Review

JOURNAL OF MULTIMORBIDITY & COMORBIDITY

Journal of Multimorbidity and Comorbidity
Volume 14: 1–13

DOI: 10.1177/26335565241249835
journals.sagepub.com/home/cob
Sage

Conceptualizing COVID-19 syndemics: A scoping review

Nicola Bulled[1] and Merrill Singer[2]

Abstract

Background: COVID-19's heavy toll on human health, and its concentration within specific at-risk groups including the socially vulnerable and individuals with comorbidities, has made it the focus of much syndemic discourse. Syndemic theory recognizes that social factors create the conditions that support the clustering of diseases and that these diseases interact in a manner that worsens health outcomes. Syndemics theory has helped to facilitate systems-level approaches to disease as a biosocial phenomenon and guide prevention and treatment efforts. Despite its recognized value, reviews of syndemics literature have noted frequent misuse of the concept limiting its potential in guiding appropriate interventions.

Objective: To review how the term 'syndemic' is defined and applied within peer-reviewed literature in relation to COVID-19.

Design: A scoping review of definitions within COVID-19 literature published between January 1, 2020 to May 15, 2023 was conducted. Searches took place across six databases: Academic Search Premier, CINAHL, JSTOR, MEDLINE/Pubmed, PsycINFO and Scopus. PRISMA-ScR guidelines were followed.

Results: Content analysis revealed that COVID-19 has varied clustered configurations of communicable–non-communicable diseases and novel communicable disease interactions. Spatial analysis was presented as a new strategy to evidence syndemic arrangements. However, syndemics continue to be regarded as universal, with continued misunderstanding and misapplication of the concept.

Conclusion: This review found that current applications of syndemics remain problematic. Recommendations are made on the design of syndemic studies. A syndemic framework offers an opportunity for systems-level thinking that considers the full complexity of human-disease interactions and is useful to inform future pandemic preparations and responses.

Keywords

COVID-19, comorbidity, social determinants of health, syndemics, scoping review

Received 1 July 2023; accepted: 10 April 2024

Introduction

Syndemics theory is now almost 30 years old. Its origin traces to community-centered research and intervention around HIV disease among people who inject drugs.[1] In its initial conception, syndemics aimed to address what was lacking in the existing health explanatory concepts of *comorbidities* (the presence of multiple diseases or health conditions) and *social determinants of health*

[1]InCHIP, University of Connecticut, Storrs, CT, USA
[2]Anthropology, University of Connecticut, Storrs, CT, USA

Corresponding author:
Nicola Bulled, Institute for Collaboration on Health, Intervention, and Policy (InCHIP), University of Connecticut, 2006 Hillside Road, Unit 1248, Storrs, CT 06269-1248, USA.
Email: Nicola.Bulled@uconn.edu

(demographics and social factors influencing disease outcomes). From the population-level perspective offered by anthropology, syndemics theory recognizes that social and structural factors create the conditions that support the clustering of diseases within certain populations and that these diseases can interact in a manner that worsens health outcomes. While initially drawing attention to the unique arrangements of HIV-related disease clustering within distinct populations, such as violence and substance use among inner-city populations in Hartford, CT,[1] or tuberculosis and HIV in mine workers in sub-Saharan Africa,[2,3] the interest and application of the syndemics concept has spread across multiple disciplines to address varied communicable and non-communicable diseases.

Adoption of the concept accelerated when in 2002 it was taken up by the Centers for Disease Control and Prevention (CDC) because of its value in assessing synergistically interacting epidemics and the role of social factors like poverty and discrimination in exacerbating adverse disease interactions. Over time, syndemics theory has helped to facilitate a holistic approach to disease as a biosocial phenomenon and to guide various prevention and treatment efforts.[4] Most recently, the CDC presented a "syndemic approach" to address MPOX that entailed comprehensive sexual healthcare given the association of MPOX cases with HIV and other sexually transmitted infections among gay, bisexual and other men who have sex with men.[5]

Despite its recognized value, reviews of the syndemics literature have noted frequent misuse of the concept to label disease events that do not adhere to the dual nature of syndemics involving both two or more interacting diseases or other health conditions and specific social drivers of vulnerability.[4,6–8] Notably, a meta-knowledge analysis of the syndemics literature published between 2001-2020 indicated a bifurcation of syndemic thought.[9] Singer, the originator of the term and the most published syndemics scholar established the principles of the theory,[1,10,11] which have been further perpetuated by other notable scholars in the field including Mendenhall. However, Stall et al.[12] presented a strategy to measure the effect of what was termed 'syndemic factors,' with the aggregate count of co-present diseases or psychological conditions predicting worse health outcomes. This paper has been cited 1,058 times, including by other influential syndemics scholars including Mustanski et al. and Parsons et al.[13,14] forming the foundation of various studies evaluating syndemic arrangements. The consequence of Stall's summative approach (which does not investigate actual disease interaction) has been a widespread misunderstanding and misapplication of the theory.[15–17]

Given the complexity of COVID-19, its heavy toll on human health and well-being, and its impact and concentration within specific at-risk groups including individuals with comorbidities and the socially vulnerable, it has become the focus of much syndemic discourse. In 2020, Richard Horton, the well-known and widely cited editor of *The Lancet*, published a Comment in which he declared "COVID-19 is not a pandemic. It is a syndemic".[18] This assertion helped to trigger a re-examination of COVID-19 because it had become clear that this grave threat to health and survival was being driven by the consequential interaction of multiple diseases: severe respiratory syndrome caused by the coronavirus 2 (SARS-CoV-2) and various non-communicable and communicable diseases. Further, this interaction was concentrated within social groups subjected to long-standing social and economic disparity, thus fitting the definition of a syndemic. However, nuancing Horton's call for considering COVID-19 a syndemic rather than a pandemic, Mendenhall[19] argued that "Calling COVID-19 a global syndemic is misguided….What is driving coronavirus to move through the population in the USA and interact with biological and social factors, however, differs from other contexts.…This matters because in other contexts COVID-19 is not syndemic."

A similar re-thinking of the pandemic was published independently by Singer and Rylko-Bauer[20] under the title "The Syndemics and Structural Violence of the COVID Pandemic: Anthropological Insights on a Crisis." This paper examined the pandemic as a complex infectious disease event driven by a rising rate of both communicable and non-communicable diseases and an array of vulnerabilities created by the structural violence experienced by specific oppressed populations.

To date, there are 329 publications listed in PubMed that reference "COVID syndemics." As such, it is important to review how the terms and definitions of the syndemics of COVID-19 have been conceptualized to help guide future research, policy, and clinical practice in COVID-19 care and prevention. In this paper, we provide a scoping review of the COVID-19 syndemics literature published since 2020. As Peters et al.[21] indicate, scoping reviews are best used to assess a body of literature that has not yet been comprehensively reviewed, and/or is heterogeneous; to map existing literature in terms of its nature, features, and volume; to clarify working definitions and conceptual boundaries of a topic; and to identify gaps in existing literature/research.

The goals of this review are to determine: (1) How extensively the syndemics framework has been utilized to respond to COVID; (2) How the syndemics concept has been deployed as an explanatory approach in scholarly COVID publications; (3) If the same definitional problems with the syndemics concept exist in the COVID literature as occurred in the pre-COVID syndemics era; (4) The key insights gained from using a syndemic framework in understanding and responding to COVID; and, (5) Existing gaps in the COVID syndemics literature. The research question guiding this review is: How is syndemics defined in relation to COVID-19 within peer-reviewed publications and what are the key conceptual components that form these definitions?

