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PERSPECTIVE

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Syndemics and clinical science

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The theory of syndemics has received increasing attention in clinical medicine since the onset of the COVID-19 pandemic, due to the synergistic interactions of the disease with pre-existing political, structural, social and health conditions. In simple terms, syndemics are synergistically interacting epidemics that occur in a particular context with shared drivers. When policymakers ask why some communities have higher death rates from COVID-19 compared with other communities, those working from a syndemics framework argue that multiple factors synergistically work in tandem, and populations with the highest morbidity and mortality experience the greatest impact of these interactions. In this Perspective, we use specific case examples to illustrate these concepts. We discuss the emergence of syndemics, how epidemics interact, and what scientists, clinicians and policymakers can do with this information.

The COVID-19 pandemic has transformed the world in myriad ways, including how we think about and study diseases, from where they originate and how they interact with other conditions, to recognizing who is most affected and where. The term 'syndemic' (Box 1) has been increasingly associated with COVID-19 (ref. [1]) because its severity and impacts around the world have not been uniformly distributed across populations. The pandemic has demonstrated how political actions to support public health and the historical patterning of chronic health conditions are situated within contexts of great inequity, which profoundly affect who is most vulnerable, as well as where and why this vulnerability exists[2]. The co-occurence of COVID-19 with pre-existing epidemics, from cancer and diabetes to HIV, has shown that people with weakened immune systems have an increased risk of morbidity and mortality[3]. But local contexts, often called social and political determinants of health, cannot be dissociated from these pre-existing conditions, particularly in areas where those conditions are most concentrated[4]. This was particularly evident in the United States, where racism (historic and current) and the distribution of resources had an extraordinary influence on which communities were affected the most by COVID-19 (ref. [5]).

The theory of syndemics focuses both on disease concentration (the where) and disease interactions (the how), and so provides a useful framework for understanding population health and disease drivers, and for formulating appropriate interventions. Syndemic theory was originally described by critical medical anthropologist Merrill Singer, who sought to explain how HIV manifested among inner-city residents of Hartford, Connecticut, in the United States[6]. Singer argued that the local HIV epidemic could not be understood in isolation, separate from the local epidemic of substance use, because the pathways of transmission were inextricably linked and deepened by structural violence. He proposed the 'SAVA' syndemic to illuminate how the epidemics of substance use, violence and HIV were intertwined and mutually reinforcing of one another in the local context[7]. The SAVA syndemic framework is now widely used to develop interventions in the field of HIV[8–10]. The interactions between diseases, which are largely biological but can also be social and psychological, are closely linked to clinical medicine. Recognizing that the concentration of, and interactions between diseases have a history and may share an origin provides a social context for clinical care, while also enhancing our understanding of how policy interventions facilitate health and healthcare.

The theory of syndemics has received increasing attention in clinical medicine, with recent applications to critical illness[11], sexually transmitted infections[12] and structural racism[5]. Syndemic frameworks emphasize the disease interactions that underlie multiple convergent public health issues such as overweight and obesity, injection drug use, poverty, structural racism, gender-based violence, climate change and so on. Indeed, it is crucial to recognize, interpret and treat non-medical conditions as well as medically diagnosable ones; this is a central tenet of the syndemic project and is fundamental for clinical practice.

In this Perspective, we provide an introduction to syndemic theory; we invite readers to apply syndemic thinking to clinical care and to consider how clinical interventions play a role in mitigating syndemic effects perpetuated through deleterious environments. We also explore two case examples: the first involving depression and diabetes in Mexican immigrants in the United States, and the second involving people from sexual and gender minority populations (LGBT+ people) confronting HIV and criminality, to illustrate the key concepts of syndemic theory. Finally, we discuss modeling syndemic care in clinical contexts.

Overview of syndemic theory

Three tenets of syndemic theory frame which co-occurring epidemics are thought to comprise a syndemic and which do not[13]. First, two or more diseases concentrate within a population; often this relationship is well documented in the epidemiological literature, for example, as a comorbid or multi-morbid relationship. Second, disease interactions are measurable through bio-bio, bio-social, or bio-psychological pathways. These may include well-documented interactions in biology (such as inflammation) or less well-documented socio-cultural processes (such as stigma[14]). Third, large-scale forces precipitate this concentration

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Box 1 | What is syndemic theory?

