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Syndemics: A Cross-Disciplinary Approach to Complex Epidemic Events Like COVID-19

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Abstract

In this review, we trace the origins and dissemination of syndemics, a concept developed within critical medical anthropology that rapidly diffused to other fields. The goal is to provide a review of the literature, with a focus on key debates. After a brief discussion of the nature and significance of syndemic theory and its applications, we trace the history and development of the syndemic framework within anthropology and the contributions of anthropologists who use it. We also look beyond anthropology to the adoption and use of syndemics in other health-related disciplines, including biomedicine, nursing, public health, and psychology, and discuss controversies in syndemics, particularly the perception that existing syndemics research focuses on methodologies at the individual level rather than at the population level and fails to provide evidence of synergistic interactions. Finally, we discuss emerging syndemics research on COVID-19 and provide an overview of the application of syndemics research.

INTRODUCTION: DEFINITION AND OBJECTIVES

Syndemics encompasses a body of theory and research about the biosocial nature of disease. Specifically, it refers to epidemic and other adverse health events that include the intersection of all of the following three components: (*a*) sequential, co-occurring, or clustering diseases or other health and biological conditions; (*b*) adverse biological interactions between these diseases/conditions (known as the biological-biological, or bio-bio, interface); and (*c*) social/environmental factors that cause or exacerbate disease or enhance vulnerability or disease interaction (known as the biological-social, or bio-social, interface). The concept emerged almost 30 years ago within medical anthropology, a field that focuses on the multiple ways that biology and society entwine to produce health. The syndemic model has diffused widely across health-related fields of study.

The 2020 emergence and global spread of coronavirus disease 2019 (COVID-19) reaffirm the importance of the syndemic biosocial interface as a risk to health (Gravlee 2020, Irons 2020). In this review, after a brief discussion of the nature of syndemics and why they merit attention, we assess anthropological work that advances the syndemics framework and current multidisciplinary debates regarding the application of syndemic theory. As Richard Horton, the editor of the medical journal *The Lancet*, tweeted on September 25, 2020, with regard to syndemics, "The anthropology community is ahead of medicine and public health." Next, we examine emerging research on syndemics that is related to and involves the contemporary global COVID-19 pandemic. Finally, we review the interface of syndemics theory and the human rights literature. The goal is to review the literature to highlight the practical applications of insights gained through syndemics research as a subtopic within and beyond medical anthropology.

ORIGIN AND INITIAL DIFFUSION OF THE CONCEPT

Development of syndemics as a concept dates to the rise of the HIV/AIDS epidemic in the United States. While it is now recognized that the HIV virus entered the United States and began to infect individuals, especially men who have sex with men (MSM), by at least the early 1970s (Thomas et al. 2007), various observers reported the appearance of what initially was called "junkie flu" or "junkie pneumonia" but was later recognized as HIV/AIDS (DesJarlais et al. 1988). Community-based anthropological researchers at the Hispanic Health Council in Hartford, Connecticut, began to see evidence that HIV infection was spreading locally in the early 1990s, and they were able to secure funding from the National Institute on Drug Abuse as part of a national HIV prevention initiative to study the epidemic among illicit drug users. This research focused on delineating the social relations, health risk behaviors and contexts, and life experiences of street drug users. As part of this research, outreach-recruited study participants were asked to identify all the diseases they had been diagnosed with by a medical provider. Members of the research team were startled by the number of serious diseases suffered by participants, triggering curiosity about the significance of disease interactions on their overall health burden.

Stemming from this research, the interaction of substance abuse, violence, and AIDS (SAVA) was the first syndemic to be described in the literature (Singer 1996). Participants in this study of active drug users routinely experienced police harassment (e.g., stopping suspected drug users, confiscating and breaking their syringes), lacked ready access to medical care, faced barriers to entering drug treatment, encountered daily discrimination and stigma across various social institutions, were demonized in the news and entertainment media and in the speeches of politicians, and had high rates of homelessness. In light of the high level of poverty experienced by many of the street drug users in the study, these prominent threats to participants' health appeared to be strongly influenced and sustained by a set of political-economic and social factors. On the basis

of this study, members of the research team published several papers that reviewed relevant new literature and recent research findings on SAVA coinfection and synergistic interaction at the biological and population levels in light of adverse social conditions (Singer 1996, 2000, 2006; Singer & Clair 2003).

In 2002, researchers at the Centers for Disease Control and Prevention (CDC) began to consider the value of a syndemics approach to public health. Their work helped to disseminate awareness of the concept nationally and even internationally and facilitated its diffusion across health disciplines.

USE OF SYNDEMIC THEORY IN ANTHROPOLOGY

HIV Syndemics

As syndemic theory was first applied to the field of HIV research, it has most often been used to explain complex biosocial dynamics in HIV risk (Singer et al. 2020, Tsai & Burns 2015) in anthropology as well as in other disciplines. For example, through a qualitatively oriented literature review, synthesis, and analysis, Ostrach & Singer (2012) examined locally specific biopolitical risks for HIV–sexually transmitted infection (STI) interactions affecting cisgender women. Wilson and colleagues (2014) identified a syndemic, produced by racism and marginalization, resulting from consequential biological and social interactions among and between HIV, substance (ab)use, trauma, incarceration, and poverty among Black and Latino cisgender men in New York City. Chakrapani and colleagues (2019b) identified the DAV (depression, alcohol use, HIV, and violence victimization) syndemic among transgender women in India.

