

## Syndemics 1



# Syndemics and the biosocial conception of health

Merrill Singer, Nicola Bulled, Bayla Ostrach, Emily Mendenhall

The syndemics model of health focuses on the biosocial complex, which consists of interacting, co-present, or sequential diseases and the social and environmental factors that promote and enhance the negative effects of disease interaction. This emergent approach to health conception and clinical practice reconfigures conventional historical understanding of diseases as distinct entities in nature, separate from other diseases and independent of the social contexts in which they are found. Rather, all of these factors tend to interact synergistically in various and consequential ways, having a substantial impact on the health of individuals and whole populations. Specifically, a syndemics approach examines why certain diseases cluster (ie, multiple diseases affecting individuals and groups); the pathways through which they interact biologically in individuals and within populations, and thereby multiply their overall disease burden, and the ways in which social environments, especially conditions of social inequality and injustice, contribute to disease clustering and interaction as well as to vulnerability. In this Series, the contributions of the syndemics approach for understanding both interacting chronic diseases in social context, and the implications of a syndemics orientation to the issue of health rights, are examined.

### The nature of syndemics

Co-infection with multiple pathogens, as Laurent Hébert-Dufresne and Benjamin Althouse<sup>1</sup> have emphasised, can be a critical factor in disease course and outcome. Concurrent infection, as described for infectious agents such as HIV and *Mycobacterium tuberculosis*, for example, is associated with more rapid disease progression, worse symptoms, and higher pathogenic load than during a single infection with either agent.<sup>2,3</sup> In addition to HIV accelerating advancement from latent to active tuberculosis, *M tuberculosis* infection speeds up the development of HIV infection. In this instance, the reason for the enhanced disease burdens of co-infection is the synergistic interaction between the two infectious agents, one a virus and the other a bacterium. The mechanism of this interaction involves the effect of HIV on granuloma and the ability of these lymphocyte-ringed macrophages to control tubercle bacilli, resulting in tuberculosis progression.<sup>4</sup> As a result of interaction, entwined co-infections tend to reduce treatment efficacies and increase treatment costs.<sup>5</sup> These adversely interacting diseases exemplify a syndemic because co-infections are disproportionately common in impoverished and otherwise marginalised populations, and in developing countries where health care is most limited.<sup>6</sup>

The case of interacting co-infections is an example of what has been termed a syndemic.<sup>7,8</sup> Syndemics are defined as the aggregation of two or more diseases or other health conditions in a population in which there is some level of deleterious biological or behaviour interface that exacerbates the negative health effects of any or all of the diseases involved. Syndemics involve the adverse interaction of diseases of all types (eg, infections, chronic non-communicable diseases, mental health problems, behavioural conditions, toxic exposure, and malnutrition). They are most likely to emerge under

conditions of health inequality caused by poverty, stigmatisation, stress, or structural violence because of the role of these factors in disease clustering and exposure and in increased physical and behavioural vulnerability. Indeed, this concept moves beyond common medical conceptualisations of comorbidity and multimorbidity—when diseases simply occur in tandem—because it both concerns the consequences of disease interaction and the social, environmental, or

*Lancet* 2017; 389: 941–50

This is the first in a Series of three papers about syndemics

See [Editorial](#) page 881

See [Comment](#) pages 888 and 889

Department of Anthropology (Prof M Singer PhD) and Department of Community Medicine (Prof M Singer), University of Connecticut, Storrs, CT, USA; Division of Interdisciplinary & Global Studies, Worcester Polytechnic Institute, Worcester, MA, USA (N Bulled PhD); Boston University School of Medicine, Boston, MA, USA (B Ostrach PhD); and School of Foreign Service, Georgetown University, Washington, DC, USA (E Mendenhall PhD)

Correspondence to: Prof Merrill Singer, Department of Anthropology, University of Connecticut, Storrs, CT 06269, USA [Merrill.Singer@uconn.edu](mailto:Merrill.Singer@uconn.edu)

### Key messages

- Syndemic theory draws attention to and provides a specific framework of disease–disease and social condition–disease interactions for the analysis of biosocial connections in health and social research, clinical care, and prevention
- Syndemics involve the adverse interaction between diseases and health conditions of all types (eg, infections, chronic non-communicable diseases, mental health problems, behavioural conditions, toxic exposure, and malnutrition) and are most likely to emerge under conditions of health inequality caused by poverty, stigmatisation, stress, or structural violence
- Social conditions contribute to the formation, clustering, and spread of disease, and, by increasing susceptibility and reducing immune function, contribute to disease progression.
- A syndemics-based focus goes beyond common medical concepts of comorbidity and multimorbidity because it concerns the health consequences of identifiable disease interactions and the social, environmental, or economic factors that promote such interaction and worsen disease
- Identification and description of a syndemic involves:
  - A clear account of the diseases and health conditions
  - Examination of the pathways or mechanisms of disease–disease interaction
  - A clear description of the socioenvironmental conditions and how they are experienced by human minds and bodies as adversity
  - Examination of the pathways of effect from socioenvironmental conditions to biological or psychological states
  - Evidence of greater health burden because of interaction (greater pathology, spread, etc)
- Syndemics tend to reduce treatment efficacies and increase treatment costs