Methods

Scoping reviews are conducted to systematically map the research evidence of a particular field and identify gaps in the literature[22] with the intention of "establish[ing] how a particular term is used in what literature, by whom and for what purpose".[23] The Arskey and O'Malley[22] scoping review framework was used, involving the following iterative steps: 1) identifying the research question, 2) identifying relevant literature, 3) literature selection, 4) charting the data, and 5) collating, summarizing and reporting the results. The Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist,[24] see Supplemental File 1, was used to ensure all of the relevant aspects required of a high-quality scoping review were completed.

Search strategy

Six databases were searched for publications dated January 1, 2020 to May 15, 2023 (present), including: Academic Search Premier, CINAHL, JSTOR, MEDLINE/Pubmed, PsycINFO and Scopus. These search engines were chosen as they cover multi-disciplinary research articles from anthropology, sociology, medicine, nursing, and public health. The following search terms were used: "COVID*" AND "syndemic*" OR "syndemics." Search terms were searched for within the entire document, not limited to title and/or abstract. The papers identified were imported to EndNote bibliographic software and duplicate papers (n=720) and those not written or translated into English (n=65) were removed.

Inclusion and exclusion criteria

The title and abstracts of the retrieved papers were screened by both authors (NB and MS) according to the PCC framework.[21] Publications were included if they presented a discussion of COVID-19 as a syndemic. Following an initial screening, 484 additional papers were removed that were not about COVID-19, specifically those that referenced the COVID-19 pandemic or syndemic as context for an issue but did not further analyze syndemic features of the health issue of concern. No restrictions were placed on the type of study or type of publication (letter, review, commentary) since it was important to gather a broad scope of the application of the term syndemic as used in the literature.

The remaining publications (n=258) were then categorized as: "not syndemic" (n=71); "syndemic substitution" – used the term "syndemic" rather than "pandemic" to align with Horton[18] but did not examine a syndemic arrangement (n=28); "misuse of the term" – either considering disease comorbidities/interactions but offering no social context to explain disease clustering, or describing disease clustering in terms of social vulnerabilities but not describing disease interactions (n=84); or "syndemic" (n=57) that met established criteria – articulating the interactions between two or more diseases or other health conditions and identifying and describing the influence of specific social drivers of vulnerability. In cases where the authors disagreed with the categorization of publications, the full text was assessed, and an agreement reached.

The full text of the articles identified as "syndemic" were reviewed. Papers were included for final review if they presented a clear definition of a syndemic including disease/health condition interactions and at least some indications of why diseases clustered within certain populations given specified social conditions.

Data charting and analysis

A data charting form was developed to extract relevant data from the articles. Data were extracted on the study characteristics (authors, year, and journal); the aim of the research; the syndemics definition used; the reference given for the definition (if one was used); the diseases/health conditions considered; and the social vulnerabilities described. Inductive content analysis was used to analyze the definitions. This method was chosen as it is a systematic and flexible approach that allows the researcher to describe phenomena and extract meaning from textual data into content-related categories.[25] Definitions provided and references given for the definition were assessed, determining if the nature of the definition (e.g., highlighting biology or social factors over biosocial interactions) was influenced by the reference selected (e.g., theory originator Merrill Singer, or theory users).

Ethics approval

Not applicable

Results

Figure 1 summarizes the flow of the screening process. Initial searches found 1,527 publications. Following the screening of titles, abstracts, and full texts, 57 publications were included for final review that contained a discussion of syndemics in relation to COVID-19.

Most publications were journal articles (n=54), including 9 reviews and 8 editorials or commentaries. Almost one half (n=24) of publications were in clinical journals. The remaining were in anthropology or sociology journals (n=7) or public or global health journals (n=16), with publications also in specialty religion, transportation, and conflict focused journals reflecting the impact of COVID-19 on all sectors and the value of the syndemics perspective as a way

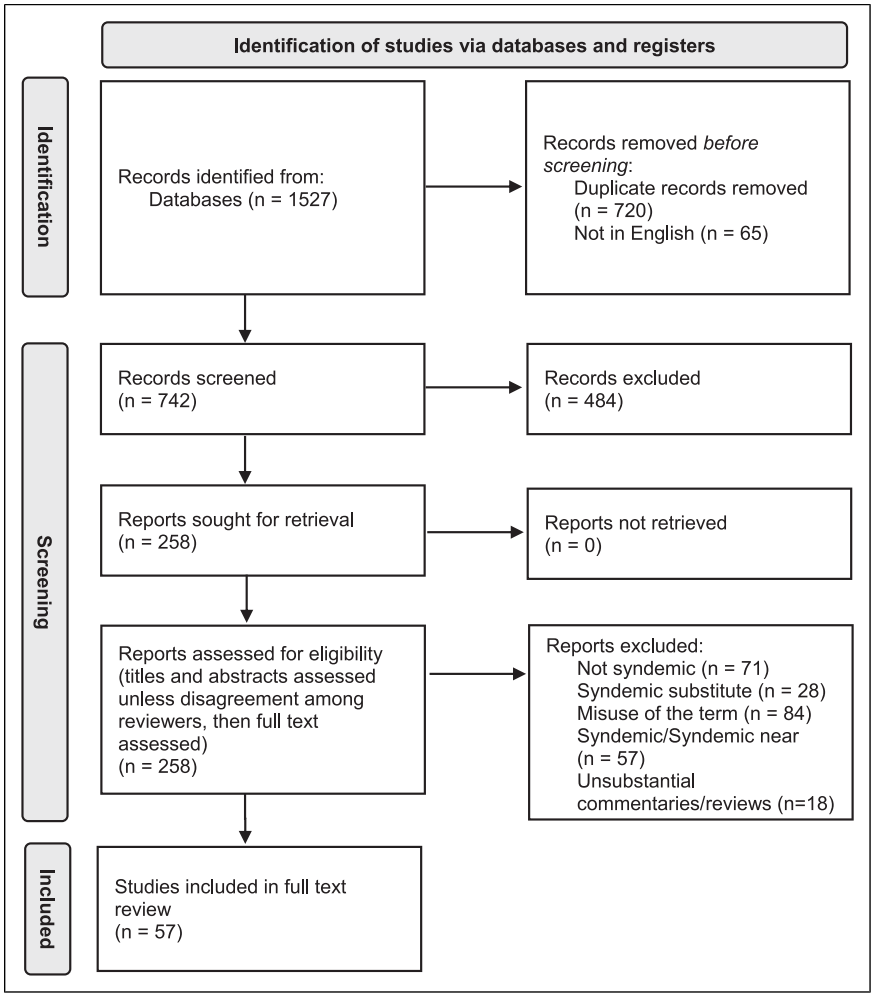

Figure 1. PRISMA 2020 flow diagram for systematic reviews of COVID-19 syndemics literature from 2020-present (May 15, 2023). *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

of systems-level thinking. One report and two book chapters were also included.

Four 'syndemics' definitions were found across the 57 publications. Over half (n=31) of publications included a complete definition. Ten publications only presented the idea of co-existing and interacting diseases or health conditions, with limited articulation of social drivers; three presented only the social aspect of a syndemic with limited articulation of disease interactions, and five identified both biological and social elements, but with no indication of the nature of the biological interactions. Despite these limitations in definitions, all papers met the criteria for a syndemic, including evidence of disease interactions and social drivers. See Supplemental File 2 for details.

References cited for syndemic definitions were mostly from the term's originator, Merrill Singer, with 22 from early publications introducing the term,[1,10,11] and 19 from more recent publications.[26,27] Other references were cited by seven publications and no reference was given in another nine publications corresponding to publications that offered no definition of syndemics.