Food and water insecurity has also been identified as involved in HIV-related syndemic arrangements. Himmelgreen et al. (2009) presented Lesotho's HIV epidemic in the context of increasing food and economic insecurity. They argued that historical, political-economic, and cultural dimensions, which limited access to HIV treatment modalities, heightened the biological interactions between HIV and food insecurity. The authors proposed that because of the synergistic relationship between HIV and malnutrition, behavioral interventions to improve nutritional status could address immune status, increase life expectancy, and reduce HIV transmission, even in the absence of widespread viral treatment access. Building on this research, Workman & Ureksoy (2017) demonstrated the additive, interactive role of water insecurity within a syndemic of food insecurity and HIV in Lesotho. Using a mixed-methods approach of qualitative interviews and quantitative assessment, the authors identified that the co-occurring epidemics enhance psychoemotional stress through their syndemic interactions.

Further demonstrating the overlap of HIV syndemics with other areas of syndemic research, Zvonareva and colleagues (2019) found that in the context of poverty and social marginalization in an isolated Russian province, HIV and tuberculosis (TB) interacted as a syndemic. The concurrent infection of both diseases worsened the progression of each disease within social conditions that increased vulnerability to coinfection. The authors' work in the Tomsk Region of Western Siberia identified poverty and occupational insecurity as increasing the risk of TB and HIV progression owing to the lack of workplace benefits, which made participants afraid to miss a day of work to see a health care provider even if they were very sick. This reluctance led to more advanced TB upon diagnosis and to drug-resistant disease patterns. The geographic and social isolation of Tomsk also contributes to high rates of substance use and incarceration, both known to be risk factors for HIV infection.

Noncommunicable Disease Syndemics

Anthropologists have continued to apply the syndemics concept to health conditions beyond HIV and infectious diseases. Some major foci of noncommunicable disease syndemics to date are the

contexts, circumstances, and policies that disproportionately promote diabetes for certain groups. Mendenhall's extensive body of work draws on syndemic theory to explain diabetes interactions and prevalence among diverse populations globally. In a mixed ethnographic and epidemiologic assessment of diabetes among Mexican immigrant women in Chicago, Mendenhall (2016b) proposed a complex syndemic interaction between violence, immigration/isolation, depression, diabetes, and abuse (VIDDA). Cultural and occupational models of gendered behavior were shown to be intricately tied to interacting diabetes and mental health outcomes. Mexican immigrant women in Mendenhall's study reported pressure to maintain traditional women's activities (cooking and cleaning), even as physicians advised that they change their diets and increase physical activity and even as their illness identities no longer adhered to traditional gender norms. Changing identities and emerging interpersonal violence by husbands who clung to traditional norms amid quickly changing environments and unemployment led to depression, which interacted adversely with diabetes.

Mendenhall has subsequently explored, through ethnographic methods, diabetes syndemics in Kenya, South Africa, and India (Mendenhall 2014, 2016a, 2019; Mendenhall et al. 2015, 2017; Mendenhall & Norris 2015). Using cross-cultural examinations, Mendenhall argues that syndemic interactions present in unique arrangements within specific social situations. For example, in Kenya and South Africa HIV presented as a component of the syndemic with diabetes, a factor that was not relevant in the specific populations that Mendenhall studied in India or among Mexican immigrants in the United States. This evidence highlights the importance of context-focused anthropology and anthropological methods in assessing, understanding, and informing interventions to address diseases within afflicted communities. In some of her work, Mendenhall (2016b, 2019) discusses the role of the fight-or-flight hormone cortisol in increasing the risk for diabetes by increasing glucose levels in the body, leading to increased levels of blood sugar. Increases in cortisol are often triggered by chronic stressors such as poverty and interpersonal violence, both known to be hallmarks of diabetes syndemics.

Lerman Ginzburg's (2020) work with a government-funded diabetes clinic as well as community-based activists and policy makers in Puerto Rico parallels and builds on Mendenhall's contributions by identifying a diabetes–obesity syndemic resulting from the structural pathways in which colonization and its sociopolitical consequences (austerity, poverty, and political and economic instability) impact food and health care access. Lerman Ginzburg traced the ways in which the 1920 Jones Act impacted economic access to food in Puerto Rico by mandating that Puerto Rico rely on US-flagged ships for its imported food (85% of its total food supply) and imposing additional taxes on imported food, requiring Puerto Rico to foot the bill. The increased price of food, abetted by skyrocketing unemployment and poverty levels, influenced health outcomes such as depression, obesity, and diabetes and ignited strident calls for increased Puerto Rican control over its own food production and political processes. Heightened cortisol levels, perpetuated by chronic food insecurity, increased the risk for diabetes. The stress of food insecurity, which can increase levels of the stress hormone cortisol, contributes to insulin resistance, particularly by contributing to increased visceral adiposity. The stress of food insecurity is also associated with a proinflammatory diet (such as junk food, which is also more accessible in the context of food deserts and imports), which is linked to higher HbA1c (hemoglobin A1c) and poorer glycemic control. Furthermore, obesity increases the body's resistance to the hormone leptin, which regulates food intake. The brain's lack of response to leptin results in increased food intake and overall increased insulin resistance. Lerman Ginzburg argued that US-based racism toward Puerto Ricans resulted in US government antipathy toward formally adding Puerto Rico as a US state. The cost of shipping foods to Puerto Rico as a US state would have declined, reducing food insecurity,

which biologically interacts with hypoglycemia (low blood sugar) by disrupting blood sugar levels owing to skipped meals and nutritionally poor meals and contributes to diabetes.

