On race, human variation, and who gets and dies of sepsis

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Funding information
National Science Foundation, Grant/Award Number: BCS-1750675

Abstract
COVID-19 has highlighted a brutal reality known for decades, that Black, Indigenous, and People of Color bear a disproportionate burden of US annual sepsis cases. While plentiful research funds have been spent investigating genetic reasons for racial disparities in sepsis, an abundance of research shows that sepsis incidence and mortality maps to indicators of colonial practices including residential segregation, economic and marginalization, and denial of care. Here we argue that sepsis risk is an immunological embodiment of racism in colonial states, that the factors contributing to sepsis disparities are insidious and systemic. We show that regardless of causative pathogen, or host ancestry, racialized people get and die of sepsis most frequently in a pattern repeatedly reiterated worldwide. Lastly, we argue that while alleviation of sepsis disparities requires radical, multiscale intervention, biological anthropologists have a responsibility in this crisis. While some of us can harness our expertise to take on the ground action in sepsis prevention, all of us can leverage our positions as the first point of contact for in depth human biology instruction on most college campuses. As a leading cause of death worldwide, and a syndrome that exhibits the interplay between human physiology, race and environment, sepsis is at the nexus of major themes in biological anthropology and is a natural fit for the field’s curriculum. In adopting a discussion of race and sepsis in our courses, we not only develop new research areas but increase public awareness of both sepsis and the factors contributing to uneven sepsis burden.

KEYWORDS
COVID-19, denial of care, human variation, racial embodiment, segregation, sepsis

1 | INTRODUCTION

By the time this paper is published, more than 2 years will have passed since the estimated emergence of the novel coronavirus (now SARS-CoV-2) in Wuhan, China. Since that time, the virus that causes COVID-19 has disseminated worldwide making so many people severely ill as to spur shelter-in-place orders, bust the international capacity for blown polymer fabrication and test and break the surge protection of emergency rooms in some of the wealthiest nations in the world (Borges, 2020; Feng & Cheng, 2020; Horowitz, 2020; Mendoza et al., 2020; Nedelman, 2020; Newsom, 2020). Among the United States’ almost surely underestimated 83,468,803 cases, and 1,002,557 deaths a disturbing pattern of vulnerability to SARS-CoV-2 infection and severity has been established (Dong et al., 2020) (Accessed, May 24, 2022). Black, Indigenous, and People of Color (BIPOC) and their communities are over-represented in the numbers of infected, severely ill, and dead in the United States. (Romano et al., 2021; Wadhera et al., 2020; Williams & Cooper, 2020). Multiple
experts on economic and social marginalization have pointed to a variety of social factors contributing to this pattern (Boggess & Gyamfi-Bannerman, 2016; Eberly et al., 2019; Hall et al., 2015; Marin et al., 2008; Strully, 2011; Williams & Collins, 2001). As many popular press articles and editorials have observed, these patterns are not new. They are caused by well-studied social determinants of chronic disease. Moreover, for at least a decade it has been recognized that sepsis, a syndrome caused by an infection of sufficient severity that it provokes a profound and damaging immune response, disproportionately kills Black and Brown people in the United States (Barnato et al., 2008; Esper et al., 2006; Mayr et al., 2014; Rush et al., 2018; Singer et al., 2016). SARS-CoV-2 causes sepsis. With nearly 20% of hospitalized COVID-19 cases resulting in sepsis prior to the advent of COVID vaccines, SARS-CoV-2’s disproportionate impact on BIPOC in the United States is many things—horrifying, reckless, a colossal systemic failing—but it is not novel (Prescott and Girard, 2020).

Billions of dollars has been spent on sepsis research over the last three decades, and no genetic basis for sepsis susceptibility by race or ethnic grouping has been found. Rather an overwhelming abundance of studies show that in the United States and other nations sepsis incidence and mortality maps to indicators of racial segregation, including economic and social marginalization (Davis et al., 2011; Koch et al., 2014; Rush et al., 2018; Xavier Moore et al., 2017). In the United States, where racial disparities in sepsis are most intensely studied, degree of segregation and social adversity have been associated with increased risk of sepsis comorbidities even when controlling for socioeconomic status (Hicken et al., 2014; Kershaw et al., 2015; Mayne et al., 2019). Here we argue that disparities in sepsis incidence are the immunological outcome of racist policy and practice, that sepsis risk is an immunological embodiment of racism in colonial states. We show that regardless of causative pathogen or host ancestry, racialized and marginalized people get and die of sepsis more frequently than heirs of colonial power in a pattern iterated again and again in colonial states across the world (Bruce et al., 2008; Davis et al., 2011; Gracey & King, 2009; Gravlee, 2009; Hennessy et al., 2020; Lewnard et al., 2014; Murthy et al., 2019; Williamson et al., 2013). The factors contributing to sepsis disparities by race are insidious and systemic. Specifically, race becomes embodied as increased sepsis susceptibility and mortality via three intersecting mechanisms stemming from segregationist practices that directly interfere with sepsis prevention and support (a) economic marginalization (b) increased social stress (c) denial of care. We show that these material conditions matter most in susceptibility to sepsis, and how all three of these mechanisms affect human biological variation via the manifestation of sepsis comorbidities and alterations in immunological function. Lastly, we argue that given that the contributing factors are systemic and that sepsis underway is a time-sensitive emergency, alleviating unequal sepsis burden requires a lifetime of radical state-level actions for prevention. As basic researchers in human biology and the first point of contact for in depth human biology instruction biological anthropologists have a responsibility to teach and enable action against racial disparities in sepsis.

1.1 | What is sepsis? A profoundly damaging immune response to severe infection

Sepsis is a clinically urgent, life-threatening syndrome stemming from severe infection and a subsequent powerful host response that can lead to mass tissue injury, widespread clotting, multi-system organ failure, shock and death (Singer et al., 2016). It is clinically categorized into two stages based on blood flow: (a) Sepsis – high blood volume pumped per minute but with low blood pressure; (b) Septic shock – a precipitous drop in blood volume pumped and blood pressure that remains very low even during the application of intravenous fluids (Deutschman & Tracey, 2014; Singer et al., 2016). Initiated by a variety of bacterial, fungal, parasitic, or viral pathogens sepsis is highly heterogenous and very difficult to treat (Opal, 2010; Singer et al., 2016). Outside of antimicrobial drugs, treatments for sepsis are largely restricted to supportive care. In ~75% of all sepsis cases in the United States before 2020, the causative microbes were not identified (Paoli et al., 2018). The immunological events of sepsis also vary by the location of the primary infection, which is also frequently not identified (Greenberger et al., 1995; Paoli et al., 2018; van der Poll et al., 1995). For cases where the site of primary infection is identified, the lungs (47%), abdomen (23%), and urinary tract (8%) are the most common locations (Martin et al., 2009). While these patterns differ by geography, lower respiratory infections (i.e., pneumonias), play an outsized role in sepsis incidence and mortality worldwide annually (Murdock & Howie, 2018). Before 2020, the leading identified causes of sepsis were dominated by microorganisms that live in or near the human respiratory tract constitutively (Novosad et al., 2016; Paoli et al., 2018; Sattar & Sharma, 2019). At that time, 1.7 million people developed and 265,000 died of sepsis annually in the United States alone (Liu et al., 2014; Rhee et al., 2017). Even in the wealthiest of nations, mortality rates for sepsis range between 30% to >70% (Angus & Wax, 2001; Singer et al., 2016). Before 2020, sepsis caused an impressive 19.7% of all annual deaths worldwide (Rudd et al., 2020). At the end of 2020, this number had radically increased, with SARS-CoV-2 alone as an agent of sepsis estimated to be the third leading cause of death in the United States and worldwide (IHME, 2021).

1.2 | In the absence of sepsis drugs, prevention and support remain the primary approach to care

There is no recovery drug for sepsis. Over the last 40 years, more than 100 clinical trials of would-be sepsis drugs aimed at modulating host immune responses to infection have failed. Proposed therapies have included a wide range of corticosteroids, receptor blockers, antibody treatments, anti-inflammatory medications and anticoagulants, often producing hopeful results in animal models or in early clinical trials, but unproductive or dangerous at scale in humans (Marshall, 2014). After decades of research, survival of sepsis relies heavily on a three-prong approach characterized by (a) early diagnosis, which is reliant on patient access to care and appropriate triaging (b) supportive...
treatment such as vasopressin to raise blood pressure, intravenous fluids, ventilation and pain management and (c) prevention of severe infections. Of the three prongs prevention remains the most effective approach to mitigating sepsis (Gaieski et al., 2010; Kempker et al., 2018; Kumar et al., 2006; Singer et al., 2016). Given the outsized role host immunocompetence plays in the current clinical approach to sepsis (i.e., do not get sepsis in the first place), prevention of sepsis is really a lifelong effort of prevention and management of infection and chronic conditions that are known comorbidities.