The research aims of the publications varied. Collectively the studies contribute to growing literature on synergistic interactions between non-communicable and communicable diseases, specifically cardiometabolic disorders (obesity, diabetes, hypertension, cardiovascular disease) and COVID-19 (n=29). The publications offer details on the pathways of interaction that have been suggested.[20] Specifically, people with COVID-19 are susceptible to an inflammatory cytokine storm that leads to acute respiratory distress, shock, and rapid deterioration. Individuals with diabetes are more at risk for this response and have amplified angiotensin-converting enzyme 2 (ACE2), a binding site for SARS-CoV-2. Finally, SARS-CoV-2 infection increases stress levels causing the release of hyperglycemic hormones which increase blood glucose

advancing pre-diabetes. SARS-CoV-2 causes myocarditis and affects the lungs, causing increased strain on the heart which is particularly problematic in individuals with existing cardiovascular disease. Infectious disease interactions with COVID-19 examined in the literature included HIV and TB (n=8) together and separately, malaria (n=2), and neglected tropical diseases (n=2). Mucormycosis (fungal infections) (n=2), food insecurity (n=4), gender-based violence (n=2), substance use (n=1), and mental health (n=1) were also presented as synergistically interacting with COVID-19.

Common social constructs included increased exposure to COVID-19 due to economic vulnerability that required front line work, continued work during epidemic outbreaks, and high-density housing. Some unique social constructs were also revealed such as police violence,[28] Redlining policies that create high density neighborhoods with limited medical resources in the US,[29] COVID-19 control practices including lockdowns that increased risk of gender-based violence,[30,31] disrupted global food systems,[32] and the availability of and subsequently unmonitored use of over-the-counter steroids and antibiotics in India due to an overburdened health care system.[33,34]

Publications focused on specific populations such as African Americans in the US,[28,35] Muslim communities in the UK,[36,37] and indigenous communities in Brazil's Amazon basin[38] drawing attention to structural factors denying access to quality housing, education, employment, food, and healthcare and systemic racism heightening stress levels that increased the likelihood of chronic conditions which interact negatively with COVID-19. Publications also recognized certain professions, such as long-haul truck drivers, as at high risk for COVID-19 syndemics given the lifestyles that involved long periods of inactivity, poor diets, limited access to healthcare and consequently poor chronic disease management, and high stress.[39,40] Finally, publications recognized the COVID-19 control efforts either independently or in addition to existing social and structural factors created conditions for the clustering of interacting diseases.[41–43] Stay at home or lockdown policies resulted in job losses and economic downturn, primarily impacting communities already experiencing socioeconomic hardship.

Content analysis of the publications revealed four key themes, namely the continued regard for syndemics as universals, the expansion of the concept to explain new observations, the development of new strategies to evidence the theory, as well as continued discrepancies between the definition of syndemic theory and its application.

Syndemics are regarded as universal

Of the publications considered "syndemic," few provided a focused assessment of the social and structural context driving disease clusters within specific populations. COVID-19 is a syndemic only among certain populations. What needs attention are the shared dynamics of the community that create a collective risk for disease. Gravlee[35] offered a comprehensive examination of systemic racism, chronic health inequities, and COVID-19 among African Americans revealing how the confluence of historical and present-day social and structural factors (e.g., race-based segregation, mass incarceration, intergenerational wealth disparities, police violence, food insecurity, housing density) support the existence of chronic conditions including diabetes and hypertension which interact poorly with COVID-19. Presenting a more focused perspective, Quinn et al.[28] explore these relationships as they occur for Black residents in Chicago, IL revealing a unique interplay of racism and violence in the city that adds to longstanding inequities (food deserts, segregated living) that contributes to poor physical (asthma, diabetes, obesity) and mental health (stress, PTSD).

Distinctions within specific populations are also revealed by Dogra and Shahid[36,37] who present the COVID-19 dynamics of British Muslims. They argue that experiences of Islamophobia translate into both social and structural inequities in housing, employment, and healthcare access, increasing stress levels resulting in high allostatic load and biological weathering. The discussion of commercial or long-haul truck drivers by Lemke et al.[39,40] reveals chronic stressors endemic to the profession (e.g., long hours spent under high stress, reduced access to quality diets, poor sleeping opportunities, limited access to healthcare and social support) that heighten not only chronic disease but also increase exposure to and poor outcomes from COVID-19. These specifics provide opportunities for better informed and positioned programming and policy that can address the unique contextual factors that create the supporting conditions for disease interactions. Nations and communities need the work of frontline laborers and frontline laborers need public health policies that protect their health.

Studies that offered localized perspectives also revealed communities within communities. While examinations at a national scale may not reveal syndemic relationships, closer examinations can indicate inequalities and vulnerabilities that create clustered health conditions. For example, four studies using geographic information systems (GIS), spatial mapping, or population level data to identify disease clusters (COVID-19 plus comorbidities) considered whether social vulnerability indicators predicted more severe COVID-19 outcomes.[44–47] The studies showed that while social vulnerabilities did predict more disease clustering, they did not have the same impact on disease severity in all communities (see more discussion below). This finding confirms the importance of context specific and locally informed explorations to understand the social

and biological dynamics driving different observed outcomes.

New revelations about syndemic interactions

Publications added evidence of new infectious disease syndemics, including COVID-19 and HIV and/or TB, malaria, and neglected tropical diseases. While the biological interactions are not well articulated, clinical data from 37 countries indicate that HIV infection is a significant independent risk factor for severe COVID-19 presentation and mortality.[48] Immune suppression, chronic inflammation, and common underlying conditions associated with HIV infection (e.g., diabetes, metabolic syndrome) likely account for greater COVID-19 severity, particularly in individuals with poorly managed HIV.[49] Publications also drew attention to social conditions of people living with HIV such as stigma, reduced access to healthcare for disease management, food insecurity, substance use, social isolation, depression and emotional distress.[49,50]

COVID-19/TB biological interactions are also not well articulated, however, existing meta-analyses indicate shared dysregulation of immune responses leading to increased risk of COVID-19 severity and TB disease progression, specifically reduced levels of IFN-γ which increases susceptibility to TB and the decreased activation of CD4+cells by TB needed to suppress COVID-19.[51] Socially, given overlapping transmission routes (droplets), individuals already at high risk for TB also were at high risk for COVID-19, such as individuals working and living in close confined spaces.[41] In addition, COVID-19 mitigation efforts disrupted healthcare services including routine TB diagnosis and treatment and reallocated already scarce resources to COVID-19 care.[41,51]

Publications examining potential malaria/COVID-19 syndemics indicate that it is unclear whether immunomodulation caused by malaria and other neglected tropical diseases might be beneficial or harmful to COVID-19 coinfections.[52,53] Malaria-induced changes to immune responses (suppressing the production of pulmonary cytokines leading to reduced inflammation and clinical symptoms) has been shown to be protective against severe manifestations of some respiratory viruses such as influenza,[53] a condition known as a counter-syndemic. However, scholars argue that even small changes in the risk of severe outcomes due to coinfections could result in substantial changes in the epidemiology and overall impact of COVID-19 in low- and middle-income countries heavily burdened by malaria and with limited healthcare and economic capacity to manage epidemic outbreaks.

