industrialization, and globalization can be unified by the fact that infectious diseases like TB will continue to drive changes in human biology and culture, and vice versa (Box 1).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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