**Panel 1: The syndemic lexicon****Syndemic**

Population-level clustering of social and health problems. The criteria of a syndemic are: (1) two (or more) diseases or health conditions cluster within a specific population; (2) contextual and social factors create the conditions in which two (or more) diseases or health conditions cluster; and (3) the clustering of diseases results in adverse disease interaction, either biological or social or behavioural, increasing the health burden of affected populations.

**Syndemic vulnerability**

Integration of epidemiological and experiential levels of analysis of multiple, overlapping social and health problems that increase morbidity and mortality as a result of syndemic clustering of social and health conditions within a certain context.

**Syndemic interaction**

The co-occurrence of social and health conditions, including social–psychological, social–biological, and psychological–biological interactions, which worsen the condition of the person or population afflicted.

**Syndemic risk factor**

Social, political, economic, and environmental factors that increase the risk for clustering of two or more diseases.

**Syndemogenesis**

The processes, pathways, and stages of syndemics development involving a disease–social context and disease–disease interactions.

**Iatrogenic syndemic**

A syndemic interaction caused or exacerbated by medical treatment, as occurred in Egypt with campaigns to inoculate against schistosomiasis using hepatitis C virus-infected intravenous tartar emetic;<sup>9</sup> or, medical treatment for one disease is weakened by the actions of another disease.

**Countersyndemics**

When one biological trait, disease, behaviour, or social condition provides a protective benefit against other disease interactions, as seen in the protection from potentially lethal Rocky Mountain spotted fever that can be conferred after exposure to *Rickettsia amglyommii*.<sup>10</sup>

**Unintended countersyndemic**

When efforts to treat one disease improves the elimination of another.

**Eco-syndemics**

Extreme weather contributes to severe conditions that foster migration, the breakdown of built environments, and metabolism of pathogenic organisms that result in increased rates of growth and cell division, as well as other interactions.

**Syndemics of war**

War and conflict are traumatic biosocial events that compromise existing conditions and health-care access, thereby increasing the likelihood of disease clustering and syndemic interaction.

economic factors that cluster with the diseases and shape their interaction (panel 1).

Syndemic interactions are of considerable importance for prognosis, treatment, and health policy. In medicine, for example, an ageing population requires management of individuals not just with multiple comorbid diseases but also with pronounced interacting diseases and compromising social conditions, such as impoverishment or social isolation. Given that social conditions can

contribute to the formation, clustering, and progression of disease, a biosocial concept like syndemics offers a holistic approach to addressing synergistic disease and context interactions.<sup>11</sup> Syndemic theory seeks to draw attention to and to provide a framework for the analysis of these kinds of biosocial connections, including their causes and consequences for human life and wellbeing, and for responding with appropriate intervention.

First developed within medical anthropology,<sup>12,13</sup> the conceptual syndemic framework has gained broad recognition in the fields of public health, medicine, psychology, nursing, oral health, chronic illness management, infectious disease prevention, and sexual and reproductive health, among others. To promote this process, the US Centers for Disease Control and Prevention created, and for several years maintained, an online Syndemics Prevention Network designed to inform epidemiological research. The concept continues to diffuse across other health-related fields, with syndemics research appearing in diverse publication venues. These developments have led to the creation of courses devoted to syndemics within schools of public health and medicine and in focused National Institutes of Health grant opportunities (eg, U38 Addressing Syndemics through Program Collaboration and Integration<sup>12</sup>).

**Syndemics research**

The first syndemic identified and described in the literature,<sup>13</sup> and the one most heavily investigated, is known as SAVA (substance abuse, violence, and AIDS). This term describes three closely linked and interdependent conditions that coexist in the human body and social life of many individuals in low-income urban environments.<sup>13</sup> Recognition of this syndemic emerged during a multiyear research programme on HIV risk prevention among drug users, in which researchers realised that the contemporary inner-city health crisis in the USA was characterised by the spread of AIDS in close conjunction with a set of other endemic and epidemic conditions (eg, tuberculosis, sexually transmitted infections, hepatitis, cirrhosis, infant mortality, drug abuse, suicide, and homicide). These conditions are intertwined and strongly influenced and sustained by a broad set of political–economic and social factors, from high rates of unemployment, poverty, homelessness, and overcrowding to substandard nutrition, infrastructural deterioration, disruption of social support networks, and social and ethnic inequalities.<sup>14–16</sup> Some of the diseases involved in the SAVA syndemic are transmitted by the same type of behaviours (eg, risky sexual practice in the case of HIV and sexually transmitted infections), whereas other diseases (eg, tuberculosis and cirrhosis) are transmitted by different behaviours but cluster with each other, sexually transmitted infections, and HIV infection because of social marginalisation, stigmatisation, and limited resources in affected populations.