Marshall's (2013) monograph likewise detailed a poverty-driven syndemic involving diabetes among the people of Oceania. In an area of the world in which the rates of diabetes, obesity, coronary heart disease, cancer, tuberculosis, and chronic obstructive pulmonary disease continue to rise, Marshall identifies smoking tobacco, in the form of industrially manufactured cigarettes, as the central interstitial element of a syndemic that produces most of the morbidity and mortality suffered by Pacific Islanders. Tobacco consumption constitutes part of the legacy of invasion, colonization, and globalization in Oceania.

Examining changes in maternal diets in a rural community in Costa Rica, as the region experienced a transition from dairy farming and coffee production to a mixed tourist economy, Cantor et al. (2013) highlighted the interacting bio-bio and bio-social elements contributing to increases in the chronic conditions of type 2 diabetes and hypertension. Food insecurity leading to malnutrition is associated with increased levels of the cytokine IL-6, which in turn is linked to tissue inflammation and general immunosuppression. Furthermore, nutritional deficiencies hamper cellular function, including the cells' ability to fight off disease. In addition to food insecurity–related immunosuppression, the researchers reveal the role of social factors such as increased availability of nonlocal foods resulting from tourism, local food production disruption, and the consequent increased reliance on processed foods, all of which are additional risk factors for type 2 diabetes and hypertension.

Bennett (2009) presented syndemics as an orientation through which to explain and address complex interactions between economic factors, social and cultural practices, geography, and flawed infrastructure that increased exposure to pathogens responsible for malnutrition and stunting in children in communities in rural Guatemala. Bennett observed that poor soil quality and small land holdings reduced the possibilities for increasing household food production, forcing a reliance on purchased food. Furthermore, local feeding practices that included high intake of sugars as well as poor food storage and hygiene practices reduced food quality and increased food contamination. Bulled et al. (2014) presented a similar argument regarding childhood diarrhea, resulting from interactions between pathogens, disease conditions, and social environments. They trace the ways in which diarrheal disease interacts with and is worsened by other endemic tropical diseases, such as helminth infections. Concurrent infections with intestinal helminth parasites have been shown to impair host immunity to enteric pathogens. Environmental enteropathy (EE), the condition resulting from chronic exposure to fecal pathogens, is also marked by alterations in intestinal architecture and increased intestinal inflammation. Given the syndemic nature of interactions between these diseases and the adverse social conditions in which they are more likely to occur, technologically advanced biomedical strategies designed to address childhood diarrhea—a symptom—would likely prove more effective over the long-term if coupled with interventions that address the underlying social conditions of disparity—the cause.

Stigma-Driven Syndemics

A growing body of work identified stigma as a structural factor driving a diverse array of disease interactions, including HIV, malnutrition, stunting, depression and anxiety, dental caries, and poor pregnancy outcomes (Lerman et al. 2017, Ostrach et al. 2017). Emard's (2017) ethnographic investigation of biomedical expectations of HIV treatment adherence among HIV-infected MSM communities revealed that in-group stigma produced "biomedical moralities" that enhanced risk engagement and worsened biomedical outcomes. Internalizing HIV stigma reinforced negative notions of their identities based on wider cultural perceptions of HIV and sexual and gender

identity, which reduced medication adherence, precipitating interactions between substance use, and increased behaviors that enhanced the risk of STI acquisition. Carney's (2017) work on the syndemic of immigration detention–induced malnutrition and mental distress provided insight into the health consequences of social, economic, and political vulnerability related to migration status and migrant stigma.

Advancing prior work on childhood malnutrition in Guatemala, Bennett (2017) expanded on ethnographic research to identify a syndemic involving interactions between malnutrition and infectious diseases driven by poverty and stigma disproportionately affecting children of rural communities and leading to impaired cognitive function and school performance.

Working on stigma-driven obesity–depression syndemics, through community-based ethnographic research Lerman (2017) found that Puerto Rican women experiencing domestic violence were more vulnerable: Depression stigma often prevented them from leaving the house for physical activity and food shopping and further contributed to leptin resistance (an obesity risk factor). In the same volume, Trainer et al. (2017) examined the contribution of stigma to a depression–obesity syndemic among bariatric surgery patients who described the stigma, depression, and shame they experienced as a result of both having obesity and having the surgery, which they perceived as a last option after struggling to lose weight through diet and exercise. For example, Trainer et al. (2017) showed that depression and stigma demotivate people from exercising and trigger binge eating as a comfort mechanism. They also showed that internalized obesity stigma aggravates depression outcomes and furthers the reliance on food intake as a coping mechanism.

Through an ethnography of homeless women staying at a rural emergency shelter in Northeastern Connecticut, Marcus & Singer (2017) identified multiple, complex, and interacting physical health problems, mental illness, substance use disorders, and abuse (sexual, physical, or emotional) that exacerbate a shared homeless experience. Social and structural factors including early parenthood, lack of education, Department of Children and Families involvement, custody battles, incarceration, and disability offered further disruption and challenges. Stigma related to many of the factors (physical health problems, abuse, mental illness, loss, instability, and substance use) in the PHAMILIS syndemic, including homelessness stigma and stigmatization of substance use, mental illness, and early parenthood, compounded and intensified the other complex interactions.