1.3 Sepsis survivors often live with physiological damage and altered immune function

When death tolls are broadcast during a pandemic, they set an unfortunately high and unrealistic bar for what constitutes disease impact. A focus on mortality as the most important outcome of severe infectious disease belies the biological reality that many pathogens maim their hosts in severe infection, and dramatically alter a host's constitution permanently. Sepsis is an assault on immune physiology, requiring major shifts in host’s energy allocation, bone marrow regulation and tissue repair. Recovery for those that survive is steep. Patients frequently experience health deterioration after the sepsis event. Nearly 60% of all people released from hospitals after sepsis are readmitted within the year. Approximately 40% die within 2 years, 80% within 5 years (Annane & Sharshar, 2015; Prescott & Angus, 2018; Shankar-Hari & Rubenfeld, 2016). Around 15% develop one to two significant functional limitations, cognitive impairments, or mental health conditions (Prescott & Angus, 2018). Common symptoms of this “post-sepsis syndrome” (PSS) include fatigue, lethargy, cognitive difficulty, executive function problems, muscle wasting and joint pain and associated difficulty moving or completing physical tasks (e.g., trouble dressing, bathing, walking), long-term immunosuppression, kidney failure, lung fibrosis, and associated hypertension (Annane & Sharshar, 2015; Arens et al., 2016; Chao et al., 2014; Denstaedt et al., 2021; Fitzgerald et al., 2016; Iwashyna et al., 2010; Vanhorebeek et al., 2020) (Burnham et al., 2014). The effects of sepsis are long-term, with 50% of survivors experiencing PSS symptoms 5 years after the sepsis event (reviewed in (Annane & Sharshar, 2015)). Sepsis can make a permanent stamp on host physiology, which means that when a group of people bear disproportionate sepsis burden, they can also experience disproportionate post-sepsis pain and disability.

1.4 Sepsis burden is disproportionately carried by Black, Indigenous, and People of Color in the United States

Even when controlling for age, the primary risk factor for sepsis, non-White people in the United States are disproportionately represented in annual sepsis incidence and mortality with Black and Indigenous people overrepresented in cases and deaths each year (Barnato et al., 2008; Mayr et al., 2014; Rush et al., 2018) (Figure 1a, sepsis deaths). Similar patterns of racial overrepresentation in severe SARS-CoV-2 infections (noted as hospitalization) have been noted by the US Centers for Disease Control and Prevention (CDC) since Spring of 2020 (Figure 1b) (CDC, 2020a; CDC, 2020b). For the first 18 months of the pandemic, highly segregated cities such as New York City and
Chicago saw the most deaths related to COVID-19 in mainly Black and Hispanic neighborhoods (Wadhera et al., 2020; Williams & Cooper, 2020). The burden of sepsis on non-White communities in the United States is likely worse than these estimates. Sepsis symptoms, rather than sepsis itself, are often recorded as cause of death on death certificates. Moreover, sepsis and COVID-19 hospitalization and mortality data is collected for the CDC in a 5-category race construct (i.e., White, Black, Asian and Pacific Islander, American Indian or Native Alaskan, with option to describe as Hispanic) which lumps and buries non-White identities. Worse, multiple US states set COVID-19 reporting standards that drastically underreported cases over 2020 and beyond (i.e., New York, Florida) (Fink, 2021; Rai, 2021). Yet despite underreporting issues, the pattern of Black, Brown, and Indigenous people being overrepresented in severe infection case and sepsis mortality numbers occurs each year, which has led some to explore the possibility that sepsis susceptibility is genetically inherent.

### 1.5 Uneven sepsis burden by race is not explained by inherent genetic factors

Over the last three decades billions of dollars have been funneled into sepsis therapeutic target and treatment research, including screens for genetic correlates for sepsis susceptibility (Marshall, 2014). While many genetic loci have been associated with risk of sepsis and septic shock (Horn et al., 2020; Rautanen et al., 2015; Scherg et al., 2016; Toubiana et al., 2010; Wurfel et al., 2008), no study has been able to reliably demonstrate a genetic basis for sepsis incidence and mortality by racial or ethnic grouping. Rather, findings that polymorphisms are associated with increased or decreased infection susceptibility or risk of severity in a single racial or ethnic grouping typically cannot be replicated by other studies. It is not unusual for the proposed protective or deleterious effects of a polymorphism to be later found associated with the opposing effect, or found in other racial groups but not associated with the specific effect identified in the original study (Baier et al., 2006; Chantratita et al., 2014; Chauhan & McGuire, 2008; Ferwerda et al., 2009; Meyer et al., 2014; Naderi et al., 2014; Saleh et al., 2004; Wurfel et al., 2008; Yavari et al., 2012; Zhang et al., 2014). For example, Ferwerda et al. (2009) found that a single nucleotide polymorphism (SNP) in the gene TIRAP (rs8177374), which encodes an important adaptor protein in several bacteria-detecting Toll-Like Receptor cascades implicated in sepsis, is both protective against septic shock and more prevalent in Western Europeans compared to an African population (Ferwerda et al., 2009). However, subsequent work has demonstrated that this non-synonymous change, which confers a switch from serine to a leucine at position 180 in the TIRAP protein, does not have a clear-cut effect on sepsis, let alone on racial lines. When combined with two common SNPs in TLR4 (Asp299Gly/Thr399Ile), rs8177374 was found to be associated with an increase in the likelihood of sepsis in two European patient cohorts (Kumpf et al., 2010). Khor et al. (2007) found TIRAP Ser180Leu heterozygosity to be associated with decreased susceptibility to Mycobacterium tuberculosis in study cohort of ~1200 individuals from Gambia, Guinea-Bissau, and the Republic of Guinea, a result they highlighted as proof of ongoing selection at this locus in “the African population” (Khor et al., 2007). At least two other small studies have generated opposing findings in non-African groups (Capparelli et al., 2013; Naderi et al., 2014). Moreover, the association reported by Khor et al., 2007 could not be replicated by two substantially larger studies that recruited 7-fold the people from Ghana, Russia, and Indonesia (Nejentsev et al., 2008), and 13,000 people from across the world (Miao et al., 2011), respectively. This pattern of opposing results is common in studies that seek to identify a genetic rationale for increased sepsis incidence and mortality in non-White groups (IL1RN [Becker et al., 2014; Carrol et al., 2011; Park et al., 2018], TLR4 [Agnee et al., 2002; Arbour et al., 2000; Rodriguez-Osorio et al., 2013; Zhu et al., 2012; Ziakas et al., 2013], TLR1 [Chantratita et al., 2014; Wurfel et al., 2008], IL-6 [Baier et al., 2006; Chauhan & McGuire, 2008; Chen et al., 2019; Hu et al., 2019], TNFα [Montoya-Ruiz et al., 2016; Oliveira et al., 2018; Shoily et al., 2021]).

The search for genetic explanations for disparities in sepsis incidence and mortality is frustrated by many factors including problems reaching statistical power in studies, a widely held practice in biomedic genetics of working with mainly White study populations, errors in and/or failure to identify causative pathogen and infection location, failure to account for epistasis and gene–environment interactions, and challenges associated with finding alleles that may have incremental effects on a complex trait that is highly heterogenous and profoundly affected by environment. The biological meanings of associations that are found are often not clear. It seems increasingly likely that, in most cases, any genetic contribution to sepsis risk is coming from combinations of alleles that have incremental effects on the pathogenesis of comorbidities given particular environmental circumstances (e.g., diabetes, hypertension), and not common variants with large effect sizes that are influencing sepsis risk directly (D’Urso et al., 2020). Ultimately, the principal problem with interpreting any of this research as suggesting there is a unique combination of genetic alleles governing severe infection in separate human groups is that it relies on finding sepsis-associated loci that hold up across such groupings. Alas, splitting humans into broad racial groupings based on genetics is really hard to do (Benn Torres, 2020; Gravlee, 2009).

### 1.5.1 ...because humans cannot be sorted into inherent genetic racial groupings

As many recent articles addressing the conflation between the notion of biological races with the occurrence of a limited number of highly penetrant human traits found in very broad geographic regions have discussed, races are functionally terrible typologies (e.g., Benn Torres, 2020; Gravlee, 2009; Van Arsdale, 2019). We are a young, highly migratory species that is fairly genetically homogenous. By and large, our genetic variation varies gradually, often in local clines, with some genetic sub-structuring around enormous geographic barriers (e.g., the Saharan desert). This sub-structuring itself is pretty minimal.
compared to what we see in older species. The genetic differences between continental populations is considerably less than the differences within a continental population (Lewontin, 1972; Livingstone, 1962; Van Arsdale, 2019). There are few penetrant phenotypes that geographically cluster. The majority of known phenotypic differences in humans substantially overlap by geography and “group”, however that group is defined. This is why nearly 400 years of trying to sort humans into biological typical types based on clusters of defining characteristics - similar to how Wedgwood organizes its ceramics catalog - has failed.

More importantly, for race and sepsis, finding true biological groupings of humans was never the point of human typology in the first place. As noted and well explained by others, human typologies as we know them emerge with the rise of European nationalism, colonialism and notions of who is and is not a citizen gaining steam in the 15th century (Armelagos & Goodman, 1998; Brubaker, 2009). The concept of race is drenched in racism that assumes purity of origins and an unchanging natural order, with Europeans at the top closest to a god, and all other humans and beings ranked below. As Europeans increasingly colonized nations, the notion of human races have been written right into past and current legislation, policy and institutions to enforce this order (Common wealth of Virginia, 1924; Kushner, 1979; Office of Public Affairs, 2012; Peckham, 1979; US District Court for the Northern District of California, 1979). Such policies have assuredly had biological consequences within racial categories as they, for example, force migrations of unrelated peoples, determine who may mate with whom, affect how many children someone may have and force dispersion as those children were sold based on race (McLean, 2020; Roseman, 2014). Most frequently, race is not used to reflect genetic shifts that might happen as the term is used to reinforce racist policy (McLean, 2020). As Benn Torres, 2020 and Gravlee (2009) have previously noted - in medicine and population genetics, where racial categories are commonly used, the use of the races tends to reduce phenotypes stemming from a combination of environmental and genetic factors down to just genetics, attributing race simply to inherent biology.