A substantial amount of research has also been done on SAVA among men who have sex with men. Stall and colleagues,<sup>17</sup> for example, found important associations among multiple drug use, intimate partner violence, childhood sexual abuse, and depression. Moreover, the percentage of the 3000 men who have sex with men who reported high-risk sex behaviour in this study increased steadily from 7·1% among those with none of the health problems noted above to 33·3% for those with all of the problems. For men who lacked any of the cofactors listed above, 13% were HIV-positive whereas 25% of participants who reported all four cofactors were HIV-positive. Consequently, researchers using data of the damaging effects of cumulative adversity have suggested (but cannot yet prove) the existence of a SAVA syndemic among men who have sex with men, consisting of interacting and mutually reinforcing health conditions. They concluded that these conditions are best addressed in concert rather than as separate threats to health. Similarly, among non-white women with low income, high SAVA scores (based on counting cumulative psychosocial factors such as substance abuse, binge drinking, intimate partner violence, poor mental health, and sexual risk taking) have been found to be associated with reduced viral suppression and diminished treatment effectiveness.<sup>18,19</sup>

The earliest identified syndemics include HIV/AIDS as a component because this disease is often an integral component in disease interactions and is greatly affected by social and structural conditions such as poverty, marginalisation, gender inequality, malnutrition, and stigma. Syndemic consequences of HIV/AIDS have occasioned a growing body of literature, with more than two dozen articles focused on HIV syndemics published in the year 2016 and included in PubMed. A few examples of HIV-related syndemics identified to date include HIV–sexually transmitted infection interactions, for which women are at particular risk<sup>20</sup> because of the combined effects of biological factors and social inequalities, an HIV–drug-use–risky sexual behaviour–stigma syndemic among men who have sex with men,<sup>21</sup> and an HIV–malnutrition–food insecurity syndemic, as seen in sub-Saharan Africa.<sup>22,23</sup>

The nature of HIV/AIDS as a syndemic generator is clearly illustrated in the particular vulnerability of marginalised and disadvantaged populations. When a population already affected by adverse social conditions is exposed to HIV/AIDS, co-occurring conditions such as malnutrition, sexually transmitted infections, malaria, and tuberculosis, lend themselves easily to syndemic interaction. Understanding biosocial interaction is integral to developing effective treatment and prevention protocols for people with HIV/AIDS because attempting to treat or prevent HIV/AIDS without addressing other biological and structural factors that contribute to its spread and progression has not produced the best outcomes.<sup>24</sup> Therefore, recognising syndemics requires

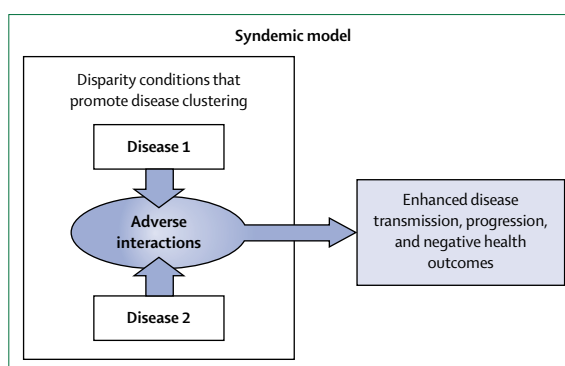


Figure: Model of a syndemic

that clinicians and epidemiologists incorporate the effect of co-occurring conditions, including social problems, in assessing adverse health outcomes as well as in establishing best treatment practices (figure).

Syndemics are not limited to infectious diseases. The VIDDA syndemic is an example of how non-communicable diseases and health conditions cluster and interact. This syndemic unites violence, immigration, depression, type 2 diabetes, and abuse as mutually exacerbating factors in the health of Mexican immigrant women in the USA.<sup>8</sup> Depression is a crucial element in other syndemics as well. Thus the WHO World Health Survey<sup>25</sup> of four chronic diseases (angina, arthritis, asthma, and diabetes) in a sample of almost 250 000 adults from 60 countries showed that comorbidity with depression incrementally worsens health beyond what was found with any of the chronic diseases alone, or with any combination of the four chronic diseases without depression. Syndemics, in short, occur across the disease spectrum and often involve adverse interactions among diverse psychiatric and biological disorders.

