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Networks, cultures, and institutions: Toward a social immunology

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ABSTRACT

This paper calls for increased attention to the ways in which immune function – including its behavioral aspects – are responsive to social contexts at multiple levels. Psychoneuroimmunology has demonstrated that the quantity and quality of social connections can affect immune responses, while newer research is finding that sickness temporarily affects these same social networks and that some aspects of culture can potentially "get under the skin" to affect inflammatory responses. Social immunology, the research framework proposed here, unifies these findings and also considers the effects of structural factors – that is, a society's economic, political, and environmental landscape – on exposure to pathogens and subsequent immune responses. As the COVID-19 pandemic has highlighted, a holistic understanding of the effects of social contexts on the patterning of morbidity and mortality is critically important. Social immunology provides such a framework and can highlight important risk factors related to impaired immune function.

1. Introduction

In socially living animals, health and sickness can be considered social phenomena. This is particularly true for infectious disease. Exposure to pathogens is often patterned along social networks. Infection results in complex, integrated immune responses at the level of the individual, who is embedded in relationships that can influence the quantity and type of necessary resources (i.e., food) available to maintain an effective immune response as well as the ability to express behaviors which could also impact the course of the infection (Lopes, 2014). Furthermore, social relationships themselves can influence immune function (e.g., Cohen et al., 1997; Pressman et al., 2005).

As the most socially complex animal, our interpersonal relationships and social networks are highly elaborate and variable, and we are embedded within sociocultural contexts that shape all aspects of our lives. I suggest that psychoneuroimmunology and related fields can be advanced by embracing the complexity and culturally contingent nature of our social lives to achieve a more holistic understanding of human immune function with downstream effects on morbidity, mortality, and pathogen transmission. Here, I outline "social immunology" as one such research framework. This approach – integrating findings from psychoneuroimmunology, anthropology, cultural psychiatry, and allied fields – seeks to understand the ways in which 1) an individual's social networks affect immune function and vulnerability to infection, 2) immune responses during infection affect social relationships, and 3) broader social contexts – including the structure of society and cultural values and norms – are able to influence immune function and vulnerability to infection (Figs. 2 and 1).

Parallels to social immunology can be drawn with ecoimmunology, which explores how environmental factors such as seasonality and day length affect immunity (Demas and Nelson, 2012). Given our species' dependence on sociality, we can reasonably expect social environments to similarly affect physiological responses. Indeed, humans may be more sensitive to perturbations in social environments than in physical ones (e.g., Slavich, 2020). There are other recent calls to extend psychoneuroimmunology by considering social contexts of health and illness (i.e., "social psychoneuroimmunology"; Muscatell, 2021). The social immunology framework takes an even broader perspective by acknowledging that social networks and relationships are embedded in larger sociocultural systems. These systems, which vary *within* and *between* countries and other sociopolitical groupings (see Singer et al., 2016 for the importance of approaching culture as a dynamic system and problems with equating culture solely with race/ethnicity, nationality, and other broad groups), shape such networks and relationships thereby contributing to differential relationships between social factors and immunological outcomes.

2. Social immunology at the individual level

The number and quality of one's social connections (i.e., social

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Fig. 1. Eric Shattuck is an interdisciplinary scholar with a background in biological and cultural anthropology, psychoneuroimmunology, and evolutionary medicine. His research centers on biological and cultural aspects of health across social contexts with a particular focus on infectious disease. Ultimately, this work is aimed at improving our understanding of immunity, inflammation, and their psychological and behavioral correlates across the diversity of human cultures and social groups. Other active projects include probing the connections between pain, anger, and opioid use and misuse, as well as sleep, social stress, and inflammation in the global South, and exploring Indigenous understandings of common infectious disease symptoms. Eric received his B.A in Anthropology from the University of Georgia in 2005, then completed an M.S. in Biomedical Anthropology at SUNY Binghamton in 2009 working with Dr. Chris Reiber on a project related to prosocial behaviors following vaccination. While pursuing that degree, he interned at the Infectious Disease Pathology Branch at the Centers for Disease Control and Prevention in Atlanta, GA. He obtained his Ph.D. in Biological Anthropology at Indiana University in 2015, working with Dr. Michael Muehlenbein and his Evolutionary Ecology and Physiology Lab. Since then, he has completed post-doctoral training at the University of Texas at San Antonio with Drs. Michael Muehlenbein and Thankam S. Sunil. He is currently an Assistant Professor of Research at the University of Texas at San Antonio and the Interim Director of the Institute for Health Disparities Research.