The theory of syndemics proposes that the synergies of epidemics are fundamental for understanding what diseases emerge, where, and why[4,10]. Three overarching characteristics define a syndemic: two or more epidemics must

1. co-occur within certain contexts;
2. interact in meaningful ways, often through biological processes but potentially through social or psychological processes; and
3. share one or more upstream factors driving their co-occurrence and interaction, which may include dynamics that are structural, social, cultural, ecological and economic in nature.

of disease, from the macro-level (such as structural violence and food insecurity) to the meso-level (such as stigma and discrimination) and micro-level (such as interpersonal violence). Clinicians may feel that attending to issues outside the narrow frame of the clinical encounter (for example, structural violence and immigration policy) may be beyond the scope of their expertise. Others may disagree[15]. We argue that understanding how structural and contextual factors drive psychological distress, safety, fear and fragmented care for chronic conditions fits within the contours of clinical care. Deciphering how these broader problems fuel interactions in the clinical encounter is essential for thinking about who needs psychotherapy, financial assistance, legal assistance, assistance with medication access, and other clinically relevant needs.

Disease interaction is a lynchpin of syndemic theory, and understanding it is an activity that sits squarely in the domain of clinical medicine. However, scholars disagree about how this aspect of the theory should be operationalized empirically, either at the individual level (that is, how two diseases interact and the implication for an individual) or at the population level (that is, how two epidemics interact and the implication for a population)[9,16–18]. Without an identified interaction, even at the individual level (such as the interaction between inflammatory bowel disease and stigma[19]), it is difficult to argue that a syndemic is present; the interaction itself is thought to significantly worsen the health of people experiencing the clustered conditions[4]. By understanding what drives diseases, and how and where diseases occur and interact, we can think more strategically and innovatively about intervening and providing effective care for not one health condition but for a cluster of social and health conditions.

The characteristics of a syndemic are given in Fig. 1, which shows how two diseases may have high rates of comorbidity in one social, economic or geographic context but may be infrequently comorbid in other contexts. The role of context is fundamental because the social, economic and geographic factors that contribute to disease interaction in one context may not be present, or may not have the same relationship with disease interaction, in another context. The contextual differences may involve healthcare systems (for example, the presence or absence of universal health insurance or universal healthcare provision), dietary practices that contribute to obesity or micronutrient deficiencies, religious or political beliefs (for example, vaccine hesitancy and refusal in different regions of Nigeria over the past two decades[20,21], or the spread of vaccine misinformation in certain segments of the US Republican party[22]), indoor air pollution resulting from different models of household food production and fuel consumption, environmental events due to climate change (for example, heat waves in Bangladesh), and gender-inequitable policies and norms.

There is evidence that some health conditions interact with COVID-19 in particular contexts, thus suggestive of a syndemic, whereas other conditions do not show contextual diversity in their COVID-19 interactions. For example, the interaction between diabetes and COVID-19 would not be characterized as a syndemic in contexts such as Rwanda, where COVID-19 mortality is not greater among people with diabetes; whereas in other contexts such as the United States, diabetes and COVID-19 are syndemic and are associated with significant morbidity and mortality[23]. Similarly, musculoskeletal conditions present a high risk for COVID-19-related fatality in lower income countries but not necessarily in higher income countries[24], possibly because of the inflammatory pathways associated with these conditions, and because of the lack of existing care for these conditions in lower income contexts.

How does syndemic thinking inform clinical care?