### 1.6 Rather, social factors connected to race have a profound effect on sepsis risk

While race does not capture inherent genetic differences between groups of people, as a tool of subjugation by and in colonial states race is experienced (Benn Torres & Torres Colon, 2015; Gravlee, 2009; Krieger, 1999). It is specifically experienced as segregation, opportunity loss and violence that contributes to lowered life expectancy compared to the heirs of colonial power. In this way, racialized identity negatively affects health and immunity both acutely and chronically, directly (e.g., experience of racist remarks can spur or worsen asthma attacks, raise blood pressure, alter infection course) and indirectly (decreased employment, lower income, healthcare, and food options) (Bissonnette et al., 2012; Jones et al., 2019; Thakur et al., 2017; Thames et al., 2019; Williams & Collins, 2001). That racialism and racialization, the experience of having a race assigned and being treated differently as a result, alters human biology and becomes embodied as a range of health conditions has been described and discussed at length elsewhere (see Gaskin et al., 2014; Gravlee, 2009; Krieger, 1999; Kuzawa & Sweet, 2009; Pemeger et al., 1995; Thames et al., 2019; Williams & Collins, 2001).

Race is often embodied as conditions that are comorbidities for sepsis. While sepsis can affect anyone, most patients have at least one comorbidity that alters immunocompetence (Banta et al., 2012; Esper et al., 2006). The leading underlying factor is age - with infants under 1 year of age and adults over the age of 55 years strongly over-represented in the annual case count (Martin et al., 2006; Novosad et al., 2016). The next most common comorbidities are highly networked conditions strongly associated with social stress and economic marginalization including diabetes mellitus, hypertension, cardiovascular disease (CVD) and stroke, obesity, chronic kidney disease and chronic obstructive pulmonary disease (COPD) (Novosad et al., 2016; Paoli et al., 2018; Papadimitriou-Olivergeris et al., 2016; Wang et al., 2012). In the United States, non-White people are over-represented in the numbers of individuals manifesting sepsis comorbidities every year (Barnato et al., 2008; Cheng et al., 2019; Mayr et al., 2014; Vart et al., 2020). While, highly penetrant genetic loci have been connected to sepsis comorbidities, a large body of work on sepsis risk factors has simultaneously found that, after age, indicators of racialized identity and income are the leading predictors of sepsis incidence and mortality (Galiatsatos et al., 2018; Rush et al., 2018; Wang et al., 2010; Xavier Moore et al., 2017).

To illustrate the intersection of severe infection risk, income and sepsis comorbidities in the United States we have plotted the aged-adjusted percent distribution of three important comorbidities for sepsis (hypertension, obesity, diabetes) and unmet medical need due to cost within race categories as recorded in the US National Health Interview Survey for 2018 (CDC, 2018a; CDC, 2018b), median family income as reported by the US Census bureau’s Current Population Survey (US Census Bureau, 2018) with age-adjusted sepsis (septicemia) mortality incidence reported by the National Vital Statistics: Death report for 2017 (Kochanek et al., 2019, table 10) (Figure 2). Multiple metrics exist for estimating sepsis/severe infection incidence. Here we use COVID-19 age-adjusted hospitalization incidence by race as captured by the CDC’s COVID-19-NET tracking program from March 2020 to February 2021 as an example of severe infection incidence (Acosta et al., 2021). In combination, a clear pattern of increased sepsis risk (age-adjusted percent of people within race/ethnic group with a sepsis comorbidity and/or reporting unmet medical need), severe infection incidence and sepsis mortality (age-adjusted percent of people within race/ethnic group who died of sepsis), with decreased median family income is observed.

An association between low income and increased sepsis risk and occurrence has been found in studies at various scales. Using county level, age and gender adjusted, US sepsis mortality data, Xavier Moore et al., 2017 found that regions in the Mississippi Valley, Middle Georgia and Central Appalachia had elevated sepsis mortality compared to the rest of the nation. Adjusting for patient
characteristics inside and outside of these “sepsis belts”, the authors found that people living in these regional sepsis belts tended to have lower median household income, college completion, and housing values than people living outside of sepsis belts (Xavier Moore et al., 2017). A prior study by Wang et al. (2010) used the National Center for Health Statistics’ Compressed Mortality File and found state-based sepsis belts crossing over similar regions (Wang et al., 2010). The impact of low income on whether or not a person gets and survives sepsis is stringent. Being unemployed has been found to be a lead predictor for being admitted to the ICU for sepsis in Canada and Denmark, two nations with robustly funded universal healthcare (Hennessy et al., 2020; Storm et al., 2018). A US nationwide retrospective cohort analysis of over 8 million hospital admissions (>600,000 for sepsis) not only found that low income was associated with the highest risk of sepsis death, but low income residents who died of sepsis were, on average, 5 years younger than people in the highest income category (Rush et al., 2018).

### 1.7 Marginalization as a mediator of sepsis is reiterated on a global scale

A highly simplified perspective of the overrepresentation of non-White people in annual sepsis numbers in the United States might highlight the nation’s expensive hybrid but largely pay-to-play health care system. However, the United States is not alone in this pattern of racialized residents bearing disproportionate sepsis burden. In colonial states that track racial and/or ethnic identity data with sepsis incidence and mortality and freely share it, the greatest sepsis burden is carried by people who are not heirs to colonial power. The 400 million Indigenous people around the world, for example, come from many different geographical regions, and yet many share economically-driven health determinants and health problems that contribute to sepsis risk. Universally, in colonial states, Indigenous people are over-represented in low-income brackets/levels, and often have restricted access to adequate housing, water, food and health care, and carry a higher severe infection burden as a result (Gracey & King, 2009). The connection between colonial practices and sepsis can be drawn on a grim and global scale. European colonialism has had complex heterogenous effects across colonized nations, launching very complexly divergent paths of economic development for nations previously under European rule. With a few notable exceptions, colonized people in these nations experienced deeply unequal access to power and finance, were often enslaved or had substantially lower incomes such that there is a strong relationship between European colonization, the style and events of colonization and a history of income inequality, local underdevelopment, stagnation and current lower national income (Bruhn & Gallego, 2012) (reviewed in Alvaredo et al., 2021). The majority of the world’s sepsis burden is borne by the least wealthiest nations, most former European colonies. An assessment of 109 million individual death records filed in 2017 and adjusted for patient characteristics found that 8.2 million of the 11.1 million sepsis deaths worldwide that year occurred in low and middle income nations (Rudd et al., 2020).

To illustrate this connection between national income and sepsis incidence, we have mapped sepsis incidence for all underlying causes per 100,000 people in 2017 by country (data acquired from Rudd et al., 2020). Gross Domestic Product of the nations cited in the Rudd 2020 data set, sepsis mortality normalized by incidence, and incidence normalized by Gross Domestic Product (Figure 3) (World Bank, 2017).
A clear relationship can be seen—the poorest nations, all former European colonies, have the highest sepsis incidence (Figure 3a–c). When we normalize sepsis mortality per 100,000 population by sepsis incidence per 100,000, and sepsis incidence by GDP it is clear that more people in middle and low income nations die of sepsis per incident than in wealthy nations. (Figure 3b–d). The economic and socio-political paths of nations after colonial rule are the complex outcomes of a multitude of factors deeply influenced by colonial institutions and practices particular to locality, however some nations see alterations in life expectancy and health after national independence (Bruhn & Gallego, 2012; reviewed in Alvaredo et al., 2021; Acemoglu et al., 2001; Dell, 2010; Verstraeten et al., 2016). Given, we compared sepsis incidence to years since independence for just former British colonies and found a general pattern of higher sepsis burden with fewer years since independence suggesting that, for some of these nations, sepsis burden may be lessened with distance from colonial rule (Figure S1). As factors contributing to post-colonial conditions vary by locality, a potentially covarying pattern of sepsis incidence such as this one warrants deeper investigation.

However, sepsis data from a range of former British colonies that track sepsis incidence by race/ethnicity and class supports the notion that people with racialized/minoritized identities in colonized states also disproportionately experience sepsis for reasons other than income access to healthcare (Ali et al., 2018; Bailie et al., 2004; Bissonnette et al., 2012; Chikovore et al., 2020; Davis et al., 2011; Fathima et al., 2019; Goodwin et al., 2016; Gracey & King, 2009; Huggan et al., 2010; O’Sullivan et al., 2011; Tyler et al., 2018; Yip et al., 2002). The trend is retained in wealthy nations with vigorous universal health care systems. For example, Māori patients in New Zealand are 2–3 fold more likely to develop sepsis than non-Māori, and across all age groups are more likely to die of sepsis than non-Māori patients (Baker et al., 2012; Huggan et al., 2017; Kaukonen et al., 2014; Williamson et al., 2013; Hill et al., 2001; O’Sullivan et al., 2011). Indigenous Canadian adults have a 1.13–1.33 increased odds of hospitalization with sepsis compared to the rest of the adult Canadian population (Hennessy et al., 2020). The robustly funded public health systems of these nations do not prevent the effects of racialization and marginalization on sepsis.