networks) can influence health in multiple ways, including through social support, access to resources, and person-to-person contact (Smith and Christakis, 2008). Interpersonal contact has obvious implications for pathogen transmission, and there is some research to suggest that repeated and/or concurrent pathogen exposure can have temporary or lasting effects on immunity and vulnerability to infection. This is particularly so for latent viral infections including cytomegalovirus (CMV), which appears linked with elevated markers of T cell senescence, namely CD57 (Elwenspoek et al., 2017). In this regard, variable frequency of pathogen exposure through social networks could have important implications for immune function through the life course. Additional research could examine the immunological effects of repeated exposure to other, non-latent/chronic pathogens such as influenza. Furthermore, there may be multigenerational effects. In resource-poor areas of sub-Saharan Africa, maternal HIV and malaria infections have been linked with skewed T cell counts, thymic atrophy, and other measures of an altered immune phenotype in children (reviewed in Glennie et al., 2012). Access to health-related resources such as adequate nutrition and medical knowledge may help ameliorate the immunological changes discussed above and can be facilitated – or hindered – by one's social networks. We might expect, then, that individuals with high

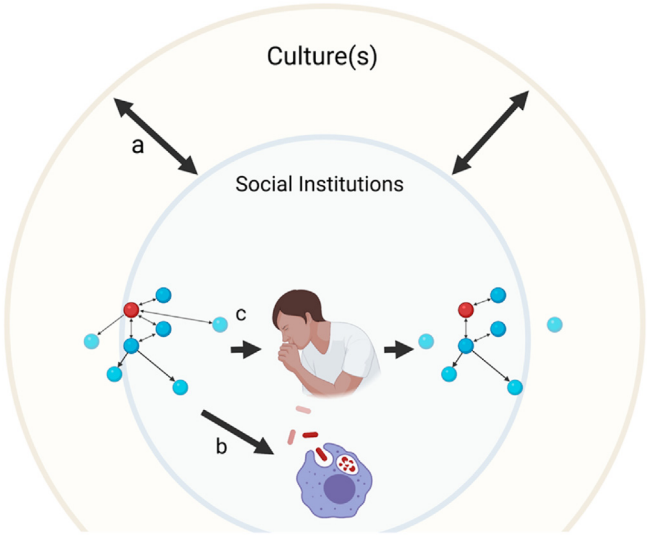

Fig. 2. Immune function occurs within multiple social contexts, including social networks, social institutions, and culture(s). a) Social structures/institutions (including social determinants of health) are co-created with culture and may affect immunity; b) Social networks affect immune function; c) Social networks are temporarily reshaped during infection, possibly feeding back on immune function. Created with BioRender.com.

interpersonal contact but low access to health-related resources would demonstrate repeated infectious "hits" with potential for earlier immunosenescence and, subsequently, elevated risk for infection.

Beyond pathogen transmission, there is ample evidence that the number and quality of social connections can influence inflammation and immune responses. A recent meta-analysis has shown robust evidence that social integration is associated with lower levels of several inflammatory markers, including tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) (Uchino et al., 2018). Conversely, negative social interactions such as targeted rejection have been shown to affect nuclear factor kappa (NF-*K*B) mRNA levels, particularly in individuals of higher social status (Murphy et al., 2013). Social isolation (i.e., small social networks) and loneliness are associated with poorer antibody production following influenza vaccination (Pressman et al., 2005). Greater diversity in social networks has shown a protective effect on developing a cold after experimental inoculation (Cohen et al., 1997) and fewer upper respiratory infections, albeit only during periods of low stress (Hamrick et al., 2002). Indeed, perceived social role conflict (i.e., the degree to which responsibilities of various roles interfere with each other) was associated with increased interleukin-1 beta (IL-1β) and TNF- α production by LPS-stimulated leukocytes in men but not women (Schreier et al., 2016), suggesting that the stresses caused by social networks themselves can affect immune function.