### Syndemic pathways

A core concern of syndemics research is the investigation of the specific pathways through which disease and other health conditions interact in the body and within populations to allow multiplication of adverse health effects. Domains of social–psychological, psychological–biological, and social–biological interaction are as fundamental to syndemics as biological interactions are. Syndemics are not characterised merely by co-occurring conditions, but rather exemplify the nature of the changes and exchanges that exacerbate the severity or progression of disease. HIV/AIDS serves as an exemplary syndemic case precisely because most of these interactive pathways involve varying socioenvironmental conditions and biological, social, and structural factors that create a distinct pattern of HIV/AIDS risk. Such pathways include pathogen–pathogen interactions in which multiple biological factors intersect and interact to increase disease susceptibility or level of affliction, as well as biosocial pathways in which social and structural factors interact

**Panel 2: Types of syndemic interaction among diseases**

- Enhanced contagiousness
- Accelerated virulence
- Alterations of the physical body
- Alterations of the emotions
- Gene reassortment
- Iatrogenic factors

with biological factors to produce a greater level of disease risk and higher health burden (panel 2).<sup>7</sup>

A common observation in cases of comorbidity is for one disease to promote or enhance the contagiousness of another disease by facilitating its access through body defences to susceptible tissues. This type of assistance is seen in the bidirectional interaction between HIV and chlamydia, leading to genital ulcerative disease.<sup>26</sup> As found in Kenya, HIV increases the incidence of genital ulcerative disease (and other sexually transmitted infections) possibly by enhancing the susceptibility to and severity of genital-tract infections through open ulceration and immune-cell depletion.<sup>27</sup> At the same time, genital ulcerative disease might affect HIV pathogenesis by increasing the plasma viral load. This relationship is also evidence of a second type of syndemic interaction, whereby the presence of one disease magnifies or accelerates the virulence of another disease. In the case of the HIV–tuberculosis syndemic, HIV increases the virulence of *M tuberculosis* by blocking the immune response sufficiently to allow the infectious agent of tuberculosis to freely replicate, a task *M tuberculosis* is unable to complete on its own.<sup>3</sup>

Changes in the body caused by one disease can also promote the success of another disease. For example, schistosomiasis is known to facilitate HIV infection. In a study with more than 500 sexually active women in Zimbabwe, an association was found between having genital lesions caused by *Schistosoma haematobium* infestation and being HIV positive.<sup>28</sup> Whereas 41% of women with laboratory-confirmed genital schistosomiasis were infected with HIV, only 26% of women without schistosomiasis were HIV-positive. This finding suggests profoundly heightened susceptibility to HIV in women with snail-induced genital lesions that serve as entry points for HIV.<sup>28</sup> A similar adverse interaction occurs between schistosomiasis and hepatitis C virus. In Egypt, where hepatitis C virus is the predominant cause of chronic liver disease, schistosomiasis has been found to cause an imbalance in hepatitis C virus-specific T-cell responses, resulting in heightened viral load, increased probability of hepatitis C virus chronicity, and accelerated onset of complications in coinfecting individuals.<sup>29</sup> These conditions are further exacerbated by poor access to health care and living circumstances that increase the risk for schistosomiasis (such as limited access to safe water).

HIV is also regularly implicated in another type of interaction, namely gene reassortment, a process that involves the movement of genes from one strain or subtype to another strain or subtype. This pattern is driven by the high error rate of its reverse transcriptase replication method and results in a high rate of mutation. This, in turn, facilitates the development of multiple viable (as well as non-viable) strains of HIV, often representing somewhat distinct local viral lineages. Circulating recombinant forms of HIV are the products of co-infection with two or more strains at the cellular level and subsequent gene mixing. Gene mixing was found to be common in the subtype C strain of HIV in KwaZulu-Natal province, South Africa.<sup>30</sup> Gene movement had a large impact on the evolutionary history of HIV, in part by enhancing its overall virulence<sup>31</sup> for a period of time.<sup>32</sup> In influenza A virus, continual gene reassortment allows the constant generation of new strains, some of which present a substantial risk for transmissibility across species, pathogenicity, and pandemic potential.<sup>33,34</sup> Other types of gene assortment involve the movement of genes across species (eg, from one bacterial species to another) or even across types of microorganisms (eg, from a bacteria to a virus).