1.8 | Being racialized contributes to sepsis susceptibility so substantially as to outstrip the impact of any one causative pathogen

Common causes of sepsis in any given nation varies, with geographic regions tending to share commonly implicated pathogens (Table 1).
However, in wealthy nations, racialized people tend to develop sepsis caused by eccentric and preventable infections that are not as commonly experienced in the general population. For example, despite living in one of the wealthiest nations in the world, Indigenous peoples of Canada are more likely than the general population to develop sepsis via invasive Streptococcus A, and Haemophilus influenzae A (Hia), two bacterial infections for which there are effective antibiotics and a widely available 40+ year old vaccine (for Hia). The magnitude of these disparities is profound—Indigenous peoples suffer invasive Streptococcus A sepsis at 8x the rate of the rest of the nation—levels that approximate those of low-income countries (Hennessy et al., 2020; Kelly et al., 2011; Loewen et al., 2017). This is a pattern reiterated in the United States, New Zealand, and Australia (Close & McAuley, 2020). Importantly, there is no particular bacterial strain to blame. Bacterial samples from invasive Hia cases in the Canadian North, for example, which is home a large proportion of Indigenous people, have found no consistent bacterial phenotype or genotype (Kelly et al., 2011). Rather host conditions appear central to these disparities. The pattern of invasive Streptococcus A and Hia infections intersects with the incidence of sepsis comorbidities in Canada, which are consistently higher among Indigenous people than non-Indigenous people and highest for First Nations people living on reserves (Carriere et al., 2016).

Living conditions, which are strongly influenced by government policy, have an outsized effect on contracting preventable diseases and manifesting them severely. For example, many Indigenous Australians are subject to a set of conditions that lead to exceptional sepsis burden, including sepsis by eccentric causes. In the Top End of the Northern Territory of Australia, a remote region with a high proportion of Indigenous peoples, the sepsis incidence for Indigenous people is 40.8/1000 (age-adjusted), a burden that is nearly 5× greater than other regions of Australia and even outstrips that experienced by any population in the United States and Europe (Davis et al., 2011). Most annual cases of sepsis worldwide are caused by lower respiratory infection (Murdoch & Howie, 2018). In remote regions of Australia where Indigenous people were forced to migrate, sepsis tends to stem from a particular cascade of co-infections associated with poverty and crowded living conditions. Human T-cell lymphotropic virus type 1 (HTLV-1) is a leukemia lymphoma causing retrovirus of Asian and African origin that is rare worldwide but endemic in the Reserve System lands in Central Australia (Einsiedel & Fernandes, 2008; Jegado et al., 2019). HTLV-1 predisposes hosts to scabies (Sarcoptes scabiei), threadworm (Strongyloides stercoralis) and pneumonia. Scabies mites and larvae cause wounds that can progress to sepsis via infection by commensal bacteria on the skin, and threadworm and pneumonia can progress to severe infections in an already immunocompromised host (Einsiedel & Fernandes, 2008; Mika et al., 2012). Progression to severe infection is so common that all three are considered preceding infections to sepsis in Central Australia. Multiple national studies have found that the primary factors driving this cascade of severe coinfections are low income, exceedingly poor housing conditions in the Australian National Reserve System, and inadequate provision of clean water (Ali et al., 2018; Bailie et al., 2004; Bailie et al., 2010; McDonald et al., 2010). Housing has a similar effect on sepsis incidence in the United States. Both community-associated and hospital-associated methicillin-resistant Staphylococcus aureus (MRSA) infections and bacteremia are higher in people with low income and living in public housing (Hota et al., 2007; See et al., 2017).

Difficulty accessing basic care due to poverty has a similarly profound effect on sepsis risk from preventable infections. At an extraordinary incidence of 17,000 per 100,000 live births, India experiences the highest rate of neonatal sepsis in the world (Fleischmann-Struzek et al., 2018). The most common causative pathogens are among the most common causes of adult and infant sepsis worldwide - Klebsiella pneumoniae and S. aureus (Brinkworth & Valizadegan, 2021; Deorari et al., 2005; Wattal et al., 2020). However, the most important risk factor for neonatal sepsis in India is being “outborn” or born outside of hospital, a common practice in impoverished rural regions of the nation (Murthy et al., 2019). While high socioeconomic status is associated with sepsis comorbidities (e.g., obesity and hypertension) in India, most sepsis cases and deaths occur among the rural, poor children and mothers who face birth with severe financial limitations and are denied preventative care (Corsi & Subramanian, 2019; Joshi & Kushwah, 2011; Lahariya & Paul, 2010). This pattern of poverty and marginalization determining sepsis risk and outcome is reiterated for the major causes of sepsis among rural Black and Indigenous Africans, with M. tuberculosis infections in HIV-1 positive (HIV-1+) people and Plasmodium falciparum, overrepresented as causes of sepsis in these groups across multiple SubSaharan African nations (Andrews et al., 2014; Chikvore et al., 2020; Cummings & O’Donnell, 2015; Jacob et al., 2013; Lewnard et al., 2014; Mathema et al., 2015; Plewes et al., 2018; Warren, 2017).

1.9 In wealthy nations racism becomes sepsis via a mesh of interconnected marginalizing experiences

Worldwide, the bulk of sepsis burden falls on marginalized peoples (Gracey & King, 2009; Rudd et al., 2020). What should raise alarm bells within wealthy nations is that the sepsis burden remains uneven despite comprehensive sepsis prevention and survival campaigns being bred right into health care. With six out of the seven G7 nations providing universal healthcare to people residing within their borders, sepsis disparities along racial lines should not exist and yet, profound disparities do. How does race and, therefore, racism become sepsis in wealthy nations?

The physiological condition of a host has an overwhelming effect on infection progression, and that condition is altered daily through living circumstances in the short and long term. Race, therefore, becomes embodied as sepsis through interconnected discriminatory practices that affect daily experience, and in turn alter immune function and immune competency. The most influential factors creating sepsis disparities are systemic, stealthy and strongly connected to racist policy and practices. Here we use examples of practices in former British colonies (Anglocolonial states) to explain how.
1.9.1 | Racial residential segregation creates and maintains wealth inequity

In wealthy nations low income is the strongest predictor of sepsis susceptibility and is reinforced by social policy intended to concentrate poverty. Residential segregation is one such discriminatory practice that is common in colonial states, where it is built into all tiers of legislation and controls everything from housing quality to grocery store access to public transportation to job opportunity (Nightingale, 2012; Williams & Collins, 2001). Though an ancient practice of colonizing powers, the segregation of people into White and non-White neighborhoods in the United States has its most recent roots in the British East India Company’s strict division of Madras, India into “White Town” for colonizers and Black Town for Indian natives in the 17th century (Nightingale, 2012). Today residential segregation is still enforced in wealthy Anglocolonial states by zoning regulations, but is substantially upheld by less organized efforts such as discriminatory deeds and the intentional restriction or redirection of non-White home ownership via mortgage loan refusal (i.e., “redlining”) (Kushner, 1979; Lamb, 2005). The impact of residential segregation on health is intergenerational and can ripple far beyond segregated regions. It is these spreading effects of racial residential segregation that create a variety of deprivations and stressors that increase a person’s likelihood of severe infection and sepsis.

In 2001 Williams and Collins published a groundbreaking paper that found racial residential segregation in the United States negatively affects health by reducing adult income for visible minorities via mechanisms that concentrate poverty - including limiting fair access to elementary and secondary education, and restricting opportunities for post-secondary education and employment (Massey & Fischer, 2000; Williams & Collins, 2001). Whether through enforced rurality in Australia, or urban housing blocks in major US cities, the