Recent research in non-human animals has shown that infection and inflammation are themselves associated with temporary changes in the structure of social networks, largely resulting from lethargy and self-isolation due to sickness behavior (Stockmaier et al., 2021). Following an immunological challenge, the number of associations and time spent with other individuals is decreased in vampire bats (Ripperger et al., 2020); mice similarly reduce their group connections after a similar challenge (Lopes et al., 2016). Increased isolation should serve to reduce pathogen transmission to other group members, though most studies have been conducted in laboratory settings and/or with dyads, limiting our understanding of effects on transmission in the wild (Stockmaier et al., 2021). A potential drawback of this isolation is the temporary suspension of salubrious social relationships, although mother-offspring interactions were less affected in immune challenged vampire bats relative to other relationships (Stockmaier et al., 2020). Additionally, a

growing body of research in humans suggests that sickness does not always result in social isolation; rather, infection and inflammation can drive desires to be closer to supportive others (Inagaki et al., 2015; Muscatell and Inagaki, 2021).

Multiple studies have found sickness-related changes in human social interactions across a variety of contexts. Unsurprisingly, sick people show a marked decrease in the number and duration of social contacts in studies conducted in the UK (Eames et al., 2010; Kerckhove et al., 2013), with a positive association between severity of sickness and reduced contacts (Eames et al., 2010). Decreased contact is likely driven – in part – by recognition of the physical and behavioral changes associated with inflammation, including changes in skin color (Henderson et al., 2017), breathing (Lasselin et al., 2018), and gait (Sundelin et al., 2015) and subsequent avoidance. While there is some evidence that recognition of some physical cues of sickness is not dependent on cultural context (Arshamian et al., 2021), changes in contact rates are not uniform across social settings, with large decreases of work-related contacts (among others) but increased contacts at home (Eames et al., 2010). This serves to alter the age structure of social contacts and patterns of potential pathogen transmission. Further examples include dengue infection leading to increased time spent at home, particularly during the early phase of sickness, and with fewer visits to others' houses in a study from Iquitos, Peru (Schaber et al., 2019). Changes were similar in rural Malawi during sickness, with a reduction in contacts with others and reduced participation in large groups (e.g., church services) (Glynn et al., 2020). In this study, reduced contacts outside the household were possibly offset by an increase in visitors to the household. If we might speculate, these visits are possibly related to social norms of caregiving, which could simultaneously bolster immune function through positive effects on mood while changing pathogen transmission routes, shifting the bulk of contacts from individuals outside the household to caregivers and close others as is likely the case with the UK studies discussed above. Further research is needed to understand how, when, and why social networks shift and change during sickness and the role of cultural and caregiving norms in shaping these changes.

In short, our social networks represent both avenues of infection and of care and support during sickness (whether material, emotional, or both) and are temporarily reshaped during those times. Detailed consideration of social networks and their implications for immune function is a key tenet of social immunology. At the same time, it must be recognized that these networks do not arise de novo but are largely shaped by wider societal factors.

3. Social immunology at the societal level

Social institutions, such as families, economic and legal systems, schools, and government, both constrain and facilitate individual behavior through expectations, rules/norms, ideologies, and other explicit or implicit guidance (Martin, 2004). As such, one's memberships in, and relations to, such institutions have considerable impact on their health.

Social determinants of health (SDoH), including work/unemployment, social support, availability of adequate food/nutrition, and others (Marmot, 2005), is one such example. Social determinants of health can affect infectious disease outcomes, as the COVID-19 pandemic has made plain. Access to testing, vaccines, and personal protective equipment, the ability to work from home and socially distance, and the unequal distributions of chronic health conditions (e.g., asthma, which is frequently associated with low SES, smoke exposure, and racial minority status) and health behaviors (e.g., smoking and alcohol use which can affect susceptibility to respiratory infections (reviewed in Cohen, 2021) in the population have intersected to shape COVID-19 morbidity and mortality in the United States and globally (Abrams and Szefler, 2020). A focus on social immunology can help us understand the patterning of SARS-CoV-2 and other infectious diseases by considering the impacts of SDoH on immune function. To give another example, differential access to adequate nutrition is a key SDoH (Marmot, 2005). Nutrition clearly affects multiple aspects of health but it can also affect immune function. Malnutrition is often linked with increased susceptibility to infectious disease due to multiple effects, including reduced energy available for immune cell differentiation and replication (Calder and Jackson, 2000). Specific instances include decreased inflammatory mediators (e.g., IL-6) in humans and animal models (reviewed in Alwarawrah et al., 2018) and decreased $CD4^+$ and $CD8^+$ T cells in malnourished children relative to well-nourished counterparts (Nájera et al., 2004). Nutritional status and infectious disease are often linked in a reciprocal relationship, with inadequate nutrition leading to increased vulnerability to infection through inadequate immune/inflammation responses such as those mentioned above, while infection affects nutritional status through symptoms like diarrhea, reduced food intake or temporary changes to diet, and intestinal malabsorption (Calder and Jackson, 2000). Additionally, the immunological effects of undernutrition/malnutrition may be multigenerational. Adolescents born small for gestational age were less likely to mount an effective long-term response to typhoid vaccine, particularly if they carried the "double burden" of small for gestational age and undernourishment during adolescence (McDade et al., 2001). Similarly, obesity is linked to multiple measures of impaired immune function (Samartín and Chandra, 2001), as well as increased influenza A viral load and extended viral shedding (Honce and Schultz-Cherry, 2019; Maier et al., 2018) and possibly decreased influenza vaccine efficacy over time (Honce and Schultz-Cherry, 2019; Sheridan et al., 2012). The global rise of obesity in recent decades has not been matched by decreases in undernutrition, leading to many instances of a "dual burden" of both obesity and undernutrition within populations, families, and even individuals (Doak et al., 2000, 2005; Wells, 2012). Indeed, obesity can be thought of as a state of malnutrition due to increased consumption of energy-rich and otherwise obesogenic foods (Wells, 2012). Importantly, malnutrition should not be considered as a problem limited to lower- or middle-income countries (LMICs). An estimated 5.6 million US households reported very low food security in 2018 and while overall food insecurity rates had been declining, it appears likely that the COVID-19 pandemic has upended these improvements (Coleman-Jensen et al., 2015; Hake et al., 2021).