Finally, researchers studying HIV-related and other syndemics recognise that it is possible for medicine to act as a pathway of adverse disease interaction, or iatrogenesis. Iatrogenesis was hypothesised to occur in a randomised, double-blind clinical trial designed as a longitudinal assessment of the promising prototype HIV vaccine V520.<sup>35</sup> In a trial with 3000 HIV-negative volunteers at high risk for infection, those assigned to the experimental group were administered the vaccine, but the trial was halted when 3·2% of the experimental groups developed HIV compared with 2·75% of participants in the control group. The infection rate was also higher in individuals with natural immunity to the common cold virus adenovirus type 5 compared to those who lacked natural immunity. Notably, the vaccine was produced using adenovirus type 5 as the delivery vector for synthetically produced HIV genes. The vaccine—created through the splicing of genes from naturally occurring viruses—might have lowered body defences to the virus, thereby iatrogenically increasing the rate of HIV infection in the study population compared with controls. Similarly, antischistosomiasis injection campaigns during the 1930s, using unsterile injection equipment, led to hepatitis C virus becoming the leading cause of liver cancer and cirrhosis in Egypt and to Egypt having possibly the highest prevalence of hepatitis C virus in the world (10–20% of the general population).<sup>36</sup>

**Syndemics and mental health**

No less than physical diseases, alterations of the emotions and of mental health, for example by trauma, stress, internalisation of social rejection, and the embodied experience of social stigma, can have a role in the onset

and exacerbation of other diseases, including somatoform diseases. The internalisation of social contempt opprobrium through a stigmatised illness or disease-related, stigmatised identity can have both psychosocial and biological effects on disease–disease interaction and adverse health outcomes.<sup>37,38</sup> Exposure to violence, for example, can trigger an increase in the severity of asthma. Children who live in comparatively violent neighbourhoods and have witnessed violence have been found to be twice as likely as unexposed children to have wheezing and three times more likely to be diagnosed with asthma.<sup>39</sup> The pathway of this relationship is believed to be stress-promoted immune-system deregulation caused by living in a pervasive atmosphere of fear and the perceived threat of ever-present violence.<sup>35</sup> Moreover, synergistic effects have been found between exposure to violence and traffic-related air pollution in the aetiology of asthma. These effects involve increased risk of asthma in children involving enhanced pollution (NO<sub>x</sub>) susceptibility within communities affected by the psychosocial stresses of perceived threat of violence.<sup>40</sup>

An emerging body of syndemics research has identified the social stigmatisation of diseases or of individuals who have highly stigmatised diseases as key to promoting certain syndemic interactions. In these syndemics, stigma is the primary social factor affecting disease interactions through the damaged identities and overt social marginalisation of patients, the stigmatisation of illnesses or health conditions, or both. This pattern has been described in populations of men who have sex with men as involving the following factors: (1) stigmatisation of sexual minorities results in their experience of enhanced stress relative to heterosexuals; (2) stress, in turn, leads to social coping dysregulation, externalising disorders such as drug and alcohol abuse, and social and hurtful interpersonal tensions, (3) cognitive processes increase the risk for comorbid psychopathology, including depression and anxiety; and (4) psychopathology triggers risk behaviours for a range of potentially interacting physical diseases (eg, HIV and hepatitis C virus) that get “under the skin”<sup>41</sup> (and into the bodies) of people in this population.

### Clinical issues

Awareness of syndemics raises important questions from a biomedical perspective. How do syndemic interactions complicate diagnosis? What is the best course of medical treatment for entwined syndemic diseases? How could clinicians address the social causes of syndemics? How can iatrogenic syndemics in biomedicine be avoided? Can counter-syndemics play an innovative part in new treatment options?

An important complication of syndemics is that they can alter landmark disease characteristics that are commonly used to confirm a diagnosis. For example, people who are severely immunocompromised by HIV infection (CD4 T-cell count of less than 200 cells per  $\mu$ L)

might not produce an antibody response to hepatitis C virus that is sufficiently large to be detected with existing standard blood tests. As such, a hepatitis C RNA viral load test is needed to confirm diagnosis.<sup>42</sup> Co-infection with malaria and leptospirosis (evident in communities along the border between Thailand and Myanmar) is similarly problematic. In malaria-endemic areas, malaria is often considered the sole cause of fever in patients found to be malaria-positive. Diagnosis of leptospirosis is difficult and slow, particularly in remote settings where diagnostic tools are not readily available. However, failure to recognise acute leptospirosis co-infection and delayed treatment can result in severe complications such as Weil's syndrome, pulmonary haemorrhage, and uveitis.<sup>43</sup> For people living along the Thailand–Myanmar border, these biological interactions could be promoted by social exclusion of refugee populations that reside in malaria-affected areas.