Uncommon health conditions were also revealed to have syndemic interactions with COVID-19, as in the case of the iatrogenic syndemics of mucormycosis and diabetes. In India, an unexpected and deadly second surge of COVID-19 placed significant strain on an already burdened healthcare system, resulting in hospitals overcapacity, the depletion of medical grade oxygen supplies, and many patients managing severe illness at home not under medical supervision.[33,34] In their desperation, doctors and infected individuals turned to corticosteroids to reduce COVID-19 induced inflammation. The steroids increased blood sugar levels in patients with diabetes and stimulated diabetes onset worsening COVID-19 outcomes (see diabetes/COVID-19 interactions described above). Poorly controlled diabetes and corticosteroids are also a major risk factor for mucormycosis, a rare disease caused by fungi found in soil and decaying organic matter. Compounding the crisis were shortages of the main drug used to treat mucormycosis. While COVID-19 associated mucormycosis was not unique to India, the confluence of social and biological factors including a high prevalence of poorly controlled diabetes, excessive use of corticosteroids, and environmental exposure given India's humid climate and reliance on homemade and unsterilized personal protective equipment created the conditions to support syndemic disease clustering.

Publications examining mental health and substance use disorders offer comprehensive pictures of how COVID-19 mitigation efforts, existing social vulnerabilities, and biological interactions created new COVID-19 syndemics. The fear generated by the threat and disruption presented by the COVID-19 pandemic impacted anxiety, depression, psychosis, suicidal ideation and drug use disorders.[54] Widespread unemployment exacerbating financial and other stressors, and reduced access to mental health services, amplified these effects. Public health control efforts further disrupted support networks, both personal and professional, which proved particularly serious for people already vulnerable, those with a history of psychiatric illness, substance abuse issues, or of lower socioeconomic status.[55] A reciprocal relationship between COVID-19 and neuropsychiatric disorders has been observed, in that preexisting neuropsychiatric disorders amplified COVID-19 infection risk, and COVID-19 infection, a consequence of its impact on brain physiology, the kynurenine pathway function, and central nervous system inflammation, increased the risk of new-onset psychiatric disorders or dementia.[56,55]

New strategies to evidence syndemic arrangements

Most syndemic studies that attempt to provide a quantitative assessment of synergistic interactions obtain data from individuals and conduct multivariate analyses to determine whether factors are mutually reinforcing. This approach often does not assess synergistic interactions and does not provide the population-level analysis important to syndemic

theory. Syndemic theory is population-based as we are looking to understand clusters of diseases within a community, believing that something in the shared culture and/or shared experience is creating the conditions for disease co-existence and interaction. How big that population is depends on what is shared.

Providing a population-level perspective, Arena et al., Chung et al., and Lee and Ramirez[44–47] present place-based assessments of disease clustering. Lee and Ramírez[46] utilize GIS mapping to evaluate social and health determinants associated with higher COVID-19 infections and deaths in counties in the US state of Colorado. County-level analysis found positive associations (not causal) between COVID-19 deaths in rural areas with lower access to information via broadband internet and routine and emergency healthcare, and COVID-19 infections in urban areas with higher population density and asthma.[47] General linear analysis of estimated census-track rates of COVID-19 indicated that comorbidities of mental health and obesity, and social vulnerabilities of poverty, living in mobile homes, and having no vehicle had the greatest positive effect of COVID-19 rates in Colorado.[46] These innovative approaches to identifying possible syndemics would be strengthened by further assessments of the causal adverse interactions in play and a closer look at social contexts.

Analysis of the Hong Kong Clinical Data Analysis and Reporting System found variations in the effects of multimorbidities on COVID-19 severity relative to income levels.[45] Medium and high-poverty areas experienced higher COVID-19 severity corresponding with multiple comorbidities (aOR = 2.88 [1.86–4.45], $p < 0.001$; aOR = 2.38 [1.52–3.74], $p < 0.001$, respectively), statistically significant on both multiplicative and additive scales. The authors suggest that underlying socioeconomic inequalities in the public-private dual-track healthcare system have contributed to both inequities in chronic disease management and COVID-19 treatment.

While these approaches are still limited in their assessments of synergy and detailing causal pathways, population level data can better account for shared social, structural, political, historical, and environmental attributes of a community, rather than the presumption of sharing based on individual demographics such as race/ethnicity, income level, and educational attainment that are standard in epidemiological analyses.

Misuse of the term

The publications that misuse the syndemics concept either focused on comorbidities, their physiological interactions and clinical presentation, on social conditions that heightened COVID-19 disease risk or the impact of the COVID-19 pandemic on certain communities, or on the impact of COVID-19 mitigation efforts on other health conditions. We present some of them here as we feel they are valuable in any discussion of COVID-19 but highlight that they do not present a COVID-19 syndemic. As such, they inform different responses.

First, publications described in detail the interactions between diseases but failed to describe the social contexts that allow diseases to cluster in certain populations. For example, Faratisha et al.[57] describe a molecular docking study to examine the effects of the compound Nigericin as an antimalarial and antiviral (anti-SARS-CoV2). Rao[58] present an overview of the "twindemics" of cardiovascular disease and COVID-19, indicating the high affinity of SARS-CoV-2 for the spike protein receptor, highly expressed on endothelial and adipose tissue and therefore vulnerable to COVID-19 infection. Pajuelo-Reyes et al.[59] analyzed case counts of COVID-19 and malaria in native communities in the Amazonas of Peru, but do not discuss why either through biological interactions or social context native communities were at higher risk for disease clusters. Considering the clustering of respiratory infections, COVID-19 and TB, Sheerin et al.[60] profile COVID-19 gene expression signatures on RNA-sequencing data from individuals infected with TB, identifying shared dysregulation of immune responses to COVID-19 and TB. Given these results the authors suggest that clinicians evaluate COVID-19 patients for potential TB co-infection. Other publications describe the clinical presentations, management, and outcomes of patients with co-occurring conditions, such as COVID-19 patients living with HIV[61] or patients with COVID-19 associated mucormycosis infections.[62]

Conversely, some publications describe social context or structural conditions that contribute to disease clustering within certain populations but offer no discussion of the nature of disease interactions. For example, Krishnamurthy[63] presents a detailed argument for the impact of mass incarceration as the driving force for high COVID-19 rates in the US, with Black Americans most impacted given existing conditions in prisons and jails that contribute to communicable disease outbreaks and delayed disease containment responses. Many of these publications draw on syndemic scholars' arguments for greater attention to social and structural context, as Mendenhall et al.[64] note: "Syndemic thinking requires a shift in clinical practice, to look beyond diseases and think about how social distress, especially when it becomes chronic, can undermine clinical interventions for co-occurring conditions." Consequently, these publications use syndemic terminology to present a 'social determinants of health' argument.

Some publications draw specific attention to racial/ethnic inequalities that became central to the public conversation on COVID-19 in the US and the UK. Given the timing of the George Floyd murder and the heightened public awareness of police killings, Curry[65] argues that anti-Black racism and

pandemic disease are interrelated and synergistically enhanced. Poteat et al.[66] argued that historic and present-day systematized racism including slavery, mortgage Redlining, political gerrymandering, lack of Medicaid expansion, employment discrimination, and health care provider bias contributed to heightened COVID-19 morbidity and mortality of Black Americans. Additional scholars[67,68,69,70] similarly argue that Chuukese and Marshallese, minority Micronesian ethnic groups in Hawaii, are at increased risk for COVID-19 due to disparities in housing (living in multigenerational households with limited opportunities for social distancing), employment (operating as low-paid frontline workers with no security or paid sick leave), and healthcare access.