Intervention in the setting of a syndemic will require public health officials and clinicians to consider the clinical and/or upstream interventions that are the most effective for a given set of patients. The need for coordinating policy and clinical interventions has long been exemplified in HIV-related syndemics, where deleterious interactions of multiple health conditions within specific contexts persist. More recently, scholars have suggested that chronic non-communicable diseases, including mental illness[25], have become critical comorbidities to HIV[26], and have suggested consequential syndemic relationships that are important to understand for HIV-related policy and clinical practice. For instance, mental health screening and treatment could be integrated into HIV care settings to improve HIV treatment and prevention outcomes as well as mental health[27], but this organization of care delivery is generally important across contexts and therefore is not specific to syndemic care. By contrast, widening the lens of screening to include specific social drivers of mental health in people living with HIV would represent syndemic care[28]. Types of discrimination according to race and ethnicity, gender and health status vary by context, therefore the particular vulnerabilities in a given setting would be important to screen for. Given the wide variability in insurance coverage, it is not enough to screen for presence or absence of insurance, instead it is necessary to screen for which particular coverage is available, including its support for mental health and other services. In this way, syndemic-oriented research aligns closely with scholarship on structural competency[29], with an emphasis on reducing exposure to negative social drivers and increasing exposure to positive social drivers, to improve the health of individuals and populations.

Although clinicians may not have the economic, political or administrative training to implement interventions to address social and structural drivers of disease, recognizing how and why certain clustered epidemics emerge is important for thinking through the complexity of intervention packages needed to improve outcomes at the individual level. In what follows, we provide a few specific examples of how syndemic thinking can inform clinical care.

Depression and diabetes in Mexican immigrants in the United States. A widely used example considers a syndemic of violence, racist immigration policy, diabetes, depression and abuse among Mexican immigrant women living in the Chicago metropolitan area[30]. In a mixed-methods study consisting of data collected through life history narrative interviews, biological specimens, and validated psychiatric instruments, this study showed how interpersonal violence and fear (bound to immigration policy) drove distress. These experiences linked stress and trauma from undocumented migration and navigating a racist immigration system, to the deleterious effects of living with chronic illness (diabetes) amidst financial uncertainty. In this case, the adverse health effects of these larger forces, often obscured, could be observed in the epidemiological data demonstrating the close biological and psychological links between depression and type 2 diabetes[30]. A central focus of this work was to describe how study participants, despite seeking

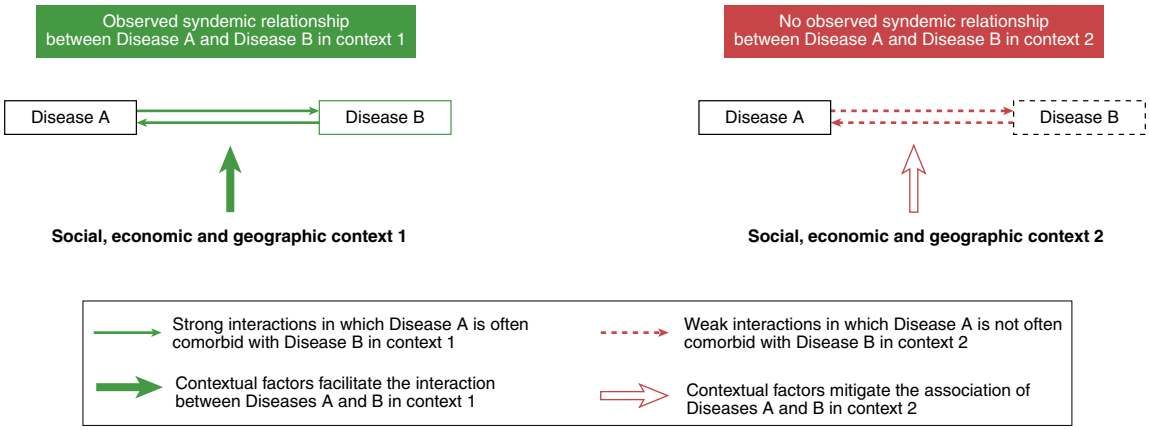

Fig. 1 | Syndemic relationships. A syndemic relationship requires the demonstration of greater morbidity or mortality for two health conditions in particular contexts (social, structural and economic conditions) compared with the health outcomes for the same conditions in other contexts. Image adapted with permission from ref. [46], Wolters Kluwer Health.

care for diabetes or being identified by the state as having diabetes (for example, via Medicaid), could not become well without healing from their emotional wounds and overcoming structural barriers such as lack of safety and food[31]. In this way, their diabetes was entangled in a feedback loop with traumatic memories, family stress, chronic financial uncertainty and untreated depression that required nuanced care and support from the clinic, their community and their families[30].