| Country      | Common causative pathogen in general population                                    | Overrepresented group in sepsis cases        | Pathogen of note affecting overrepresented group (“vaccine or other prophylaxis exists”) | References                                      |
|--------------|-----------------------------------------------------------------------------------|---------------------------------------------|------------------------------------------------------------------------------------------|------------------------------------------------|
| Uganda       | Mycobacterium tuberculosis, Plasmodium sp., Streptococcus pneumoniae,            | Rural poor, Indigenous                       | M. tuberculosis* + HIV-1 Plasmodium sp*                                                  | (Jacob et al., 2013; Lewnard et al., 2014; Moore et al., 2019) |
|              | (HIV-1, and Cytomegalovirus infections are co-associated with all)                |                                             |                                                                                          |                                                 |
| Zambia       | S. pneumoniae, Staphylococcus aureus, M. tuberculosis                             | Rural poor, Indigenous                       | M. tuberculosis* + HIV-1                                                                  | (Andrews et al., 2014; Chimese et al., 2012; Loevinsohn et al., 2021) |
|              | (HIV-1 co-associated with all)                                                    |                                             |                                                                                          |                                                 |
| South Africa | Klebsiella sp., S. aureus, Serratia marcescens, M. tuberculosis + HIV-1, Plasmodium falciparium | Rural poor, Indigenous, neonates             | M. tuberculosis * + HIV-1, P. falciparium*                                               | (Chikovore et al., 2020; Mathema et al., 2015; Reddy et al., 2021; Warren, 2017) |
| India        | Acinetobacter sp., Klebsiella sp., Pseudomonas sp., Escherichia coli             | Rural poor neonates, Rural poor mothers     | Klebsiella pneumoniaiae, S. aureus                                                       | (Chatterjee et al., 2017; Murthy et al., 2020; (Corsi & Subramanian, 2019; Joshi & Kushwah, 2011; Lahariya & Paul, 2010). |
| Canada       | E. coli, S. aureus, K. pneumoniae, Streptococcus pneumonia                        | Indigenous                                  | Invasive Streptococcus A* Haemophilus influenzae A *                                      | (Savage et al., 2016) (Hennessy et al., 2020; Kelly et al., 2011; Loewen et al., 2017) |
| United States| Staphylococcus spp., Pseudomonas sp., E. coli, Klebsiella sp., Streptococcus spp. | Black, Indigenous, Hispanic                 | Pneumococcus*                                                                             | (Barnato et al., 2008; Marrie, 1999; Mayr et al., 2014; Novosad et al., 2016; Nowalk et al., 2019; Rush et al., 2018) |
| Australia    | E. coli, Streptococcus spp., Staphylococcus spp.                                 | Indigenous                                  | Pneumococcus* S. aureus + HTLV, S. aureus                                                 | (Davis et al., 2011; Douglas et al., 2020; Einsiedel & Fernandes, 2008; Sundararajan et al., 2006) |

#Note: Please note that in some nations, including Canada and the United States, influenza deaths are counted separately from other causes of sepsis.
concentration of poverty created by residential segregation starts cycles of opportunity loss and restricted life choices. These cycles compound into lower levels of tax dollars feeding the education, public transportation and healthcare systems locally. Lower public funds perpetuate reduced opportunities, lower quality and devalue housing, and lower adult income, subsequently creating and maintaining racial wealth inequity (Massey & Fischer, 2000; Orfield et al., 2008). Moreover, the effects of segregation are intergenerational, with the efforts of non-White families in segregated regions of the United States, for example, to accumulate wealth that can be passed to the next generation stymied (Bhutta et al., 2020; Ray et al., 2021). The repercussions of segregation are pernicious for even wealthy non-White people in Anglocolonial states. In a nationwide analysis of neighborhood and spatial inequality of US census tracts and households, Sharkey (2014) found that no matter the socioeconomic configuration, majority Black neighborhoods were more often physically close to regions that were severely disadvantaged. Majority Black neighborhoods were so substantially segregated and poverty so concentrated within them that even Black residents with an annual income of $100,000 or more a year lived with higher levels of neighborhood disadvantage (e.g., poor public school funding, poor housing, lowered grocery options) than White families earning less than a 1/3rd of that amount (Sharkey, 2014). The disadvantage reinforced by residential segregation practices have a substantial impact on life expectancy. In the United States, for example residential segregation is strongly associated with a 9%-14% lower probability of survival from age 35–75 among Blacks than Whites, a particularly grim statistic given the hyper-segregated nature of at least 20 US cities (Intrator et al., 2016; Popescu et al., 2018).

1.9.2 | ...which fosters living conditions associated with sepsis comorbidities

The lowered life expectancy of Black versus White people in segregated regions of the United States is partially due to increased levels of chronic disease stemming from disadvantage. A robust body of research clearly associates residential segregation with the severity of multiple chronic conditions that are also comorbidities for sepsis, including hypertension, obesity, chronic kidney disease, coronary heart disease and stroke (e.g., Gee & Ford, 2011; Kershaw et al., 2011; Kershaw et al., 2015; Rodriguez et al., 2007; Usher et al., 2018; Williams et al., 2019; Yu et al., 2018). The mechanisms by which segregation generates sepsis comorbidities are multitudinous. As a function of residential segregation, for example, income inequality alters household conditions and quality such that sepsis comorbidities become more likely. Lower income housing tends to be older, poorly ventilated, and contain higher levels of volatile organic compounds (VOCs), lead, pests and associated allergens and lipopolysaccharide; all of which are associated with or worsen comorbidities for lung infections that can progress to sepsis, including chronic bronchitis, asthma and COPD (Adamkiewicz et al., 2011; Levy et al., 2018; Pahwa et al., 2017; Wang et al., 2008). The housing inequity in housing in Anglocolonial states is profound. In the United States, for example, 7.5% and 6.3% of Blacks (non-Hispanic Blacks) and Hispanic people live in substandard housing, compared to 2.8% Whites (non-Hispanic Whites) (Jacob et al., 2013). This housing is thought to be a play a role in Black people experiencing the highest asthma prevalence in the United States, with low quality housing associated with 50% increased odds of a child making an emergency room visit for asthma in the previous 12 months (Adamkiewicz et al., 2011; Hughes et al., 2017). It’s a theme repeated in other Anglocolonial states, where crowding, inadequate ventilation, poor cleaning facilities and even lack of running water in rural housing settings that are often under government fiduciary responsibility, are strongly associated with severe infection in Indigenous peoples (Ali et al., 2018; Bailie et al., 2004; Bailie et al., 2010; Baker et al., 2012; Boyd, 2011; Kovesi, 2012; McDonald et al., 2010; Pahwa et al., 2017).

Via neighborhood design, an outcome of government (e.g., residential zoning, Crown land protection) and social policy (e.g., redlining), segregation impacts the development of other leading sepsis comorbidities via resource access. Food insecurity and lowered access to nutrient rich and fresh foods are factors in the development and management of obesity and other highly networked illnesses (i.e., diabetes, hypertension, chronic kidney disease, and coronary heart disease) (Davies, 2016; Morland et al., 2006; Sun et al., 2020) (reviewed in Gucciardi et al., 2014). Restricted access to food through residential zoning and business investment plays an important role in this regard. In US cities, for example, lower income predominantly Black neighborhoods, tend to have fewer grocery stores and less fresh food access than predominantly White neighborhoods of the same or higher income level (Baker et al., 2006; Bower et al., 2014; Morland et al., 2006). Forced rurality can have similar effects. The Canadian Reserve System incorporated a “pass” requirement in 1885 specifically intended to restrict Indigenous food security by limiting hunting and other food seeking practices off reserve. Without this permission, Canadian Indigenous peoples faced the threat of indefinite incarceration (reviewed in Ray et al., 2019). Today, these communities are disproportionately affected by severe and chronic food insecurity, where traditional food loss, climate change and limited infrastructure design drives food insecurity in remote regions, and low income is a major barrier to food access in urban regions (Fieldhouse & Thompson, 2012; Laurie et al., 2019; Richmond et al., 2020; Skinner et al., 2016). Similarly, Australian Indigenous peoples, 29.7% of whom live in the remote Northern Territory, experience food insecurity primarily due to their distance from a city center [reviewed in (Davy, 2016)]. In each of these populations, the incidence of chronic disease associated with food insecurity is very high (Domingo et al., 2021; Gracey, 2007; Gracey & King, 2009).

1.9.3 | ...and restricts access to preventative care

Segregation practices do not just increase the risk of developing sepsis comorbidities via resource deprivation. The creation of economic disadvantage obstructs chronic disease prevention and management by impeding health care access. The inability to afford insurance and
comprehensive care in the United States has been strongly linked to increased prevalence of sepsis comorbidities such as hypertension and end-stage renal disease in Black Americans, for example, 11% of whom were uninsured in 2020 (Artiga et al., 2021; Kershaw et al., 2011; Volkova et al., 2008). The expensive, and inequitable hybrid healthcare system in the United States is not the only factor to blame for such health disparities. In the robustly publicly funded healthcare systems found in Canada and Australia, imbalanced use of healthcare by neighborhood is also common. For example, people living in low socioeconomic status (SES) Canadian neighborhoods, experience increased use of physicians’ services and hospitalization (suggesting increased need), while Australia Indigenous peoples from low SES isolated regions are more often hospitalized for severe infection than the general population (Davis et al., 2011; Yip et al., 2002). In both the United States and Canada access to quality health care in both rural and urban areas is very dependent on and can be frustrated by government and corporate policy decisions that determine how healthcare centers are spaced, and what kind of healthcare supply is made available (Caldwell et al., 2017; Carr et al., 2017; Dai, 2010; Elting et al., 2009; Hayanga et al., 2009; Lee, 2019). Access to health care in the Toronto region is noted to be lowered for language minorities and recent immigrants, who tend to experience more difficulty accessing primary care physicians rather than walk-in clinic care because fewer primary care physicians have offices in language minority and immigrant neighborhoods (Bissonnette et al., 2012). In highly segregated US counties, each percentage increased in numbers of Black and Hispanic residents is associated with a decrease in surgical resources including the number of general surgeons (Hayanga et al., 2009). Unequal health care worker access, by social policy or social neglect, affects sepsis comorbidity development and severity because it hampers preventative care, disease monitoring and management via therapeutics. The more severe the comorbidity, or the more comorbidities a person has, the higher their susceptibility to severe infection (Goodwin et al., 2016; Singer et al., 2016).