Raskin (2015, 2017) offers an ethnographic account of the dental safety net complex among low-income families in central Appalachia, a fragile, unpredictable, and complex network of treatment opportunities, to examine sociopolitical and moral negotiations regarding health governance and health disparities. Poverty, gendered violence, trauma (specifically child sexual abuse and intimate partner violence), family caregiving expectations, lack of access to health care, lack of transportation, and class-based stigma related to dental beauty standards all interact to worsen biological interactions between poor nutrition, diabetes, obesity, opioid use, and poor oral health, which ultimately result in caries and tooth loss.

Everson & Ostrach's (2017) and Ostrach & AbiSamra's (2017) contributions establish a new arena of pregnancy-related syndemics within stigma syndemics. In each, pregnancy is pathologized through stigmatization and pregnancy outcomes worsened as a result of synergistic interactions between structural and biological factors. In the former, differential treatment of pregnant teens in biomedical settings—prompting biological interactions between pathologized pregnancy and the sequelae of unnecessary biomedical procedures that trigger the "cascade of interventions"—leads to worse birth outcomes and more complications for the teens and their neonates. In the latter, widespread stigmatization of abortion pathologizes the pregnancies of those who seek to terminate them, leading to higher risks of complications and impeding care seeking for complications, less availability of follow-up care, and greater reliance on less-safe procedures. In "embed[ding] syndemics within local moral contexts" (Kleinman & Hall-Clifford 2009, p. 418), Ostrach and

colleagues situated stigma and its consequences within a larger social milieu, allowing for a detailed examination of how stigma underlies and reinforces other structural factors such as socioeconomic status and interpersonal violence.

Syndemics of Race, Identity, and Sexuality

Anthropologists contributing to and applying syndemic theory have tended to centralize race, identity, or sexuality in their syndemic constructs. Mendenhall's work on the VIDDA syndemic in the United States focused on Mexican immigrant women as a population heavily burdened by diabetes (Mendenhall 2016b). Marcus's work on the PHAMILIS syndemic focused specifically on homeless women (Marcus 2014, Marcus & Singer 2017). In the syndemic outlining cisgender women's biopolitical risks for HIV/STI syndemics, physical aspects of bodies assigned female at birth as well as the social, cultural, and political status of being perceived as women independently and collectively increase vulnerability to HIV and STIs, impede treatment, and worsen disease outcomes (Ostrach & Singer 2012). Lyons et al. (2013) offered a qualitative syndemic assessment of health disparities affecting young MSM related to their sexual identity, specifically substance use, intimate partner violence, victimization due to sexual orientation, and HIV infection. The authors' findings support established syndemic theory considerations that multiple social and structural factors, including an absence of role models and identity-specific sexual health education, interact with biological factors to enhance disease outcomes.

Beyond the discipline of anthropology, scholars have positioned gender, identity, and sexuality as predictive components or syndemic factors. As previously mentioned, Chakrapani and colleagues (2019a,b) identified a DAV syndemic among transgender women in India. Identifying a syndemic consisting of deleterious health interactions between substance use, HIV, mental health, and intimate partner violence, González-Guarda et al. (2011) recognized that Latinx women who were victims of intimate partner violence were more likely than women from other racial/ethnic groups to report unmet mental health needs. Lack of access to care for Latinx women was found to be related to racialized discrimination, including linguistic and cultural barriers, poverty, and unemployment, as well as to fear of reprisal over a lack of legal documentation and limited access to public health resources and social services due to migration status. Willie et al. (2021) found that racism played a significant part in attitudes toward pre-exposure prophylaxis (PrEP) for HIV prevention and sexual risk behaviors. While Latinx women had more positive attitudes toward PrEP than did non-Hispanic Black and White women, biomedical racism led to Latinx women making fewer medical appointments for potentially life-threatening health conditions and having less access to necessary medications. Latinx women also experienced weakened immune systems and an increased risk of coexisting infections. Assessing disengagement in care or suboptimal treatment adherence among Black men infected with HIV, Quinn et al. (2018) proposed syndemic factors of stigma, depression, substance use, and poverty.

Wilson and colleagues (2014) analyzed ways in which HIV, substance use, trauma, incarceration, and poverty interact syndemically for Black and Latinx men, with Black and Latinx MSM being at higher risk for HIV in particular. Black and Latinx drug users, especially those living in poverty, were more likely to initiate injection drug use earlier in adolescence and return to use after treatment. Institutional racism in the United States, including disproportionately higher rates of incarceration and harsher sentences among Black and Latinx men for minor offenses compared with White men, as well as residential segregation leading to fewer resources for areas populated by ethnic minorities contribute to poorer health outcomes and higher risk of exposure to HIV among Black and Latinx men. For example, exposure to racism and homophobia was associated with psychological distress and engagement in risk behaviors as a coping mechanism.

EXPANDING THE SYNDEMICS CONSTRUCT

Countersyndemics

Recognizing that not all bio-bio and bio-social relationships enhance poor outcomes, Singer (2009) proposed the idea of countersyndemics: when an element of an interacting set of disease and social conditions confers a protective benefit against the others. For example, Everson & Ostrach (2017) proposed that doula care, when offered during teen pregnancy, creates a countersyndemic by reducing the use of unnecessary biomedical labor interventions and increasing self-advocacy during pregnancy. Snodgrass and colleagues (2019) advanced the idea of countersyndemics by proposing that within a population how syndemics components interact can vary, offering protection (countersyndemic) among some but exacerbating harm (syndemics) in others. Through a mixed-methods study that included qualitative approaches, the authors proposed the term syndaimonic, applied to the context-specific benefits or harms of Internet gaming. Among some groups, excessive gaming can be harmfully addictive, whereas in other groups increased engagement with the gaming community offers "increased resilience to negative psychosocial and physical suffering" (p. 2).