Diagnostic complications also occur with mixed non-infectious and infectious disease syndemics and with syndemics that do not involve an infectious disease. For example, patients with pulmonary tuberculosis and diabetes have frequent lung lesions within the lower lung field and are likely to present with atypical radiological features.<sup>44</sup> Diabetes increases the risk of active tuberculosis among those who are exposed to *M tuberculosis*, illustrating how individuals with diabetes living in conditions that pose a high-risk for tuberculosis transmission have a compounded risk. Diabetes tends to weaken the immune system and contribute to activation of pre-existing, latent tuberculosis. Overall, diabetes has been found to increase the risk of failure and death in people who also have tuberculosis.<sup>45</sup> Additionally, findings from a growing body of research show that major depression is much more common in patients with medical conditions like cardiovascular disease, diabetes, and cancer than in the general population, especially among people who have multiple psychobiological effects of poverty.<sup>46</sup> Although depression is ten times more prevalent in individuals who are medically ill, it presents substantial diagnostic and therapeutic challenges for physicians because treating depression pharmacologically might not ensure swift recovery when symptoms stem from problems in the patient's social life and place in the social hierarchy.<sup>47</sup> Consequently, it is estimated that as many as half of the depressive episodes in patients with medical illness are not accurately diagnosed and therefore not sufficiently treated.<sup>48</sup> As these cases suggest, syndemics can obscure the identities of their constituent disease components and confuse the diagnostic process. Awareness of syndemics, of commonly interacting diseases that are locally prevalent, and of the signs and symptoms of syndemic expression will become a fundamental constituent of biomedical education and knowledge as new social–biological, psychological–biological, and social–psychological disease interactions are recognised in clinical settings and the intimate

**Panel 3: Why syndemics emerge**

- Changing political and economic conditions
- Shifting ecological and environmental conditions
- Altering demographics and changing social behaviours
- Rapidly developing technology
- Expanding patterns of globalisations
- Ongoing microbial adaptation
- Breakdown of public health protective measures

relationships of these interactions within social contexts are more fully understood.

Syndemic theory also highlights the need to identify best practices for the simultaneous treatment of interlocked conditions. At present, however, the randomised controlled trials that produce much of the evidence for clinical treatment guidelines do not adjust for comorbidities in trial participants and even exclude participants with comorbidities from research samples.<sup>49</sup> The effect of comorbid conditions as a way to inform clinical care has been studied. Investigators examining neglected tropical diseases,<sup>50</sup> for example, have found that simultaneous treatment of several of the most prevalent neglected tropical diseases with combined drug regimens or even single pharmacological agents can facilitate effective and efficient syndemic treatment. However, syndemic treatment is not always so simple.

Heightened awareness of the nature of syndemic interactions, including both the effects of interaction and of the channels and mechanisms of interaction, is needed in clinical settings to diminish the likelihood of triggering iatrogenic syndemics. Similarly, fuller recognition of the complex interactions that occur across disease categories and are commonly assumed to be separate would enhance assessment of what the potential iatrogenic consequences of treating one disease might be for other comorbid conditions. For example, patients with Parkinson's disease often suffer from daytime sleepiness and sleep disorders such as apnoea. The treatment of Parkinson's disease with dopaminomimetics can exacerbate sleepiness in some patients<sup>51</sup> and therefore compromise their care. Inattentiveness to comorbidity and disease interactions might diminish the effectiveness of disease-specific treatment. Similarly, inattentiveness to social problems that affect diseases alone and together with comorbid conditions can exacerbate adverse health outcomes, such as treating depression to increase diabetes compliance when the root of depression is social.<sup>8</sup> This suggests the need for multifactorial, multilevel treatment models.

Alternatively, knowledge of counter-syndemic disease interactions, wherein the presence of one disease diminishes or eradicates another, might lead to new medical therapies.<sup>7</sup> Bacteriophage therapy is currently being proposed as a medical response to the emergence of drug-resistant bacteria and the resulting antibiotic crisis.<sup>52,53</sup> Companies have initiated clinical trials of phage

therapies, which include phage cocktails that contain multiple bacteriophages in a single medicine and phage patches for skin and wound infections.<sup>54,55</sup> Nevertheless, caution needs to be taken because bacteriophages, like all lifeforms, are self-replicating entities that have the capability to evolve in unforeseen ways.

**The social origins of syndemics**

Broadening biomedical care to consider not only the biological but also the social components of disease is an inherent part of the syndemics perspective. Farmer and colleagues<sup>56,57</sup> at Partners in Health have shown that structural interventions within the biomedical setting can have a greater impact than conventional clinical interventions on disease control. Using their model in Haiti, Peru, Rwanda, Lesotho, Boston (MA, USA), and elsewhere, Partners in Health have: removed clinical and community barriers to care, providing free diagnostics and treatment to patients living in poverty; delivered health care in community settings where patients live and work; addressed health-related social conditions (eg, by distributing kerosene stoves); modelled treatment plans to the realities of patients' lives; paid for transportation costs; and adopted a comprehensive approach that addresses disease comorbidities.<sup>54,55</sup> Although advocates of this model of socially conscious medicine recognise that clinicians are not trained for such tasks, they also recognise, however, that such activities must become central to health-care delivery in low-income settings to help underserved patients in wealthy and poor countries alike (panel 3).<sup>38</sup>

**Syndemics, multicausal models, and health policy**

The syndemics orientation has the potential to affect health policy by drawing attention to how social, economic, and environmental factors affect the health of human beings, provided that these factors are not separated in analysis from disease emergence or comorbidity. Instead, the clustering of diseases and the vulnerability of populations to disease must be recognised to incorporate inherent social and environmental risk factors. Doing so becomes an ever more pressing issue as populations face growing health risk due to profound and diverse environmental changes, many of which are of human origin.<sup>59</sup> These changes are intensifying existing social and health disparities—challenges that have proven to be of great consequence and notoriously resistant to overcome. As a result, new ways of thinking and working are needed to resolve the health tests of the present and the future.