Finally, responses to COVID-19, specifically severe and prolonged lockdowns, were presented as structural factors creating conditions driving heightened disease or health condition risk, although not always interacting or comorbid with COVID-19 infection. Lockdowns worsened economic, social, and healthcare marginalization for some communities or population segments which in turn heighten disease risk for unmanaged/untreated diabetes, HIV, TB, and malaria. Burns and Albrecht[71] present increase substance use disorder and drug overdose risk in small-town America because of COVID-19 control policies that diminished or halted efforts focused on safe drug use or overdose prevention. A theoretical increase in dengue transmission was presented as related to restrictions on mobility.[72] Restricted mobility was also recognized as increasing cases of gender-based and domestic violence.[73,74] Finally, border closings, travel restrictions, disruptions to globalized economies, supply shortages, increased costs, and inflation influenced food access globally.[75]

In one way or another, all publications mentioned above provided a partial description of "syndemics" but failed to complete the picture of adversely interacting diseases/health conditions, the promotion of negative disease/health condition interface and/or the creation of disease/health condition vulnerability, and the consequent pathways of disease/health condition interaction. As such, these publications tend to muddy the definition and conceptual understanding of syndemics. This pattern risks redefining syndemics in ways that water down the usefulness of the concept in addressing the health burdens of affected populations (e.g., identifying pathway interventions, blocking disease interactions).

Discussion

This review addressed the research question: How is syndemics defined in relation to COVID-19 and what are the key conceptual components that form these definitions? COVID-19, like HIV before it, is a highly syndemogenic disease. This term refers to diseases that frequently interact with other diseases to produce syndemics. Infectious diseases, especially those that downgrade or disrupt the immune system, like COVID-19, are often syndemogenic. In the case of COVID-19, it appears that the disease causes stem cells to produce more white blood cells that send inflammatory signals than the comparable cells of people without COVID-19. These changes suggest why this disease damages so many different organs and why some people with long COVID have high levels of body inflammation.[76]

There are a growing number of documented physiological interactions with both communicable and non-communicable diseases (NCD) that cluster in populations with specific social dynamics. This has contributed significantly to our understanding of communicable disease and NCD interactions. It underscores the heavy burden of disease in countries currently undergoing epidemic transitions,[41,53] and the importance of preventing or closely managing NCD's in countries where communicable diseases are no longer endemic. Evidence is still developing with regard to some physiological dynamics, such as relationships between malaria, NTDs, dengue, and COVID-19. Understanding these dynamics will prove particularly important in disease-endemic areas, not just for the containment of COVID-19, but in preparation for future pandemics.

COVID-19 laid bare the social and structural inequities that drive much disease and allowed for the interaction of COVID-19 with other health conditions. Socially, economically, and politically marginalized populations already struggling with underlying health conditions including NCDs, substance abuse, mental health conditions, and other chronic communicable diseases (HIV and TB) were at particular risk for COVID-19 morbidity and mortality given increased exposure, reduced access to routine disease management, and delayed onset of COVID-19 care or even mismanaged COVID-19 care as was the case in India's reliance on corticosteroids.[33,34] Even COVID-19 control efforts established or worsened existing structural and social inequities, generally within already vulnerable populations. Disruptions in global food supplies and job losses influenced local food insecurity, contributing to challenges in syndemic disease management.[32,42,77,78] Rising global rates of gender-based violence followed the shutdown of support services and the implementation of stay-at-home orders which not only trapped individuals with their abusers, but enhanced or initiated violent behaviors given economic and disease-related stressors.[30,31]

While the reviewed literature offered multiple attempts to invoke a syndemic approach or at least apply syndemic language, definitional problems with the concept remain. Multiple reviews of syndemics literature have noted what appears to be a branching of the concept.[4,7–9,79] On one hand, scholars are retaining the foundational definition

which recognizes the interaction of both biological and social elements. On the other hand, syndemics has become a catch-all phrase to imply independently or collectively co- or multi-morbidities, social determinants of health or social injustice, with no consideration for either interaction or causal pathways. Much of the misuse of the concept has occurred because of efforts to empirically measure highly complex dynamics, resulting in oversimplification and a disregard for the *syn*-ergy aspect of *syn*-demics.

Some have argued that the concept itself is limited in its utility largely because of this misapplication.[15,17] However, scholars who fully apply the concept recognize its potential in offering insights that require a systems-thinking approach. In a commentary titled, "A systems approach to preventing and responding to COVID-19," Bradley et al.[80] note:

> Systems thinking can help policymakers understand and influence the spread of infection and its multifaceted consequences across the community since society is itself a complex adaptive system. It can provide a framework to look beyond the chain of infection and better understand the multiple implications of decisions and (in)actions in face of such a complex situation involving many interconnected factors.

Before COVID-19, scholars warned of impending pandemics and numerous simulations revealed that inadequate preparation would worsen the overall impact. Following a pandemic simulation exercise, Clade X, run with US White House and Congress leaders in May 2018, Jeremy Konyndyk, senior fellow at the Center for Global Development, noted, "We have a strong end game once there is a vaccine, and we have a strong opening game if countries contain an outbreak when case numbers are low".[81] However, he pointed out systemic deficiencies in the public health system and the often overlooked "middle game" in advance of pandemics.

Evidencing a complex system, or syndemic arrangement, remains a methodological challenge. As noted by Boes et al.[82] it is difficult to find suitable causal models of disease interaction, and adding social and structural context only exacerbates the challenge. Studies that only consider the social dynamics and fail to lay out biological disease interactions or, conversely, studies that only recognize disease comorbidities and fail to acknowledge interactions of social drivers, are unlikely to unravel the complex causal pathways that promote disease clustering.

The literature does indicate a movement towards a rigorous application of the full syndemics framework to help focus COVID-19 and other disease interventions beyond case-by-case individual treatment. These include quantitative spatial analyses to recognize disease clustering in geographic locations followed by assessments of social dynamics to offer an explanation of the observed relationships.[44–47] They also include deep qualitative assessments of communities that share the experiences of systemic racism, disease-related, religious, or ethnic-based discrimination, or even livelihoods, with clearly laid out causal pathways to explain interacting disease clusters and their social drivers evidenced through existing scholarship.[28,35–37] Further efforts to explore strategies or approaches to understand the complexities of disease experiences will only enhance the utility of the syndemic concept.

Key recommendations for how to conduct a rigorous syndemic assessment:

1. Observe the clustering of diseases or health conditions within defined populations. Populations can be defined by a multitude of different shared attributes including spatial, race/ethnicity, gender, sexual identity, or economic class. Given the social meanings ascribed to certain diseases, such as HIV, diabetes, or substance use disorders, these chronic conditions may present a dual social and biological burden, with physiological interactions of the chronic disease occurring with other health conditions and creating the social dynamics such as stigma or social isolation that increase vulnerability to disease clustering.
2. Determine if there are known or likely physiological associations between the observed diseases. This may require thinking across disciplines including epidemiology to identify disease burdens, and biomedical literature to understand clinical manifestations of disease and disease physiology. Interactions should be synergistic, not summative. The existence of one disease enhances the poor outcome of the other due to interactions, not just because of co-existence.
3. Interrogate social dynamics that might explain why health conditions cluster in populations. Detailed observations and rich qualitative data, ethnographic literature, historical accounts, social studies (anthropology, economics, political science, sociology), and demographic data can help to capture the unique social dynamics at play in the past and present.
4. Theorize, or employ empirical strategies to measure social and biological dynamics to evidence, causal pathways that explain interacting disease clusters across populations.