Singer (2009) also recognized that the biomedical environment, including treatments and interventions, can be deemed a component of a syndemic arrangement, termed iatrogenic syndemics. Bulled & Singer (2011) highlighted iatrogenic syndemics in their discussion of syringe-mediated syndemics as a possible avenue of disease transmission, including hemorrhagic fevers, malaria, and hepatitis C, given the reuse of unsterilized syringes within biomedical settings.

Ecosyndemics

Advancing the syndemics framework to acknowledge the role of the physical environment on human health, Singer (2009) offered the concept of ecosyndemics. Ecosyndemics recognizes that climate change and human-altered physical environments foster new bio-bio and bio-social interactions. Migration into previously uninhabited areas, the breakdown of built and natural environments, and changes in the metabolism of pathogenic organisms that result in increased rates of growth and cell division (Singer & Bulled 2012, 2016) result in interactions that previously did not exist. Recent work by Tallman et al. (2020) examines the cases of the Southern Interoceanic Highway in Peru and the Belo Monte hydroelectric dam in Brazil. Both cases reveal that changes in environments create conditions for increases in vector-borne illnesses, surges in STIs (through increased sex work), and increased psychological stress, given eroding social cohesion and increasing violence and delinquency. The authors acknowledge that these interactions are complex but suggest that synergistic interactions enhance an individual's immune burden and a population's overall morbidity.

Climate change is also implicated in both respiratory and tick-borne infection ecosyndemics. In the former, the intersection of global warming with other forms of anthropogenic environmental degradation, such as vehicular air pollution, has resulted in impactful increases in the frequency of a range of respiratory diseases such as asthma, especially among poorer and disadvantaged populations in both developed and developing nations (Singer 2013). Lungs have become a primary body nexus for various environmental threats to cluster, intermingle, and multiply their adverse impacts (e.g., diesel fuel droplets and bacteria, allergens, and infectious agents). Notably, climate change increases the production of allergens, exposure to airborne toxins, and the diffusion of pathogens, multiplying the increase in syndemically linked respiratory diseases. In the latter, climate change has been found to contribute to the spread of tick species to new areas and thereby to contribute to polymicrobial ectoparasitic syndemics (Singer & Bulled 2016).

Moreover, while we know that a range of economic, political, and social factors trigger the migration of populations, climate change is proving to be a significant "threat multiplier" that exacerbates these drivers of human relocation (Schwerdtle et al. 2018). Environmental changes associated with increasing greenhouse gas concentrations cause human migration through droughts, crop failures, water scarcity, and a rise in sea levels that makes living in coastal areas unsustainable. Climate migration negatively impacts both physical and mental health. Health challenges common to climate refugees and other displaced persons are a consequence of a lack of adequate shelter, poor hygiene, and undernutrition during and following migration. Research has shown that rural populations forced by climate change to migrate to cities suffer from an increase in the prevalence of noncommunicable diseases, including obesity, cardiovascular disease, and type 2 diabetes. Also of importance are climate-sensitive infectious diseases, including malaria, leishmaniasis, and diarrheal diseases. Mental wellness is further undermined by a profound loss of social connections, in addition to the direct effects of trauma on mental health (Gracey & King 2009, King et al. 2009, Torres & Casey 2017). All these health burdens can potentially interact with disastrous consequences for climate refugees (Heffernan 2013, McMichael 2013).

CURRENT DEBATES IN SYNDEMIC SCHOLARSHIP

As the syndemic theoretical framework has become more widely used beyond the originating discipline of anthropology, scholars have interpreted the theory in ways that are inconsistent with the classic definition. Two published reviews, one examining recent syndemics scholarship (Singer et al. 2020) and the other analyzing HIV-specific syndemic scholarship (Tsai & Burns 2015), identified that most syndemics literature fails to present a synergistic arrangement of biological and social factors. And most of the reviewed literature described only an additive relationship, popularized by Stall et al. (2003), whereby specified biological and social factors collectively contribute to disease clusters. Assessment of the literature utilizing a syndemics label helps to clarify what is and what is not a syndemic.

Using data from the Urban Men's Health Study 1996–1998, Stall et al. (2003) examined the co-occurring and interacting conditions, described as "syndemic factors," of substance abuse, partner violence, depression, and childhood sexual abuse, which appeared to amplify HIV risk among MSM in Chicago, Los Angeles, New York, and San Francisco. The syndemic factors were summed to determine if the presence of multiple factors corresponded with greater engagement in HIV risk behaviors. The greater the number of syndemic factors experienced, the higher the prevalence rates were for high-risk sexual behavior and HIV infection—a sum score approach. Stall et al. argued that the sum score drew on relevant literature that demonstrated that disease concentrations worsen health outcomes (Stall et al. 2015) but recognized that the interactions were not necessarily synergistic.