Many clinicians and public health researchers have made progress in moving beyond simple linear and reductionist understandings of disease causation to a recognition of the need for multicausal models.<sup>60</sup> Yet, as Sylvia Tesh<sup>61</sup> emphasised in *Hidden Arguments: Political Ideology and Disease Prevention Policy*, some multicausal

models offer little direction for what to prioritise and where to begin in building public health responses. Consequently, some epidemiologists mistakenly look for identifiable risk factors, just as they might look for particular disease agents.<sup>61</sup> In doing so, investigators often overlook the implicit social and environmental factors that could promote disease clusters among socially and economically disadvantaged populations as well as the relative effect of psychiatric, behavioural, or biological conditions on each other. Public health programmes and divisions continue to function as semi-independent silos in academic research, funding sources, and political advocacy, with few opportunities to address interactions between syndemically linked diseases. The need to develop a sense of the system (of the human body as well as health-care delivery) in both public health and clinical practice is crucial.<sup>62</sup> A syndemic approach provides a very different orientation to clinical medicine and public health by showing how an integrated approach to understanding and treating diseases can be far more successful than simply controlling epidemic disease or treating individual patients. This approach involves not only recognising how co-occurring social and health problems can affect disease progression but also how non-pharmacological interventions can severely change health outcomes. The syndemic perspective therefore necessitates movement past narrowly conceived efforts towards the development of a big-picture awareness of diseases, disease clustering, and disease interactions in biological, ecological, and social contexts and ultimately towards correspondingly broad-based public health policy initiatives.

### Programmatic initiatives

Approaches to health promotion that are appropriate from a syndemics perspective have been implemented at the national level in various countries through progressive social policies aimed at poverty alleviation and inequality reductions. Such initiatives operate through multiple mechanisms, in line with the syndemic perspective: improving social conditions by decreasing poverty and barriers to health care; improving food access and education; and providing health-care access and biomedical technologies that directly address specific diseases and disease-disease interactions. For example, large scale social welfare programmes related to health, education and training, food, housing, and cash assistance are designed to address both the biological and underlying social factors that generate the conditions for disease clustering. One of the most inclusive, and possibly most successful, of such social welfare initiatives is Brazil's Bolsa Familia Program, the world's largest conditional cash transfer programme for poverty reduction designed specifically to promote health. Initiated in 2003, the Bolsa Familia Program distributed funds to more than 25% of Brazil's population in 2011.<sup>63</sup> The conditional cash transfers require that children attend school, where they receive at least one meal per day, get routine vaccinations, health

check-ups, and growth monitoring, and that women attend postnatal care services and receive health and nutritional education. An analysis of the effects of Bolsa Familia Program on child survival revealed that mortality among children younger than 5 years decreased as programme coverage increased, with the greatest positive effect on poverty-related malnutrition and diarrhoeal disease.<sup>64</sup>

Another development is in health-specific initiatives that recognise the syndemic nature of disease interactions among certain populations. In most cases, such programmes recognise how negative biofeedback processes can have a large impact on very expensive health interventions. For example, syndemic HIV and food insecurity occurs because food uncertainty increases the risk of HIV transmission (by promoting involvement in risky behaviours such as commercial sex activities) and worsens HIV clinical outcomes; in turn, HIV increases the risk and severity of food insecurity for individuals with HIV and members of their households.<sup>62</sup> Multidimensional non-governmental programmes have been developed to address both food and economic insecurity among people with HIV. Catholic Relief Services began establishing a Household Urban Gardens programme in Lesotho in 2006. The programme promotes the production of vitamin-rich vegetables through keyhole and trench gardens, which in turn increases food security, promotes income-generation, and provides nutrition education in the context of HIV, while maximising the use of limited land and water resources.<sup>65</sup> By 2013, Catholic Relief Services had built nearly 23 000 gardens across Lesotho.<sup>66</sup> Analysis of a similar programme in Zimbabwe indicates that such gardens are not necessarily cost-effective relative to other supplemental nutrition programmes; however, they do offer other positive benefits, such as stigma reduction.<sup>67</sup> Similarly, the Academic Model Providing Access to Healthcare (AMPATH) in Kenya, in partnerships with the UN World Food Programme, has developed an HIV treatment programme that provides persons affected by HIV with food, school fees, and enrolment in income-security programmes, including agricultural extension services, microfinancing, and small business initiatives.<sup>68,69</sup>