However, even when physicians are available, their availability does not ensure appropriate care. Lack of provider cultural sensitivity has been found to compound chronic disease pathogenesis in patients, and impede provider to patient communication, care use, and health outcomes (Wakerman et al., 2019; Yashadhana et al., 2020). While these patterns appear diverse, they are connected to a similar phenomenon of increased disease incidence and unmet medical need. Delayed preventative and managed care for infectious disease comorbidities has an outsized impact on sepsis mortality. People who are medically underserved often die of sepsis, even after adjustment for age, race and sepsis severity (Goodwin et al., 2016).

The severity of comorbidities increases with segregation even when controlling for disease risk factors, income and resource access. In a survival analysis (multivariate proportional hazards analysis) of residential segregation degree and cardiac events experienced by over 5000 racially categorized people, Kershaw et al. (2015) found each standard deviation of increased residential segregation experienced by Black patients was linked to a 12% higher hazard of cardiovascular disease (CVD) even when adjusted for CVD risk factors and socioeconomic status. Similar findings have been made by Mayne et al., 2019, which points to the messy reality that the impact of segregation on sepsis risk is entangled in more than income, neighborhood disadvantage, and housing quality – it is reflective of other effects of being racialized (Mayne et al., 2019). Segregation promotes racism. Receipt of racist behavior and action alters a person’s immune function and tissue biology.

Mammalian immune physiology is highly responsive to social environment such that there are predictable white blood cell transcriptional patterns that correlate to degree of such social adversity (Thames et al., 2019) (reviewed in Cole, 2013; Cole, 2014). Received and perceived discrimination, and vigilance (e.g., racism vigilance, anticipatory stress over finances) induce stress responses that alter immune and other physiological functions (Forde et al., 2020; Hicken et al., 2014; Saban et al., 2018). In what neuroimmunologist Stephen Cole refers to as the Conserved Transcriptional Response to Adversity (CTRA), increased chronic social adversity is associated with white blood cells amplifying transcription and expression of proinflammatory cytokines (Irwin & Cole, 2011). Cytokines are small pleiotropic proteins important in cell signaling. The proinflammatory ones are powerful, nonspecific antimicrobial factors in their own right. Proinflammatory cytokine release invariably kills many infecting microorganisms, at the cost of bystander tissue damage in the host (reviewed in Brinkworth & Valizadegan, 2021). When a host experiences increased adversity, white blood cells tend to decrease production of small signaling proteins known as type I interferons, many of which serve important functions in clearing viral infections and restricting cancerous tumors (Kopitar-Jeralja, 2017). A pattern of upregulated proinflammatory cytokine production and/or lowered interferon production is reiterated across multiple mammalian species and multiple forms of adversity that create acute or chronic stress including received racism, physical harassment, repeated defeat, post-traumatic stress disorder, received cynicism and living with low income (Barrett et al., 2021; Janicki-Deverts et al., 2010; Kinskey et al., 2008; Miller et al., 2009; O’Donovan et al., 2011; Snyder-Mackler et al., 2016; Thames et al., 2019). So how does the acute or chronic daily stress of social adversity become increased susceptibility to sepsis?

To better appreciate how stress becomes sepsis, it’s important to understand that the immune system is highly physiologically promiscuous and multiple physiological systems connect social stress to immune function (Brinkworth & Babbitt, 2018). The best known systems connecting stress responses to immunity are the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal (HPA) axis. Under acute and chronic stress both the ANS and HPA activate white blood cells and affect networks of communication between...
them. This has been excellently reviewed elsewhere (Nicolaides et al., 2015; Vasconcelos et al., 2020; Won & Kim, 2016). Briefly, responding to social stress, neurons in the hypothalamus release corticotropin-releasing hormone (CRH) directly into the spinal cord and brain stem, sparking the additional release of CRH and quick release of epinephrine and norepinephrine from the adrenal glands (reviewed in Won & Kim, 2016). The α- and β-adrenoceptors on white blood cells then receive epinephrine and norepinephrine and activate pathways leading to the transcription and expression of proinflammatory cytokines under the control of transcription factor NFkB, activation of complement signaling cascade activation, and the release of antibacterial peptides (Scanzano & Cosentino, 2015). Under chronic stress, however, proinflammatory immune responses are not quelled by a parasympathetic response but continue, along with proinflammatory immune responses, for unusually protracted periods contributing to continuous low level tissue damage (reviewed in Won & Kim, 2016).

As an evolved strategy to ensure readiness to physical threat, the ANS response to stress is highly coordinated with HPA axis activation which can also contribute to continuous low level proinflammatory immune activation if a stress is chronic. The HPA axis is responsible for flight or fight responses. When activated by stress the hypothalamus releases CRH and arginine vasopressin into blood circulation, triggering the release of adrenocorticotrophic hormone (ACTH) by the pituitary gland. ACTH is received by the adrenal gland, which in turn produces glucocorticoids (GC). GCs bind with the GC receptors on white blood cells activating immune pathways that suppress NFkB transcription factor production, boost the transcription of anti-inflammatory gene products, and initiates large scale changes in white blood cell migration and release from the bone marrow (see Bellavance & Rivest, 2014). Under chronic stress GC receptors can become desensitized to GCs. Stress-induced white blood cell programming then shifts towards continuous proinflammatory cytokine expression stemming from the failure of glucocorticoid receptors on white blood cells to trigger suppression of the translocation and action of the NF-kB transcription factor. The result is continuous transcription and release of proinflammatory cytokines, while repressing transcription factors associated with interferon responses and antiviral action (Cole, 2019; Miller et al., 2008; Miller et al., 2009). The downstream effects are aberrant cell differentiation, odd cellular dynamics during infection, hampered wound healing and sepsis comorbidity progression.

For example, chronic social adversity makes an individual more susceptible to infection and any subsequent bystander tissue damage. Such chronic stress dramatically alters bone marrow regulation such that cellular decisions leading to the production of white and red blood cells favor production and development of myeloid white blood cells (e.g., monocytes, neutrophils, basophils, eosinophils) primed with inflammatory profiles. This cell production is very aberrant from normal function, with cells developing entirely outside of the bone marrow, in small clusters on other organs (Heidt et al., 2014; McKim et al., 2018). Increased numbers of highly-reactive bactericidal antigen presenting cells (neutrophils) that migrate oddly and produce abnormally low quantities of antibacterial superoxides are released from the bone marrow (Heidt et al., 2014; Khanfer et al., 2011). At the same time, levels of circulating lymphocytic white blood cells (B cells, T cells, and natural killer cells) drop, and cells produced often show altered cytotoxic and proliferative abilities (Dominguez-Gerpe & Rey-Mendez, 2001; Fleschner et al., 1989; Glaser et al., 1986; Irwin et al., 1990; Regnier & Kelley, 1981; Wyman et al., 2007). These shifts have important implications for infections. B cell ability to facilitate memory B cell development, for example, is impeded (Fleschner et al., 1989; Glaser et al., 1986; Irwin et al., 1990; Regnier & Kelley, 1981). Wound healing slows making infections more likely (Ebrecht et al., 2004). Antibody seroconversion is hampered, antibody levels in response to infection become abnormally low and T cell-mediated responses are inhibited such that influenza vaccination, for example, is less effective (Phillips et al., 2005; Vedhara et al., 1999; Wong et al., 2013). Overall, antiviral responses, tumor mitigation, and a myriad of critical actions for launching and supporting the adaptive arm of the immune system (responsible for specialized responses and the development of immune memory) are impeded (see Figure 4). Promoted, and even persistently activated, is the generalized pro-inflammatory defense of the innate immune system. It’s a strategy presumably beneficial in fight or flight responses, where a fleeing host might be injured and have an acute need to stave off incoming microorganisms (Segerstrom & Miller, 2004). Under chronic stress, however, a host simultaneously experiences a kind of immunosuppression in the presence of continuous and damaging immune activation.

The resulting cellular level changes support what has been observed for decades – that there is a strong association between chronic stress and the incidence and progression of infection, including sepsis (Cohen et al., 1991; NeSmith et al., 2020; Ojard et al., 2015; Song et al., 2019). While immunosuppressive effects of stress are associated with enhanced infection susceptibility so are the large-scale tissue changes that contribute to sepsis comorbidity pathogenesis stemming from this cellular reprogramming. For example, low-level inflammation expressed during chronic stress triggers the proliferation of fibroblasts in the subintimal space of arteries, creating and destabilizing atherosclerotic plaques (Fioranelli et al., 2018). Inflammatory monocytes are also recruited to existing atherosclerotic plaques, promoting further plaque development and making the plaques more fragile (Heidt et al., 2014; McKim et al., 2018). This action can continue for weeks after chronic stress ceases (McKim et al., 2018). Alone, the promotion of atherosclerotic plaques ushers the development of at least three of the most common sepsis comorbidities – CVD, hypertension and chronic kidney disease. Long-time stress appears to also contribute to pathogenesis of other sepsis comorbidities including obesity, diabetes, asthma and immunosenescence (de Heredia et al., 2012; Epel et al., 2004; Epel et al., 2008; Rod et al., 2012; Thakur et al., 2017). It may also increase the probability of infection by specific pathogens by increasing cellular permissiveness. Acute stress-induced hypertension is resolved by elevated expression of angiotensin converting enzyme 2 (ACE2), a receptor used by SARS-CoV-2 for cellular entry (Donoghue et al., 2000; Hoffmann et al., 2020).
Each sepsis comorbidity alters infection management in varied, complex and not always understood ways. Central to the relationship appears to be comorbidity-driven alterations in the efficiency of pathogen defense. For example, chronic inflammation associated with sepsis comorbidities has been proposed to alter infection responses such that additional bystander tissue damage is more likely during severe infection (Wang et al., 2012). Obesity and diabetes are associated with suppression of cell activities central to launching adaptive immune responses, and increase the risk of vaccine failure and severe infection (Allard et al., 2010; Chandra, 1980; Smith et al., 2009; Eliakim et al., 2006; Sheridan et al., 2012). CVD, often the top ranked comorbidity after age for severe infection, involves multiple dysfunctions of the vascular endothelium. CVD alters thickness and permeability of the vasculature and those alterations are made worse by endothelium damaging pathogens such as SAR-CoV-2, potentially increasing the likelihood of sepsis-related lung injury (i.e. acute respiratory distress syndrome [ARDS]) (reviewed in Fortini et al., 2021). Since sepsis is highly heterogenous in cause, infection location and symptoms, no one cascade, pathway or cell action altered by a comorbidity can explain its occurrence in a patient with that comorbidity. Rather, sepsis pathogenesis is very complex and increases in complexity over a very short period time, which is why timely identification and treatment is critical for a patient's survival.