Conclusion

Given the occurrence of COVID-19, HIV, and other communicable diseases before them, we can assume with high confidence that pandemic disease will be a routine part of the future. Furthermore, history is clear, in a time of

radical environmental change, we should expect new zoonoses to emerge. With new human-animal-environment interactions, there are likely to be new and unexpected disease interactions and new social dynamics that create risk for disease clusters. Present literature on COVID syndemics indicates that evidence is still developing concerning physiological dynamics between clustering disease, there remain definitional problems with and application of syndemics theory, and evidencing complex systems presents a methodological challenge. Despite these limitations, the syndemic construct offers an opportunity for systems-level thinking, considering the full complexity of social life inclusive of public health and healthcare systems, as well as economies, welfare policies, housing dynamics, anthropogenic climate and environmental change, and social structures to inform future pandemic preparations and responses.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Nicola Bulled https://orcid.org/0000-0002-9699-3937

Supplemental Material

Supplemental material for this article is available online.

References

1. Singer M. (1996). A dose of drugs, a touch of violence, a case of AIDS: conceptualizing the SAVA syndemic. *Free Inquiry in Creative Sociology*, 24(2), 99-110.
2. Abdool Karim S. S., Churchyard G. J., Karim Q. A. and Lawn S. D. (2009). HIV infection and tuberculosis in South Africa: an urgent need to escalate the public health response. *Lancet*, 374(9693), 921-933. doi:10.1016/S0140-6736(09)60916-8
3. Stuckler D., Basu S., McKee M. and Lurie M. (2011). Mining and risk of tuberculosis in sub-Saharan Africa. *Am J Public Health*, 101(3), 524-530. doi:10.2105/AJPH.2009.175646
4. Singer M., Bulled N., Ostrach B. and Ginzburg S. L. (2021). Syndemics: A cross-disciplinary approach to complex epidemic events like COVID-19. *Annual Review of Anthropology*, 50, 41-58. doi:10.1146/annurev-anthro-100919-121009
5. McQuiston J. H., Braden C. R., Bowen M. D., McCollum A. M., McDonald R., Carnes N. and Mermin J. (2023). The CDC Domestic Mpox Response - United States, 2022-2023. *MMWR Morb Mortal Wkly Rep*, 72(20), 547-552. doi:10.15585/mmwr.mm7220a2
6. Bulled N. (2022). A new approach to measuring the synergy in a syndemic: Revisiting the SAVA syndemic among urban MSM in the United States. *Glob Public Health*, 17(9), 2070-2080. doi:10.1080/17441692.2021.1974513
7. Mendenhall E. and Singer M. (2020). What constitutes a syndemic? Methods, contexts, and framing from 2019. *Current Opinion in HIV and AIDS*, 15(4), 213-217. doi:10.1097/COH.0000000000000628
8. Singer M., Bulled N. and Ostrach B. (2020). Whither syndemics?: Trends in syndemics research, a review 2015-2019. *Global Public Health*, 15(7), 943-955. doi:10.1080/17441692.2020.1724317
9. Hossain M., Saha N., Rodela T., Tasnim S., Nuzhath T., Roy T. and Ma P. (2022). Global research on syndemics: a meta-knowledge analysis (2001-2020) [version 1; peer review: 2 approved with reservations]. *F1000Research*, 11(253). doi:10.12688/f1000research.74190.1
10. Singer M. (1994). AIDS and the health crisis of the US urban poor; the perspective of critical medical anthropology. *Social Science & Medicine*, 39(7), 931-948.
11. Singer M. and Clair S. (2003). Syndemics and public health: Reconceptualizing disease in bio-social context. *Medical Anthropology Quarterly*, 17(4), 423-441.
12. Stall R., Mills T., Williamson J., Hart T., Greenwood G., Paul J. and Catania J. (2003). Association of co-occurring psychosocial health problems and increased vulnerability to HIV/AIDS among urban men who have sex with men. *American Journal of Public Health*, 93(6), 939-942. doi:10.2105/ajph.93.6.939
13. Mustanski B., Garofalo R., Herrick A. and Donenberg G. (2007). Psychosocial health problems increase risk for HIV among urban young men who have sex with men: preliminary evidence of a syndemic in need of attention. *Ann Behav Med*, 34(1), 37-45. doi:10.1007/bf02879919
14. Parsons J. T., Grov C. and Golub S. A. (2012). Sexual compulsivity, co-occurring psychosocial health problems, and HIV risk among gay and bisexual men: further evidence of a syndemic. *American Journal of Public Health*, 102(1), 156-162.
15. Tsai A. C. (2018). Syndemics: A theory in search of data or data in search of a theory? *Social Science and Medicine*, 206, 117-122. doi:10.1016/j.socscimed.2018.03.040
16. Tsai A. C., Mendenhall E., Trostle J. A. and Kawachi I. (2017). Co-occurring epidemics, syndemics, and population health. *The Lancet*, 389(10072), 978-982. doi:10.1016/s0140-6736(17)30403-8
17. Tsai A. C. and Venkataramani A. S. (2016). Syndemics and Health Disparities: A Methodological Note. *AIDS and Behavior*, 20(2), 423-430. doi:10.1007/s10461-015-1260-2
18. Horton R. (2020). Offline: COVID-19 is not a pandemic. *The Lancet*, 396(10255), 874. doi:10.1016/S0140-6736(20)32000-6
19. Mendenhall E. (2020). The COVID-19 syndemic is not global: context matters. *Lancet*, 396(10264), 1731 doi:10.1016/S0140-6736(20)32218-2