Other institutional characteristics, such as systemic racism and discrimination, can contribute to increased chronic inflammation with important differences between racial and ethnic categories. For instance, Black adults have been shown to have elevated levels of CRP and fibrinogen compared to their white counterparts, with daily discrimination predicting elevated levels within Black participants (Surachman et al., 2021). Discrimination and other social stressors are also known to affect telomere length, a biomarker of aging (Chae et al., 2014; Epel et al., 2004). Intriguingly, shorter telomere length has also been associated with decreased immune function (Damjanovic et al., 2007; Wilson et al., 2019), perhaps an early manifestation of immunosenescence. Thus, the stresses of lifelong, systematic discrimination can accelerate biological aging with concomitant effects on immunity, morbidity, and mortality. Importantly, systemic disadvantages can interact to increase risk, as evidenced by significantly elevated IL-6 levels in adolescent black females relative to white females and both black and white males (Mac Giollabhui et al., 2021). This likely reflects increased risks associated with the intersection(s) of black and female identities, both of which have been – and continue to be – systematically disadvantaged in the US and elsewhere (ibid). Additionally, findings like these highlight the ability of disadvantage to affect biologies even relatively early in life.

Social institutions can also help shape social networks and associated infection risks. For instance, larger households and higher population density – both generally associated with low SES – may contribute to increased influenza risk (Cardoso et al., 2004; Sloan et al., 2015). On the other hand, social deprivation (a lack of social cohesion and support often linked with low SES) appeared to have a protective effect against hospitalization or outpatient clinic visits due to influenza in Quebec, possibly due to fewer social contacts and so fewer opportunities for

Box 1
Social immunology research questions

To what extent do cultural values/norms (e.g., stoicism, familism, collectivism) "get under the skin" to affect immune function?
What are the immunological effects of repeated pathogen exposure/infection as a function of social network measures (e.g., integration, diversity, etc.), do the effects vary throughout growth/development, and do some aspects of social networks offset the costs of repeated exposure/infection?
What are the effects of sickness on social networks and how do they vary across contexts (cultural, demographic, severity of illness, and others)?
What are the health effects (positive or negative) of sickness-induced changes in social networks?
To what extent can aspects of social networks (e.g., social support) offset – or exacerbate – the effects of social determinants of health on immune function?
Does childhood exposure to pathogens/parasites in high-income countries as a consequence of structural discrimination and other socioeconomic forces lead to altered immune profiles and vulnerability to infectious disease in later life?
Is immune function affected during acculturation and instances of cultural change, and what are the implications for infectious disease burden and pathogen transmission?

exposure to the pathogen (Charland et al., 2011). A testable social immunology prediction here is that infectious disease cases would be relatively less common in socially deprived individuals but more severe when they do occur (other factors being equal) because of the established relationships between sociality and immune function discussed above.