Lack of evidence to articulate the synergy in syndemic arrangements constitutes the current controversy regarding the theory. Ethnographic methods employed by anthropologists provide rich descriptions of observations and offer detailed arguments for the relationships between syndemic components, which draw on existing biomedical evidence and epidemiological studies. As described, the SAVA syndemic was born from observations of coexisting biological and social conditions, the nature of which was further understood on the basis of scientific evidence of disease interactions and social epidemiology to explain the synergistic nature of the social-biological interactions. Mendenhall's (2016b) study of the VIDDA syndemic used life histories to provide rich details on the complex interactions between the components of the robust syndemic arrangement. Yet, even with rich observational data and clearly articulated established biomedical and epidemiological relationships, the synergy of neither SAVA nor VIDDA has been fully confirmed.

Consequently, critics argue that the "literature on syndemics can best be characterized as following a problematic trajectory . . . [as] it remains unclear whether [the social and biological conditions] co-occur independently, whether they co-occur and are mutually enhancing (i.e., interact with each other), or whether they co-occur and are mutually causal (i.e., cause each other)" (Tsai & Venkataramani 2016, p. 423).

Understanding the nature of the relationship between factors associated with a disease cluster is relevant for public health interventions and therefore must be a consideration for anthropologists studying and describing syndemics. Synergistic relationships result in exacerbated health outcomes beyond the impact of the sum of their separate effects. This notion "implies that one epidemic or health risk can be addressed in isolation while leaving the other intact, and that doing so should be expected to result in a greater reduction in disease burden than otherwise would be expected if no interactions were present" (Tsai 2018, p. 119), which could significantly reduce the cost of effective population-based interventions for comorbid conditions. Consequently, any scholar involved in informing public health intervention must accurately apply syndemics theory by richly describing the interactions and rigorously working to provide evidence for the proposed syndemic relationship.

This observation has stimulated debate among syndemics scholars about what empirical evidence is necessary to identify synergy among multiple health states and underlying social conditions. Stall et al. (2015) proposed reconsidering research design to extend beyond the commonly used cross-sectional approaches that rely on self-reported behavioral outcomes and consider long-term cohort studies among populations who are anticipated to experience particular syndemics, given high levels of disease states or experiences of social determinants of disease. These kinds of studies are costly and require significant time investments. An alternative may be to examine populations retrospectively. Large or national data sets such as demographic health survey (DHS) data could be used to assess syndemic relationships within populations across time. Furthermore, the effect of interventions on the syndemic arrangement could be determined by comparing DHS data, presenting a population-level perspective on individual-level data. This approach is subject to threats to internal validity, however, such as historical bias, because it cannot isolate the effect of single interventions and multiple interventions may have occurred concurrently to influence different aspects of the syndemic simultaneously.

Tsai (2018) has suggested additional approaches, such as mapping the temporal cascade of health risks using combinations of social network analysis or path analysis and agent-based models, to understand interactions between diseases and interventions, combined with anthropological fieldwork insights. Using these strategies in tandem, he argues, would allow investigators to extend analyses beyond the level of the individual and map the dynamic nature of disease interactions. Calling on scholars to implement these approaches in syndemics research, guest editors Tsai, Newfield, and Mendenhall commissioned a special issue of *Social Science and Medicine* titled "Rethink Syndemics Through Method, Over Time, and Across Spatial Boundaries." The call for papers indicated an aim to "revisit the kinds of quantitative and qualitative data useful for analyses of syndemics, how to evaluate the implications of syndemics for the burden of disease, and what these interactions convey."

Published in the *Social Science and Medicine* special issue, Brewis et al. (2020) examined associations between food insecurity, discrimination, crime exposure, and mental illness (depression and anxiety) in three distinct communities in Haiti. Food insecurity, crime exposure, and discrimination were independently associated with mental illness, but there was little evidence of interaction between these variables. A quantitative analysis of the previously described cholera–smallpox syndemic in Gibraltar in 1865 (Singer 2009) assessed the associations between disease comorbidities and social conditions at a population level (patios) (Sawchuka et al. 2020). The results revealed that

the odds of death from cholera decreased significantly with increasing markers of economic status (including number of servants, cistern presence, well presence, Jewish coresidents). Conversely, the likelihood of death from cholera increased with increasing numbers of smallpox cases within the housing community. These factors were not assessed in combination, thus failing to expose any synergies. Indications of improvements in sanitation services following the 1865 outbreaks and consequently lower death rates in 1866 may provide some evidence of the synergistic nature of the relationships. Testing for syndemic interactions of interpersonal violence (IPV) perpetration, alcohol use, and HIV risk behaviors among peri-urban heterosexual men in South Africa, Hatcher et al. (2019) found that the likelihood of engaging in risky sex (not HIV status) is significant and 12 times greater among men with inequitable gender views, problem drinking, and a history of IPV perpetration. The combined likelihood was greater than the sum of the individual odds. Himmelgreen et al. (2020) offer structural equation modeling as an effective approach to model complex relationships between directly and indirectly observed variables, and they propose applying this approach to assess food-insecurity syndemics. Boateng et al. (2020) apply structural equation modeling to assess the potential syndemic relationship between food insecurity, water insecurity, HIV, and depression among Kenyan women. The four-way interaction resulted in a significant increase in depression scores as compared with women who have no HIV, food insecurity, or water insecurity.