20. Singer M. and Rylko-Bauer B. (2021). The Syndemics and Structural Violence of the COVID Pandemic: Anthropological Insights on a Crisis. *Open Anthropological Research*, 1(1), 7-32. doi:10.1515/opan-2020-0100
21. Peters M. D., Godfrey C. M., McInerney P., Soares C. B., Khalil H. and Parker D. (2015). *The Joanna Briggs Institute reviewers' manual 2015: methodology for JBI scoping reviews*.
22. Arksey H. and O'Malley L. (2005). Scoping studies: towards a methodological framework. *International journal of social research methodology*, 8(1), 19-32.
23. Anderson S., Allen P., Peckham S. and Goodwin N. (2008). Asking the right questions: scoping studies in the commissioning of research on the organisation and delivery of health services. *Health research policy and systems*, 6(1), 1-12.
24. Tricco A. C., Lillie E., Zarin W., O'Brien K. K., Colquhoun H., Levac D. and Weeks L. (2018). PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Annals of internal medicine*, 169(7), 467-473.
25. Elo S. and Kyngäs H. (2008). The qualitative content analysis process. *J Adv Nurs*, 62(1), 107-115. doi:10.1111/j.1365-2648.2007.04569.x
26. Singer M. (2009). *Introduction to Syndemics: A Critical Systems Approach to Public and Community Health*. Hoboken: John Wiley & Sons.
27. Singer M., Bulled N., Ostrach B. and Mendenhall E. (2017). Syndemics and the biosocial conception of health. *Lancet*, 389(10072), 941-950. doi:10.1016/s0140-6736(17)30003-x
28. Quinn K. G., Harris M., Sherrod D., Hunt B. R., Jacobs J., Valencia J. and Walsh J. L. (2023). The COVID-19, racism, and violence syndemic: Evidence from a qualitative study with Black residents of Chicago. *SSM - Qualitative Research in Health*, 3. doi:10.1016/j.ssmqr.2023.100218
29. Boutin-Foster C., Hastings J., German J. R., Hites L., Eng E., Turner E. and Sutton V. (2022). Reconsidering Community-Engaged Research Through a Syndemic Theoretical Framework: Lessons from COVID-19. *Progress in community health partnerships : research, education, and action*, 16(2), 83-90. doi:10.1353/cpr.2022.0042
30. Meinhart M., Vahedi L., Carter S. E., Poulton C., Mwanze Palaku P. and Stark L. (2021). Gender-based violence and infectious disease in humanitarian settings: lessons learned from Ebola, Zika, and COVID-19 to inform syndemic policy making. *Conflict & Health*, 15(1), 1-9. doi:10.1186/s13031-021-00419-9
31. Vahedi L., Anania J. and Kelly J. (2021). *Gender-Based Violence and COVID-19 in Fragile Settings*A Syndemic Model. Retrieved from https://www.jstor.org/stable/resrep34111
32. Singer M. (2020). Deadly Companions: COVID-19 and Diabetes in Mexico. *Medical Anthropology*, 39(8), 660-665. doi:10.1080/01459740.2020.1805742
33. Gandra S., Ram S. and Levitz S. M. (2021). The "Black Fungus" in India: The Emerging Syndemic of COVID-19-Associated Mucormycosis. *Annals of Internal Medicine*, 174(9), 1301-1302. doi:10.7326/M21-2354
34. Rocha I. C. N., Hasan M. M., Goyal S., Patel T., Jain S., Ghosh A. and Cedeño T. D. D. (2021). COVID-19 and mucormycosis syndemic: double health threat to a collapsing healthcare system in India. *Tropical Medicine & International Health*, 26(9), 1016-1018. doi:10.1111/tmi.13641
35. Gravlee C. C. (2020). Systemic racism, chronic health inequities, and COVID-19: A syndemic in the making? *American Journal of Human Biology*, 32(5), 1-8. doi:10.1002/ajhb.23482
36. Dogra S. A., Shahid H. J., Waqar S., Bingham D., Rahman A., Maynard S. A. and Scott-Baumann A. (2023). COVID-19, HEALTH INEQUALITIES AND THE LIVED EXPERIENCE OF BRITISH MUSLIMS. In Dogra S. A. (Ed.), *British Muslims, Ethnicity and Health Inequalities* (pp. 19-46): Edinburgh University Press.
37. Shahid H. J. and Dogra S. A. (2022). The Muslim Gaze and the COVID-19 Syndemic. *Religions*, 13(9), N.PAG. doi:10.3390/rel13090780
38. Daboin B. E. G., Bezerra I. M. P., Morais T. C., Portugal I., Echeimberg J. O., Cesar A. E. M. and de Abreu L. C. (2022). Deciphering Multifactorial Correlations of COVID-19 Incidence and Mortality in the Brazilian Amazon Basin. *International Journal of Environmental Research and Public Health*, 19(3). doi:10.3390/ijerph19031153
39. Lemke M. K., Apostolopoulos Y. and Sönmez S. (2020a). A novel COVID-19 based truck driver syndemic? Implications for public health, safety, and vital supply chains. *American Journal of Industrial Medicine*, 63(8), 659-662. doi:10.1002/ajim.23138
40. Lemke M. K., Apostolopoulos Y. and Sönmez S. (2020b). Syndemic frameworks to understand the effects of COVID-19 on commercial driver stress, health, and safety. *Journal of Transport & Health*, 18. doi:10.1016/j.jth.2020.100877
41. Bulled N. and Singer M. (2020). In the shadow of HIV & TB: A commentary on the COVID epidemic in South Africa. *Global Public Health*, 15(8), 1231-1243. doi:10.1080/17441692.2020.1775275
42. Diderichsen F., Friedrich K. and Da Silva Giraldo L. A. (2023). Agribusiness and the COVID-19 syndemic: The unsustainable pathways. *Scandinavian Journal of Public Health*. Online. doi:10.1177/14034948231168175
43. Rálaigh C. Ó. (2021). What's in a name? Applying the syndemic perspective to COVID-19 in Ireland. *Irish Journal of Sociology*, 29(2), 241-247. doi:10.1177/07916035211009147
44. Arena R., Pronk N. P., Laddu D., Whitsel L. P., Sallis J. F., Lavie C. J. and Network H.-P. (2022). Mapping One Million COVID-19 Deaths and Unhealthy Lifestyle Behaviors in the United States: Recognizing the Syndemic Pattern and Taking Action. *American Journal of Medicine*, 135(11), 1288-1295. doi:10.1016/j.amjmed.2022.06.006
45. Chung G. K. K., Chan S. M., Chan Y. H., Yip T. C. F., Ma H. M., Wong G. L. H. and Woo J. (2021). Differential impacts of multimorbidity on covid-19 severity across the socioeconomic ladder in Hong Kong: A syndemic perspective.

International Journal of Environmental Research and Public Health, 18(15). doi:10.3390/ijerph18158168