With regard to pathogen exposure, research among Amazonian horticulturalists has found highly divergent immune profiles relative to those in the Global North that are likely due to a high pathogen environment (albeit one characterized by high intestinal helminth parasite prevalences; (Blackwell et al., 2016). These immune profiles are characterized by elevated inflammation markers, eosinophils, and immunoglobulins (among others), as well as elevated NK cell counts beginning in childhood that persist into adulthood (Blackwell et al., 2016). This persistent elevation is in contrast to age-related NK cell declines found in wealthy, industrialized samples. Despite decades of public health efforts to eradicate parasite infections in the US, areas of relatively high prevalence still exist, particularly in low-income rural areas with inadequate sanitation (Hotez, 2008; McKenna et al., 2017; Singer et al., 2020). Future research can determine whether childhood exposure to pathogens (including parasites) and/or a chronic pathogen burden in these areas affects immune function as they appear to in other populations. If so, and if these changes in immune profiles contribute to susceptibility to other infectious diseases, this represents an additional burden of infectious disease among already disadvantaged communities.

Relationships between social institutions, social networks, pathogen exposure, and immune function can also operate above the level of the individual or household to shape infectious disease patterns at the county or state level. Social capital – resources or other benefits gained through connection and cooperation with others (Kawachi et al., 2008) – varies widely across the United States. Recent analyses have found that the geographic patterning of social capital at the county level was related to COVID-19 outcomes (Borgonovi et al., 2021). Counties with a high degree of social capital generally had fewer COVID-19 deaths and hospitalizations than counties with the least social capital. Early in the pandemic, close connections between individuals may have facilitated the spread of important COVID-19 health information and adoption of non-pharmaceutical interventions. Over the course of the pandemic, this cohesion may have helped to maintain behaviors that reduced the spread of the virus. The extent to which social capital affects immune function specifically is a fruitful line of research.

4. Social immunology at the cultural level

Culture has been defined as "an internalized and shared framework […] through which both the individual and the collective experience the world" (Singer et al., 2016). Cultural processes shape social institutions, including those discussed above, and mold – and are in turn molded by – members of a given cultural or subcultural group (Singer et al., 2016). Cultural norms can have important implications for health outcomes, including driving total social withdrawal – often followed by rapid

decline and death – following HIV diagnosis among Indigenous Papuans (Butt, 2013), as well as relationships between self-appriasal and diagnosis (particularly for chronic illnesses) among many Indigenous Warlpiri in Australia (Saethre, 2013).

Importantly, "culture" is not limited to Indigenous populations, nor are the effects of such norms on health, disease, and immunity. Results from a large (n = 1259), diverse national survey in the US have shown that self-reported, recalled sickness behavior severity was influenced by factors such as stoic endurance of pain and illness and familism, or the degree to which one values close family connections (Shattuck et al., 2020). In a pluralistic society such as the US, the strength of such norms likely varies from person to person depending on their unique engagement with multiple cultures and sub-cultures, and could have potential ramifications for pathogen transmission if sickness behavior is ignored. While there is the possibility of recall bias in these results, it may be that more stoic individuals in this survey were opting to avoid treating their illness (agreeing with the wider literature on stoicism and treatment seeking; e.g., Murray et al., 2008; Yong, 2006), thereby letting it progress and their sickness behavior become worse. To the extent that sickness behavior functions to optimize immune responses (Hart, 1988), prolonged or more severe sickness behavior may indicate the need for further energetic investment in immune responses to completely clear the infection. Ignoring this evolved cue of sickness may therefore result in longer recovery times.

Furthermore, cultural norms like stoicism can interact with structural factors. Presenteeism, or continuing normal activities while sick and infectious, is common (Webster et al., 2019) and is perhaps partially related to stoicism in the face of sickness. In their systematic review of presenteeism, Webster and co-authors (2019) find an overall prevalence of 35–97% and a range of 37–97% in healthcare settings. There are multiple potential structural antecedents of presenteeism, such as high workloads and limitations on sick leave, which is known to increase influenza burden in low SES individuals and communities (Zipfel et al., 2021). Of particular interest within the social immunology framework, however, are perceptions on the part of the sick individual, namely that presenteeism is the organizational norm or that they are simply "not sick enough" to justify using sick leave (Webster et al., 2019), which are both related to cultural norms. The degree to which norms like stoicism or capitalistic ideals of productivity influence presenteeism (either on their own or through interacting with structural antecedents) in the United States has not been explored to my knowledge. Future research along these lines can explore presenteeism as a cultural construct and better understand its effects on pathogen transmission and, perhaps, an individual's own immune response as they ignore the biological imperative of sickness behavior.