This body of work collectively reveals the challenges that remain in evidencing syndemic relationships. However, opportunities to use the tools are currently available across disciplines to both richly describe the clustering of diseases within populations, as has been modeled by anthropologists studying syndemic interactions, and understand the nature of the synergistic relationships. First, clear understanding of the syndemics definition must be the starting point for any assessment of relationships. Neither the coexistence of disease and social conditions nor serially causal disease and social conditions adequately describes a syndemic arrangement. Second, syndemic arrangements are always unique to communities. Analyses cannot simply assume that the same factors present in a syndemic arrangement in one community are the same in another community. Beginning with rich descriptions of observed disease clusters will allow investigators to identify interacting and potentially syndemic factors. Third, epidemiological studies largely use statistical analyses that show associations between factors to predict risk outcomes. A shift to recognizing the disease outcome as a variable in the analysis may reveal associations more clearly.

COVID-19 AS A DEADLY SYNDEMIC

Like HIV/AIDS, which appeared over 20 years ago, COVID-19 has emerged as a deadly syndemic. As Horton (2020) stresses, "COVID-19 is not a pandemic. It is a syndemic." He makes clear the implications of this assertion: "[N]o matter how effective a treatment or protective a vaccine, the pursuit of a purely biomedical solution to COVID-19 will fail." Also needed to overcome the COVID-19 syndemic are policies and programs that eliminate the profound disparities in society if we are to ever be safe from COVID-19.

Although COVID-19 is global in its impact, its on-the-ground expression is defined by local social, political, economic, demographic, and health conditions. Consequently, in the context of COVID-19, anthropologists turned their attention to local emergence of syndemic interactions. In one example involving the impact of local conditions and history, Bulled & Singer (2020) analyzed South Africa's response to the threat of COVID-19. South Africa has one of the highest numbers of people living with HIV in the world (8 million), an estimated 320,000 are ill with TB annually, and approximately half of the adult population live below the upper-bound poverty line (Bulled & Singer 2020). Recognizing the potential for syndemic interactions between the ongoing HIV

and TB epidemics and the long-standing social inequities, Bulled & Singer posit that despite the shared nature of the global pandemic, South Africa's public health responses are shaped by local health, socio-environmental, and historic factors. South Africa continues to have the highest number of diagnosed COVID-19 cases on the African continent, despite having instituted one of the most severe temporary shutdowns in the world. The local epidemic has roots among affluent European travelers, but densely packed, economically marginalized townships on the outskirts of major cities have subsequently become hot spots. Local hospitals are exceeding capacity, exposing weaknesses in the national health infrastructure (Harding 2020). Bulled & Singer warned that not only does the current situation pose COVID-19 risks, to which people affected by HIV/TB would be more susceptible, but also pandemic-related confinement could delay HIV/TB treatments and have other unanticipated consequences. There is heightened local and global concern that border closures and economic shutdowns will increase the costs of antiretrovirals for HIV treatment by 10–25% (UNAIDS 2020), and resources for TB monitoring and treatment are being exhausted.

Exemplary of the local context in the COVID-19 syndemic is Singer's (2020) analysis of the interaction of COVID-19, diabetes, and obesity in Mexico, a country in which diabetes is the second leading cause of death. While COVID-19 is suspected of causing direct pancreatic and pancreatic islet damage, diabetes is associated, in various studies in and beyond Mexico, with adverse COVID-19 outcomes, suggesting a two-way syndemic. In Mexico, a middle-income country, diabetes is more widespread and has a much greater impact on mortality than it does in major high-income countries such as the United States. Mexico, in fact, has one of the highest national rates of mortality attributable to diabetes in the world (almost 15% of all deaths). Moreover, diabetes is the leading cause of adult nonobstetric hospital admissions and hospital mortality in the country. In his analysis, Singer (2020) links the diabetes epidemic in Mexico to the effects of the modern "nutritional transition," namely significantly increased consumption of cheap, calorie-filled diets that are high in oils, animal fat, sugar, and processed foods, combined with less active daily life patterns. Mexican diets have changed extensively in recent decades, owing to (*a*) the effects of climate change as a driver of rural to urban migration; (*b*) neoliberal governance and economic restructuring, which transformed the Mexican state from a provider of public welfare and backer of the social safety net into an active promoter of market-based access to needed resources, including food, and to health care; and (*c*) the global food system, which has converted Mexico into the seventh largest food importer worldwide, with half of Mexican diets based on imported unhealthy food items. The Mexican case underlines the bidirectional nature of COVID-19's interaction with noncommunicable diseases (NCDs). Yadav et al. (2020) affirm, "COVID-19 and NCDs have a reciprocal effect on each other; NCDs increase vulnerability to COVID-19, and COVID-19 increases NCD-related risk factors."

Further sounding the alarm on potential COVID-19 effects on respiratory illnesses and TB syndemics, a group of medical anthropologists (Houston et al. 2020) outlined the syndemogenic nature of US immigration detention and the particular threats of COVID-19 for detainees and surrounding communities, given crowding, inadequate screening, and deprivation of health care and adequate healthy food. The authors pointed to the likelihood of syndemic interactions between COVID-19 and asthma in conditions of detention.

Gravlee (2020) adds an important contribution that suggests a framework useful in the development of hypotheses about how COVID-19 interactions with cardiometabolic diseases such as hypertension and diabetes are socially patterned. He shows how the same physiological systems that are at play in interactions among hypertension, diabetes, and COVID-19 are also involved in the pathways that link community disadvantage, racial discrimination, and poverty to racial inequities in hypertension and diabetes. Singer & Rylko-Bauer (2021) similarly analyzed intersections of structural violence, including racism, and a range of resulting disease interactions that

harm the health of affected populations in relation to COVID-19. All COVID-19 syndemics, in short, demonstrate entwined bio-bio and bio-social interaction.