LGBT+ people confronting HIV and lack of human rights protections. A second case example involves synergistic interactions between HIV, depression and substance use resulting from intersectional stigma and criminalization of LGBT+ people. Intersectional stigma refers to a social process by which people holding multiple socially devalued identities are mistreated and deprived of power and opportunities (for example, due to racism, homophobia, transphobia, and HIV-related stigma, among others)[28,32]. The synergistic interactions between these factors have been highlighted in research in Canada, Scotland, Wales, Northern Ireland and the Republic of Ireland[33], illustrating how poorer health outcomes are conditioned by social experiences of stigma and discrimination[33] as well as how protective factors such as community cohesion may shield people from poorer health. These HIV-associated syndemics have been documented in diverse settings, although to much more severe degrees in settings in which there are no human rights protections for sexually diverse people. For instance, in a setting such as Nigeria, where same-sex sexual practices are punishable by imprisonment and, in 12 of the northern states, death and there are no human rights protection for LGBT+ people, the introduction of the 2014 Same Sex Prohibition Act was associated with reduced HIV care engagement in sexually diverse people, owing to a fear of seeking healthcare and healthcare avoidance[34]. Relatedly, stigma and family rejection contributed to mental health challenges, poor sleep[35] and substance use which, in turn, contributed to sexual practices associated with elevated disease risk[36].

Training for clinicians to provide LGBT+-affirming care and to link patients with needed social, legal and mental health resources[37] is crucial; for example, the provision of gender-affirming documents has been associated with improved mental health outcomes among transgender adults in the United States[38]. Even in contexts in which same-sex practices are not criminalized, a lack of human rights protections for LGBT+ people can mean that legislative changes have a substantial impact on health and wellbeing. For instance, in the United States many states have not legalized same-sex marriage, despite the fact that this is linked to improved mental health in LGBT+ people in this context[39] as well as other contexts[40]. Recent legislative changes in Florida regarding the so-called 'don't say gay' bill (Florida Senate house bill 1557; ref. [41]), which prohibits classroom instruction on sexual and gender identity for young children, could present syndemic co-conditions. The threats and limitations placed upon health providers, educators and others who support and provide social, educational and health resources to LGBT+ youth may lead to a greater risk of undiagnosed and untreated mental health conditions, alongside risks for the transmission of HIV and other sexually transmitted infections. Syndemic thinking applied in contexts that criminalize LGBT+ people, such as the example of Nigeria, and contexts in which the rights of LGBT+ people are not protected, such as regions in the United States, would involve not only consideration of the interactions between sexual, mental and physical health outcomes and the influence of social drivers of stigma and violence, but also attending to structural contexts of legal protection, healthcare mis/treatment, availability of affirming and competent healthcare, and access to human rights.

Modeling syndemic care in clinical contexts. A holistic and translational research approach can yield appropriate clinical interventions to mitigate syndemic interactions. First, basic research is needed to understand the pathways linking social, developmental and environmental factors to biological processes. Second, preclinical research that tests applicable models for the impacts of social and physical environments (for example, neurodevelopment in conditions simulating high stress[42]) can be fundamental for recognizing which interventions require further evaluation in the clinical setting. Third, clinical research may involve ethnographic studies and randomized trials with different populations across diverse social, economic and geographic contexts. This point is crucial because syndemics are context dependent. Fourth, evaluating how interventions may perform differently across contexts is central to clinical implementation. In other words, local cultural beliefs, social practices, ways of knowing, and healthcare systems may affect which clinical interventions work most effectively and where. Finally, public health is central to mitigating syndemics by identifying different patterns of comorbidity explained by social, economic and geographic contexts.

Conclusion

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. For this reason protective factors,

including community support groups[43], social support and cultural resources[44], home visits, and mental healthcare[45] are essential components of syndemic interventions. Future efforts in syndemic thinking should seek to evaluate and incorporate these multiple levels of influence into clinical care in a way that enhances health and wellness for people throughout their lives.

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Additional information

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