There is also some evidence that sociocultural factors can contribute to variation in immune function and inflammation. Comparing levels of IL-6, soluble IL-6 receptor (sIL-6r), CRP, and fibrinogen between American and Japanese participants in the MIDUS (Midlife in the United States) and MIDJA (Midlife in Japan) datasets, Coe and colleagues (Coe et al., 2011) found that all measures were lower in the latter participants. Although they focus on differences in diet and nutrition to explain these findings, the authors also note that differences in social integration and emotional or stress-related processes could play a role. While negative affect was related to poor health in both the US and Japan, Curhan and co-authors (Curhan et al., 2014) found that the effect was much more pronounced in the US, which they attribute to differences in beliefs surrounding negative states. In the US, negative affect is often interpreted as a fault of the self, whereas it is more likely to be attributed to external forces in Japan. These differences in attribution may therefore have important implications on the biological impact of negative affect on multiple physiological systems, including the immune system. Differences in acceptance of negative emotions also appear to have similar consequences. Greater acceptance of negative emotions among Japanese participants compared to their American counterparts may be associated with reduced elevations of IL-6 during these emotional states in the former group (Miyamoto et al., 2013). Similarly, increased anger expression (i.e., physically or verbally aggressive behavior) was linked with greater biological health risk – indexed by IL-6, CRP, systolic blood pressure, and cholesterol – in Americans but with reduced risk in Japanese participants (Kitayama et al., 2015). The authors suggest that anger may reflect accumulated stressors and annoyances in Americans, while Japanese cultural norms result in anger indexing personal empowerment, whereby socially dominant (and likely healthier) individuals are more likely to be permitted to express anger.

Finally, culture(s) should not be conceived as monolithic (Singer et al., 2016). Rather, individuals and groups engage with norms differently and multiple culturally constructed identifies (e.g., gender, class) often interact to shape health outcomes across different contexts (i.e., intersectionality; Dhamoon and Hankivsky, 2011). As globalization and migration continue (and accelerate), cultures come into contact, creating space for conflict and change. Conflicting or incongruous cultural schema can be a significant source of stress. For instance, Dominican men engaging in culturally "unsanctioned' behaviors had elevated levels of salivary cortisol (Decker et al., 2003). This stress can have immunological consequences. In Western Samoa, elevated Epstein-Barr virus (EBV) antibodies were found in regions with higher exposure to Western (i.e., less traditional) cultural influences and presumably a lower degree of cultural consonance (Dressler et al., 2016; McDade et al., 2000). EBV, a ubiquitous herpesvirus, generally persists in a latent state in infected individuals due to adequate cell-mediated immunity; elevated antibodies indicate a recrudescent infection due to immunosuppression. Seeking social support in culturally appropriate ways has also been associated with lower levels of CRP in Brazilian adults (Dressler et al., 2016). This latter finding exemplifies the social immunology perspective by combining the strengths of psychoneuroimmunological research (i.e., relationships between social support and immune function) with a broader view of the role that culture plays in shaping social support and social networks.

5. Conclusion

Social immunology extends PNI into novel, but entirely complementary, directions. It is my hope that the framework presented here will spark new directions in research by considering the ways that cultural and social contexts (which are deeply intertwined) shape biological and behavioral responses to infection and how, in turn, infection can feedback into social contexts. It should be noted that this short introduction to the topic is far from exhaustive. While the paradigm seeks to bring together strands from multiple disciplines to better understand the role of social contexts on immunity, its interdisciplinarity introduces a high degree of complexity in terms of its methods, vocabulary, and its challenge to better conceptualize "culture" in research. In this regard, collaborations across disciplines may be particularly fruitful for research. A list of some potential social immunology research questions are presented in Box 1.

The COVID-19 pandemic has shown us, in stark detail, how pathogen transmission, morbidity, and mortality are shaped by the economic and social structures of different societies as well as contested beliefs about risk and the collective good. These same forces, and others like them, shape other outbreaks – whether local or global – and will shape future pandemics. Understanding how they affect immune responses can provide fundamental insights into human health, much in the same way that ecoimmunology has improved our understanding of immunity across ecological and environmental contexts in humans and other animals. Culture and sociality are the human context and warrant similar attention.

Declaration of competing interest

None.

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