APPLICATION OF THE SYNDEMICS CONCEPT

As Gravlee (2020) notes, "The concept of syndemics has a broader reach than most anthropological ideas." Studies framed by syndemic theory have drawn attention to the potential for resolving multiple life-threatening health disparities within marginalized populations (Stall et al. 2015). A scoping review of recent syndemics literature (Singer et al. 2020) did not identify any published evidence in the international literature of interventions that applied a full syndemics approach.

The Determined, Resilient, Empowered, AIDS-Free, Mentored, and Safe (DREAMS) program of the US President's Emergency Plan for AIDS Relief, designed to address the syndemic of IPV and HIV among adolescent and young women in sub-Saharan Africa, offers an example of a comprehensive multipronged and multilayered approach that in many ways appears to be informed by syndemic thinking (Saul et al. 2018). The approach addresses both diseases: HIV risk, by improving the availability of condoms, postexposure prophylaxis, PrEP, HIV testing services, and comprehensive family planning services; and IPV risk, through community mobilization and norm change, caregiver programs, and school-based violence prevention curricula and programs. Evidence of a synergy between HIV, IPV, and social factors, including gender norms [as described among men in South Africa by Hatcher et al. (2019)], would indicate an opportunity to address one of the factors without having to address them all.

Published subsequent to the scoping review of syndemics literature, Chakrapani et al. (2020) attempt just such an informed approach. Addressing a syndemic of alcohol use, depression, international homonegativity, and HIV risk behaviors among MSM in India, the researchers developed an intervention that involved motivational interviewing to improve condom use self-efficacy. The syndemic nature of the relationships between depression, alcohol use, and homonegativity among MSM was initially established. Problematic alcohol use, depression, and inconsistent condom use as well as internalized homonegativity, depression, and inconsistent condom use showed synergy with male partners but not with female partners. Consequently, the intervention increased the consistency of condom use with male partners and decreased problematic alcohol use, depression, and internalized homonegativity. This intervention shows that given the synergistic nature of the relationships, intervening in only one aspect can result in changes with all aspects. However, participants who met criteria for depression and problematic alcohol use were referred for additional treatment from mental health professionals, and education was provided to participants with depression and problematic alcohol use who did not meet the criteria for referrals, participants who reported using alcohol before sexual intercourse, and participants who indicated internalized homonegativity. These actions suggest that a multipronged approach was applied in the intervention, addressing many aspects of the syndemic arrangement simultaneously rather than applying a single focus on motivating condom use self-efficacy.

Perlman & Jordan (2018) propose focusing predominantly on structural factors to address the disease outcomes of syndemic arrangements. They hypothesize that structural changes can directly influence individual health-risk behaviors or work at a social network level to increase agency to reduce individual risk through social capital. Most importantly, they argue that changing structural factors influences environments of risk that extend beyond specific changes in the behaviors of individuals. Focusing on the United States, they offer structural interventions to address what they argue is a syndemic consisting of HIV, hepatitis C (HCV), and opioid use—namely, regulating the marketing and distribution of opioids, housing and criminal justice reforms, lack of health insurance, and un- and underemployment.

Because the sharing and reuse of syringes among drug users have been a source of syndemic interaction among various diseases (e.g., HIV/AIDS, hepatitis B, HCV, leishmaniasis, malaria) (Bulled & Singer 2011), syringe access programs and over-the-counter pharmacy syringe dispensing policies are well-demonstrated, effective syndemic-prevention strategies (Abdul-Quader et al. 2013, Zaller & Ostrach 2019). For example, in a meta-analysis of the effects of structural-level needle exchange programs and changes in HIV or HCV infection prevalence/incidence, researchers (Abdul Quader et al. 2013) identified nine studies that reported decreases in HIV prevalence, six in HCV infection prevalence, and three in HIV incidence.

Although still limited, a growing body of research is affirming the utility of a syndemics approach to addressing disease burden. This value is being recognized beyond anthropology in fields such as medicine, nursing, psychology, epidemiology, and dentistry, as well as among plant pathologists (F. Ochoa-Corona, M. Singer & H. Hassan Melouk, unpublished document, "Syndemics of Plant Viruses") and beyond academia in the mass media (Ahuja 2020, Daley 2019, Ellis 2019). In all these arenas, syndemics research is drawing attention to both the complexities of human disease and the enmeshment of disease in the structures of society and the impact of humans on environmental health. As a result, syndemics theory is adding to the recognition of disease as a biosocial process and the need for social intervention to improve health, especially for minority and disadvantaged populations.

Finally, there is growing interest in the intersection of syndemics and human rights. As Hart & Horton (2017, p. 888) note, a "human rights approach can facilitate implementation and evaluation of a syndemic approach among vulnerable groups." Ravnbøl's (2017) research with Roma in Denmark documents how the syndemic conditions of poverty, social exclusion, homelessness, and poor access to health services fuel the colliding conditions of hepatitis, tuberculosis, diabetes, hypertension, and asthma. Ravnbøl argues that these factors coalesce because a universal human right to health does not exist in the everyday lives of this destitute population. Focusing on the health of migrant populations, Willen and colleagues (2017) argue that uniting insights gained from research on syndemics and human rights will provide clinicians and other key stakeholders with concrete tools and strategies to tackle the health inequities that affect migrants and other vulnerable groups.

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