1.9.5 | Race determines whether sepsis is recognized and treated

Despite its urgency, sepsis is often not treated in a timely fashion. Rather, sepsis is notoriously under-triaged, meaning suffering patients are often not appropriately ranked for treatment or even diagnosed. Sepsis under-triaging occurs even in wealthy nations, with patients in early stages often sent home with erroneous diagnoses (Singer et al., 2016). Some of this under-triaging occurs because while sepsis is a profound immune response to raging infection internally, externally the signs of developing sepsis in a patient are unfortunately subtle, often painless and manifest over multiple days (Vincent, 2016). Unlike a gunshot wound or a heart attack, sepsis patients arrive in the emergency room or doctor's office often without immediate obvious signs of urgency. If the patient is older or suffering chronic disease, that person may have developed sepsis and not even mount a fever (Rowe & McKoy, 2017). Very advanced patients might present with a...
moderately noticeable combination of fever, low urine volume, changes in awareness, and difficulty breathing. Once sepsis is underway, delays in diagnosis by minutes are associated with increased mortality which is why the Surviving Sepsis Campaign, a leading organization developing and promoting evidence-based care bundles for sepsis diagnosis and treatment, has emphasized precautionary diagnosis and intervention within the first hour of patient contact (Evans et al., 2020).

Not all faulty triaging and care in sepsis, however, is due to the comparative subtly of sepsis versus, say, the symptoms of a major heart attack. There is increasing evidence that patient income and identity impacts emergency sepsis care. Low income and racialized people experience poor triaging for sepsis worldwide. Kumar et al. (2014) examined over 1.6 million US hospital administrative records of adult discharges with sepsis from 2000–2008 and found that uninsured people comprised 7.5% of sepsis admissions and had a higher adjusted odds of dying than people carrying insurance. After adjusting for other patient characteristics, the authors found that not only were uninsured people released from hospital earlier and to inadequate facilities more often than insured people, but that they did not receive, on average, five of six common sepsis interventions while hospitalized (Kumar et al., 2014). Rather, they were less likely to receive critical interventions such as total parenteral nutrition, blood transfusions, dialysis, tracheostomy or central venous or pulmonary artery catheters than individuals who were insured. They were also much more likely to be placed on a ventilator, a procedure that comes with risk of injury and indicates worsening condition. Insurance status is not the only factor associated with poor emergency care. Across wealthy Anglocultural states, including those with single-payer healthcare systems, racialized peoples are under-triaged for sepsis in emergency rooms. Black and Hispanic sepsis patients in the United States have been found to be under-treated and even under-transferred to specialized sepsis care, even after adjustment for income and sepsis severity (Barnato et al., 2008; Tyler et al., 2018). Systemic barriers to timely care play a substantial role in the under-triaging of sepsis. In Australia, Indigenous populations in remote areas of the Northern Territory account for over 50% of sepsis patients in the region, with under-triaging implicated in racial disparities in the progression of the condition (Davis et al., 2011; Secombe et al., 2019). In remote regions of the Canadian North, which maintains a high proportion of Indigenous peoples, there are substantial geographic barriers to accessing emergency care. A person’s main point of medical access might be a nursing station or a phone call to a distant provider, and under-triaging can happen because sepsis diagnoses have to occur in the absence of critical tests and physicians, and hours (by boat or air) from a location outfitted for emergency treatment (Topfer & Spry, 2019).

Under-triaging and mis-triaging happens for more insidious reasons as well. A critical diagnostic tool for sepsis, the Sequential Organ Failure Assessment (SOFA) score, for example, relies heavily on measures of organ dysfunction known to vary between people on racial lines. The backbone data for SOFA comes from largely from White patients and uses creatinine as key measure of kidney function, with higher levels considered a sign of dysfunction. For reasons that cannot be ruled out as environmental or a product of care, Black patients are noted to often have higher creatinine levels than White patients with the same level of kidney function (Diao et al., 2021). High creatinine levels when incorporated into SOFA scores, however, often result in US Black patients having a higher SOFA score than White patients, but not higher in-hospital mortality, suggesting that in Black sepsis patients are more likely to be assessed as being more pathologically advanced than they are (Miller et al., 2021; Roy et al., 2021; Tolchin et al., 2021). The systemic error generated by SOFA scoring can alter the end of care treatment based on a score-based assessment of likelihood of intervention benefit, or prioritization for care at all when hospitals are overwhelmed and must implement Crisis of Care Standards that prioritize patients with the highest likelihood of survival (Tolchin et al., 2021). However, controlling for higher creatinine levels on the basis of race has a similar deprioritizing effect. In the United States, numerous providers continue to apply a “race coefficient” when estimating kidney function using creatinine (via estimated glomerular filtration rate), which tends to underdiagnose Black patients for kidney dysfunction leading to life endangering care disparities (reviewed in Ahmed et al., 2021). Via different mechanisms, Like eGFR, SOFA scores can act as quantifiable justification for denial of care, because the score is not reflexive – it is not sensitive to variation between biomarkers and organ function known to occur across the human population, and most importantly, is does not account for the multitude of problems known to delay treatment and lower the standard of care that BIPOC patients experience and that increase indicators of organ dysfunction (Tolchin et al., 2021).

There are very real problems with the standard of emergency care that People of Color, but particularly Black and Indigenous people receive in the Anglocultural states. The pattern of being deprioritized for sepsis care in a crisis is a reiteration of denial of care for many other emergency conditions. Breathett et al. (2018), for example, found that Black Americans have a higher risk of mortality from heart failure than their white American counterparts, in part because Black Americans are 40% less likely to see a cardiologist when admitted to the ICU or as part of primary care visits (Breathett et al., 2018). Black Americans are also less likely to be listed for kidney transplants when they have chronic kidney disease (Norton et al., 2016). Should the reader wonder how such deprioritization of a person in crisis is possible, other examinations have found that decisions to deprioritize ill patients of Color are readily shaped by the inherent beliefs of healthcare staff. In Manitoba, Canada, investigations into the emergency waiting room death of 45 year old Indigenous man Brian Sinclair after waiting 34 hours unattended, found that hospital staff dismissed calls to attend to him because they assumed he was intoxicated with nowhere to go. He, in fact, had a treatable bladder infection and was in rigor mortis by the time a security guard demonstrated to medical staff that he had died (Geary, 2017; Pritchard, 2013). The kinds of biases that led to Mr. Sinclair’s experience have been quantified and replicated in other states and other aspects of healthcare. In New Zealand, for example, non-White women have significantly higher rates of severe maternal morbidity from preventable causes, including sepsis, with physician bias and failure of care cited as the main reason for this morbidity (Lawton et al., 2019). Non-White and low income patients are more often
undertreated for severe pain than White and high income patients in the United States, even when pain is noted in their medical chart, with providers’ beliefs of increased likelihood of opioid addiction cited as the primary reason to deny medication to Black patients (Joynt et al., 2013). In a particularly chilling report, Hoffman et al.’s (2016) found that the majority of White medical students at the University of Virginia, regardless of study year, believed Black people did not feel as much pain as White people and cited supposed but false inherent biological reasons for this difference. Beliefs reported included Black people’s skin as thicker, blood clotting faster, and nerve endings not as sensitive as those of White people (Hoffman et al., 2016). An especially disappointing study found that over 2/3rds of US cardiologists surveyed on racial disparities in healthcare felt there were none, a notion that stands in opposition to data that shows Black heart attack patients wait longer than the recommended 90 min between ER entry and blockage mitigation and suffer increased mortality compared to White patients (Cavender et al., 2013; Lurie et al., 2005).

In 2022, we are in an extraordinary 2+ year period of high intensive care demand, and disparate sepsis mortality by race (CDC, 2020a). One does not have to look far to find a multitude of examples of how denial of care manifests as sepsis mortality. In December of 2020, Susan Moore, a Black physician being treated for COVID-19 in a hospital, caught international attention for describing in detail how she was repeatedly denied basic exploration of her symptoms and care by a White male physician who each time responded that she should be discharged. Moore entered the hospital with severe COVID-19, and died of bacterial and COVID-19 sepsis shortly after reporting her concerns about denial of care to hospital administration (Genai, 2020).