46. Lee J. and Ramírez I. J. (2022). Geography of Disparity: Connecting COVID-19 Vulnerability and Social Determinants of Health in Colorado. *Behavioral Medicine*, 48(2), 72-84. doi:10.1080/08964289.2021.2021382
47. Ramírez I. J. and Lee J. (2020). COVID-19 emergence and social and health determinants in Colorado: A rapid spatial analysis. *International Journal of Environmental Research and Public Health*, 17(11), 1-15. doi:10.3390/ijerph17113856
48. Nomah D. K., Reyes-Urueña J., Llibre J. M., Ambrosioni J., Ganem F. S., Miró J. M. and Casabona J. (2021). HIV and SARS-CoV-2 Co-infection: Epidemiological, Clinical Features, and Future Implications for Clinical Care and Public Health for People Living with HIV (PLWH) and HIV Most-at-Risk Groups. *Current HIV/AIDS Reports*, 18(6), 518-526. doi:10.1007/s11904-021-00579-6
49. Kalichman S. C. and El-Krab R. (2022). Social and Behavioral Impacts of COVID-19 on People Living with HIV: Review of the First Year of Research. *Current HIV/AIDS Reports*, 19(1), 54-75. doi:10.1007/s11904-021-00593-8
50. Shiau S., Krause K. D., Valera P., Swaminathan S. and Halkitis P. N. (2020). The burden of COVID-19 in people living with HIV: A syndemic perspective. *AIDS and Behavior*, 24(8), 2244-2249. doi:10.1007/s10461-020-02871-9
51. Trajman A., Felker I., Alves L. C., Coutinho I., Osman M., Meehan S. A. and Schwartz Y. (2022). The COVID-19 and TB syndemic: The way forward. *International Journal of Tuberculosis and Lung Disease*, 26(8), 710-719. doi:10.5588/ijtld.22.0006
52. Di Gennaro F., Marotta C., Locantore P., Pizzol D. and Putoto G. (2020). Malaria and covid-19: Common and different findings. *Tropical Medicine and Infectious Disease*, 5(3). doi:10.3390/tropicalmed5030141
53. Gutman J. R., Lucchi N. W., Cantey P. T., Steinhardt L. C., Samuels A. M., Kamb M. L. and Lindblade K. A. (2020). Malaria and parasitic neglected tropical diseases: Potential syndemics with COVID-19? *American Journal of Tropical Medicine and Hygiene*, 103(2), 572-577. doi:10.4269/ajtmh.20-0516
54. Saqib K., Qureshi A. S. and Butt Z. A. (2023). COVID-19, Mental Health, and Chronic Illnesses: A Syndemic Perspective. *International Journal of Environmental Research and Public Health*, 20(4). doi:10.3390/ijerph20043262
55. Hall P. A., Sheeran P., Fong G. T., Cheah C. S. L., Oremus M., Liu-Ambrose T. and Morita P. P. (2021). Biobehavioral aspects of the COVID-19 pandemic: A review. *Psychosomatic Medicine*, 83(4), 309-321. doi:10.1097/PSY.0000000000000932
56. Cisneros I. E. and Cunningham K. A. (2021). Covid-19 interface with drug misuse and substance use disorders. *Neuropharmacology*, 198, 204. doi:10.1016/j.neuropharm.2021.108766
57. Faratisha I. F. D., Cahyono A. W., Erwan N. E., Putri A. M., Ariel D. G., Yunita K. C. and Fitri L. E. (2022). The Potential Effect of Nigericin from Streptomyces hygroscopicus subsp. Hygroscopicus Against the Syndemic of Malaria and COVID-19 through Molecular Docking Perspective. *Pharmacognosy Journal*, 14(2), 268-275. doi:10.5530/pj.2022.14.33
58. Rao G. H. R. (2021). Twindemic of coronavirus disease (COVID-19) and cardiometabolic diseases. *International Journal of Biomedicine*, 11(2), 111-122. doi:10.21103/Article11(2)_RA1
59. Pajuelo-Reyes C., Rojas L. M., Campos C. J., Saavedra-Samillan M., Tejedo J. R., Bustamante P. and Tapia-Limonchi R. (2022). MALARIA AND COVID-19 IN NATIVE COMMUNITIES OF AMAZONAS, PERU. *Revista de la Facultad de Medicina Humana*, 22(3), 533-539. doi:10.25176/RFMH.v22i3.5044
60. Sheerin D., Abhimanyu, Wang X., Johnson W. E. and Coussens A. (2020). Systematic evaluation of transcriptomic disease risk and diagnostic biomarker overlap between COVID-19 and tuberculosis: a patient-level meta-analysis. *medRxiv*. Preprint. doi:10.1101/2020.11.25.20236646
61. Hadi Y. B., Naqvi S. F. Z., Kupec J. T. and Sarwari A. R. (2020). Characteristics and outcomes of COVID-19 in patients with HIV: a multicentre research network study. *AIDS (02699370)*, 34(13), F3-F8. doi:10.1097/QAD.0000000000002666
62. Mehta R., Nagarkar N. M., Jindal A., Rao K. N., Nidhin S. B., Arora R. D. and Thangaraju P. (2022). Multidisciplinary Management of COVID-Associated Mucormycosis Syndemic in India. *Indian Journal of Surgery*, 84(5), 934-942. doi:10.1007/s12262-021-03134-0
63. Krishnamurthy A. (2022). COVID-19, Race, and Mass Incarceration. In Wright G. L., Hubbard L. and Darity W. A. (Eds.), *The Pandemic Divide* (pp. 87-108): Duke University Press.
64. Mendenhall E., Kohrt B. A., Logie C. H. and Tsai A. C. (2022). Syndemics and clinical science. *Nature Medicine*, 28(7), 1359-1362. doi:10.1038/s41591-022-01888-y
65. Curry T. J. (2020). Conditioned for Death: Analysing Black Mortalities from Covid-19 and Police Killings in the United States as a Syndemic Interaction. *Comparative American Studies*, 17(3-4), 257-270. doi:10.1080/14775700.2021.1896422
66. Poteat T., Millett G. A., Nelson L. E. and Beyrer C. (2020). Understanding COVID-19 risks and vulnerabilities among black communities in America: the lethal force of syndemics. *Annals of Epidemiology*, 47, 1-3. doi:10.1016/j.annepidem.2020.05.004
67. Richard-Eaglin A., Muirhead L., Webb M. and Randolph S. D. (2022). A syndemic effect: Interrelationships between systemic racism, health disparities, and COVID-19. *Nursing*, 52(1), 38-43. doi:10.1097/01.NURSE.0000803424.08667.c6
68. Williams C. and Vermund S. H. (2021). Syndemic Framework Evaluation of Severe COVID-19 Outcomes in the United States: Factors Associated With Race and Ethnicity. *Frontiers in Public Health*, 9. doi:10.3389/fpubh.2021.720264

69. Cokley K., Krueger N., Cunningham S. R., Burlew K., Hall S., Harris K. and Coleman C. (2022). The COVID-19/racial injustice syndemic and mental health among Black Americans: The roles of general and race-related COVID worry, cultural mistrust, and perceived discrimination. *Journal of Community Psychology*, 50(6), 2542-2561. doi:10.1002/jcop.22747
70. Hosaka K. R. J., Castanera M. P. and Yamada S. (2021). Structural racism and Micronesians in Hawaii: The COVID-19 syndemic. *Asia-Pacific Journal of Public Health*, 33(6-7), 775-776. doi:10.1177/10105395211012188
71. Burns A. and Albrecht K. A. T. (2022). Localized Syndemic Assemblages COVID-19, Substance Use Disorder, and Overdose Risk in Small-Town America. *RSF: The Russell Sage Foundation Journal of the Social Sciences*, 8(8), 245-262. Retrieved from https://www.jstor.org/stable/48704792
72. Cavany S. M., España G., Vazquez-Prokopec G. M., Scott T. W. and Perkins T. A. (2021). Pandemic-associated mobility restrictions could cause increases in dengue virus transmission. *PLoS Neglected Tropical Diseases*, 15(8), 1-19. doi:10.1371/journal.pntd.0009603
73. Hall B. J. and Tucker J. D. (2020). Surviving in place: The coronavirus domestic violence syndemic. *Asian Journal of Psychiatry*, 53, 39. doi:10.1016/j.ajp.2020.102179
74. Khanlou N., Vazquez L. M., Pashang S., Connolly J. A., Ahmad F. and Ssawe A. (2022). 2020 Syndemic: Convergence of COVID-19, Gender-Based Violence, and Racism Pandemics. *Journal of Racial and Ethnic Health Disparities*, 9(6), 2077-2089. doi:10.1007/s40615-021-01146-w
75. Ezirigwe J., Ojike C., Amechi E. and Adewopo A. (2021). 'COVID-19/Food Insecurity Syndemic': Navigating the Realities of Food Security Imperatives of Sustainable Development Goals in Africa. *Law and Development Review*, 14(1), 129-162. doi:10.1515/ldr-2020-0071
76. Cheong J. G., Ravishankar A., Sharma S., Parkhurst C. N., Grassmann S. A., Wingert C. K. and Josefowicz S. Z. (2023). Epigenetic memory of coronavirus infection in innate immune cells and their progenitors. *Cell*, 186(18), 3882-3902. doi:10.1016/j.cell.2023.07.019
77. Nagata J. M., Seligman H. K. and Weiser S. D. (2021). Perspective: The Convergence of Coronavirus Disease 2019 (COVID-19) and Food Insecurity in the United States. *Advances in Nutrition*, 12(2), 287-290. doi:10.1093/advances/nmaa126
78. Pryor S. and Dietz W. (2022). The COVID-19, Obesity, and Food Insecurity Syndemic. *Current obesity reports*, 11(3), 70-79. doi:10.1007/s13679-021-00462-w
79. Tsai A. C. and Burns B. F. O. (2015). Syndemics of psychosocial problems and HIV risk: A systematic review of empirical tests of the disease interaction concept. *Social Science and Medicine*, 139, 26-35. doi:10.1016/j.socscimed.2015.06.024
80. Bradley D. T., Mansouri M. A., Kee F. and Garcia L. M. T. (2020). A systems approach to preventing and responding to COVID-19. *EClinicalMedicine*, 21, 8.
81. Maxmen A. (2020). Two Decades of Pandemic War Games Failed to Account for Donald Trump. *Scientific American*, August 6. Retrieved from https://www.scientificamerican.com/article/two-decades-of-pandemic-war-games-failed-to-account-for-donald-trump1/
82. Boes S., Sabariego C., Bickenbach J. and Stucki G. (2021). How to capture the individual and societal impacts of syndemics: The lived experience of COVID-19. *BMJ Global Health*, 6(10), 210. doi:10.1136/bmjgh-2021-006735