1.10 Insidious, systemic factors cause racial disparities in sepsis, so what if decreasing uneven sepsis incidence was less about wound washing and more about dismantling big problems?

The conditions that make someone more susceptible to or more likely to die of sepsis can be acute (i.e., work conditions, being immobilized, being under-triaged, and under-treated acutely). However, sepsis likelihood is increased by the presence of comorbidities and the most common ones are acquired incrementally, via the conditions, events and choices of each passing day, over a lifetime. As such, a combination of material and social conditions that have the potential to alter immunological function and phenotypes such as financial mobility, housing quality, food and clean water availability, daily adversity and receipt of preventative and urgent care really matter. Current approaches to sepsis put extraordinary responsibility on the individual for preventing the syndrome in a very acute sense – wash wounds effectively, wash hands frequently, get preventative vaccines, and, in our current crisis, wear face masks according to your own sense of risk (CDC, 2021; Dellinger et al., 2013; Evans et al., 2021; Sepsis_Alliance, 2021). However, sepsis is also the biological confluence of social and political environment. Sepsis disparities are the outcome of a lifetime of experience and systemic failures at multiple scales and they require years of radical measures at the state level on down to resolve. Sepsis is an urgent syndrome for which there is little extant knowledge worldwide that halt can most cases once they are underway. Prevention of the physiological changes that increase risk is everything.

There is ample evidence that each of the contributing factors altering human biology such that sepsis risk increases can be lessened by government action. For example, in the wake of findings that Australian Indigenous peoples suffered invasive Haemophilus influenzae B (Hib) and pneumococcal disease at nearly 20 fold that of non-Indigenous Australians, Australia introduced national immunization programs for both of these diseases in the mid-1990s (Krause et al., 2000; Meder et al., 2020; Peltola, 2000). Cases of both diseases have since substantially lowered, and the incidence ratio between Indigenous and non-Indigenous peoples lessened, though the campaigns still face challenges with vaccine delivery and difficult to control Pneumococcus strains (Meder et al., 2020; Webster et al., 2019).

Similar effects have been found for improved affordability and quality of housing, and unconditional income supplements, both of which reduce infection and sepsis comorbidities risk (Enns et al., 2021; Foster & Hall, 2021; Jackson et al., 2011; UNICEF SEWA, 2013). There is even evidence that reduction of social adversity can alleviate the effects of stress on white blood cell reprogramming and transcriptional activity. Snyder-Mackler et al. (2016) found that a powerful proinflammatory program that white blood cells from low ranked rhesus macaques initiated against immune stimulus, was alleviated when those monkeys were reorganized to be high rank (Snyder-Mackler et al., 2016). Multiple works have found that stress induced white blood cell programs and associated chronic diseases can be alleviated via social buffering (e.g., maternal warmth, social support, and family intervention) (Jiang et al., 2021; Miller et al., 2014; Tuchscherer et al., 2016). Change material and social conditions, change human immune function, and sepsis risk (Global Burden of Disease Risk Factor Collaborators, 2018).

1.11 Biological anthropologists have a deeply underused role in changing sepsis inequities

When comes to alleviating sepsis disparities, biological anthropologists occupy a unique and totally underutilized role in prevention of sepsis and its uneven burden. Most biological anthropologists are well versed in evolutionary biology, human variation and the social constructs and biological ramifications of race. This is a collection of people with intersecting specializations particularly attuned to teaching human infectious disease disparities not found in most biology departments. Biological anthropology classes are the often the first spaces where university students receive in depth instruction human evolution, biology, variation, race, and even lethal human infectious disease. The patients that get sepsis are among the most medically and biologically complex that there are. They express a host of phenotypes that are the products of gene and environment interactions, readily altered by social context. Sepsis as a teaching opportunity should be of intense interest to biological anthropology. Sepsis has been a major cause of
death for millennia and is, itself, a source of human variation via post-sepsis syndrome (Brinkworth & Valizadegan, 2021). The topic of uneven sepsis burden is at the intersection of many research themes important to biological anthropology including race, variation in physiological regulation, growth and development, primate evolution, diet and physiology, exercise and endurance, and gene and environment interactions. Sepsis is the leading cause of infectious disease mortality worldwide and every human will be affected by it in some way during their lifetime (WHO, 2020). Sepsis is critically, evolutionarily and culturally important to humans – so why is it largely absent from available biological anthropology course materials?

Sepsis and its most common causes (e.g., Escherichia coli and S. aureus) do not generally appear in biological anthropology textbooks, increasing the likelihood that the syndrome is entirely absent from applicable biological anthropology courses. This a profound missed opportunity for biological anthropologists, as clinical professions are commonly claimed as careers our curricula prepare undergraduates to pursue (See the American Anthropology Association career page, or Anthropology departmental career pages such as these ones at Queens College and University of California at Davis). Early instruction on sepsis and sepsis inequities are direly needed to improve health workers’ ability to identify the condition. Multiple studies have found that practicing physicians struggle to reiterate the consensus definitions and implement best practices for sepsis, despite the syndrome being the leading cause of infectious disease mortality among their patients (Poeze et al., 2004; Brunkhorst et al., 2008). Worse, public awareness of the syndrome and its symptoms are exceptionally low, with nearly 88% of people surveyed in an international study reporting they had never heard of sepsis (Rubulotta et al., 2009). This low literacy varies by study, but it is routinely low and has been a stumbling block for sepsis mitigation (Brizuela et al., 2019; Mellhammar et al., 2015). If both the public and clinicians struggle with the definition and practices around sepsis, they cannot engage, as they are desperately needed to do, in the equity and social justice issues around it.

As a main point of contact for human biology in undergraduate education biological anthropologists have responsibility to their students and the public to include sepsis and the evolutionary, social, and environmental conditions that contribute to its manifestation in our four-year curriculum. A very basic insertion of material into human variation and human evolutionary biology course would be using sepsis as an example of how daily life experience has an outsized impact on disease phenotype. When we teach race in our classes we can question and correct government and scientific narratives that conflate inherent susceptibility and race, place the responsibility of infection on individuals, and fail to address how racism is embodied as infectious disease. As a field now perpetually engaged in discussions of dismantling the effects of colonization we should be leaping at the opportunity to address the intersectionality of sepsis – a syndrome that disproportionately affects People of Color and people in low and middle income nations, is deeply influenced by racist policy and practice, made worse by low awareness, and is rapidly published on by researchers in the global South and North. As we proceed with 2022, and our third year where COVID-19 and associated sepsis will likely be a leading cause of death worldwide, we ask our colleagues to consider their actions, expertise and curricula and engage with the topics of sepsis and race how you can, to make incremental positive change.

**ACKNOWLEDGEMENTS**

The authors would like to thank Lyle Konigsberg for his editorial oversight. Thanks also to our reviewers for their feedback, as well as Adia Benton, Jeremy Sykes, and Charles Roseman for their helpful suggestions. Jessica F. Brinkworth is supported by National Science Foundation grant BCS-1750675, University of Illinois Urbana-Champaign Student Sustainability Committee Joint Pollinator Garden and Composting Systems, and SUPER Labs Single Use Plastics Elimination and Reuse grants, and University of Illinois Urbana-Champaign Center for Social and Behavioral Science grant Identifying SARS-CoV-2 Critical Control Points at Rantoul Foods and the Community.

**CONFLICT OF INTEREST**

The authors declare no conflicts of interest.

**DATA AVAILABILITY STATEMENT**

While the data presented in this article is presented in novel ways, it is public data and no new primary data was generated for this article. Data presented in Figure 1 was gathered from the US Census Bureau for 2019, Centers for Disease Control and Prevention Vital Statistics report on Deaths for 2017, and Centers for Disease Control and Prevention COVID-NET March 1–August 22, 2020 (CDC, 2020b; Kochanek et al., 2019; US_Census_Bureau, 2020). In the United States, annual causes of death are reported on delay, while census statistics are in partial format in between major census years. We found the datasets that occur closest in time to one another. Data presented in Figure 2 was gathered from the US Centers for Disease Control and Prevention Vital Statistics report for 2019 (2017 sepsis statistics), US National Health Interview Survey for 2018 (unmet medical need, comorbidities), and the US Census Bureau and Department of Labor Statistics Current population survey for 2018 (income). When reporting median family income we used data from all primary families (e.g., regardless of marriage status). Figure 2 was constructed in Prism 5.0 (GraphPad). All data reported here was aggregated at source into race groupings. Sepsis incidence and mortality data presented in Figure 3 and Supplemental layer 1, was collected from Rudd et al., 2020, and National Gross Domestic Product for 2017 from the World Bank. Ratios of years since independence of former British colonies and sepsis incidence per 100,000 by nation were calculated. Maps were generated in ArcGIS Pro 2.9 (Belgium, 2021). Tabular data was extracted from the Rudd et al. (2020) supplemental materials and was imported into ArcGIS Pro as a new feature layer. Data on Gross Domestic Product (GDP) in 2017 was downloaded from the World Bank Open Data resource and imported into ArcGIS Pro as a new feature layer. Layers were spatially joined to the UIA World Countries Boundaries feature layer that is publicly available in the ArcGIS Hub. Figure 4 was created with BioRender.com. All US disease incidence and mortality data presented in this article is age adjusted at source.
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