Yet these kinds of programmes rarely take centre stage in public health because funding sources are outcomes-oriented, disease programmes continue to be vertical with unfounded prioritisation of some diseases, and efforts to build national health systems can face steep opposition. In such contexts, what might clinicians do to address the syndemic nature of disease, especially when health-care costs are extreme, payment systems complex, or formal health care inaccessible? The primary care physician's ability to deliver syndemic care faces clinical impediments, such as workload demands, time restrictions, insurance reimbursement requirements, limitations on clinical facilities, and a limited health-care team that cannot provide holistic medical and social care to the patient. As such, a reorganisation, or at least reconsideration of existing structures, is essential. Primary care providers

should consider developing closer associations with community advocates and service workers to build healthy structural change. Additionally, in treating individual patients, awareness of the effects of syndemic interaction in a wide range of health conditions, from interacting tick-borne infections to co-infections of HIV to food disorders among people with diabetes, can contribute to improved histories, examinations, diagnoses, and treatment plans. By applying the syndemic perspective with equal or greater emphasis on improving structural conditions and social equity, the syndemic nature of many diseases can be more effectively addressed.<sup>70</sup>

### Conclusion

As emphasised by Littleton and Park,<sup>71</sup> a syndemics approach to disease is valuable because of the degree to which disease comorbidity and noxious social conditions are concentrated together in populations. Syndemics underline the importance of the disease clustering within populations, the social, psychological, and biological reasons that diseases cluster, the ways comorbid diseases affect each other, how important these interactions can be to the health burden within the populations, the pathways of disease interaction, and the way in which the health of human beings is affected by the physical and social environments in which they live. Clearly, more explicit research is needed to measure differences between merely cumulative versus multiplicative effects of syndemic interaction. As Tsai and Burns<sup>72</sup> argue in their review of the SAVA syndemic, primarily among men who have sex with men, showing a relationship between the number of psychosocial problems present in a population and the adversity of outcomes does not affirm that actual interaction has occurred. Consequently, some syndemic relationships are only suggestive at this point, whereas others (eg, tuberculosis and HIV, sexually transmitted infections and HIV) are clear,<sup>73</sup> as are the adverse effects of social, environmental, and psychological interactions on disease.<sup>24</sup> This recognition underlines the need to advance the technology for interaction assessment, a growing issue given that diseases cluster rather than exist in isolation.<sup>74,75</sup> Moreover, it affirms a call continuously made in the syndemics literature for identification and description of the pathways of disease interaction.

Recognition of the potential for syndemic interaction provides an avenue for novel public health and clinical research that is attentive to the multiple dynamics at play in health. A syndemic approach offers a biosocial framework that supports extensions of health–science understandings of disease while suggesting the need for new strategies to both improve public health and treat individual patients.<sup>76</sup> These strategies include both interventions designed to simultaneously identify and treat multiple interacting health problems as well as social–medical initiatives intended to change adverse social and physical environments. Specifically, a syndemic approach offers a productive and effective way to assess

and design multidisciplinary approaches to mitigating disease by way of understanding how diseases in tandem afflict a population in any particular time and place.<sup>71</sup>

### Contributors

MS conceived and wrote major sections of this paper. NB wrote text, edited the paper, and provided references. BO wrote text and edited the paper. EM wrote text and provided suggests for changes in the paper.

### Declaration of interests

We declare no competing interests.

### References

- 1 Hebert-Dufresne L, Althouse BM. Complex dynamics of synergistic coinfections on realistically clustered networks. *Proc Natl Acad Sci USA* 2015; **112**: 10551–56.
- 2 Corbett EL, Watt CJ, Walker N, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; **163**: 1009–21.
- 3 Pawslowski A, Jansson M, Sköld M, Rottenberg M, Källénius G. Tuberculosis and HIV co-infection. *PLoS Pathogens* 2012; **8**: e1002464.
- 4 de Noronha A, Báfica A, Nogueira L, Barral A, Barral-Netto M. Lung granulomas from *Mycobacterium tuberculosis*/HIV-1 co-infected patients display decreased in situ TNF production. *Pathol Res Pract* 2008; **204**: 155–61.
- 5 Griffiths EC, Pedersen AB, Fenton A, Petchey OL. Analysis of a summary network of co-infection in humans reveals that parasites interact most via shared resources. *Proc Biol Sci* 2014; **281**: 20132286.
- 6 Bonds MH, Keenan DC, Rohani P, Sachs JD. Poverty trap formed by the ecology of infectious diseases. *Proc Biol Sci* 2010; **277**: 1185–92.
- 7 Singer M. Introduction to syndemics: a systems approach to public and community health. San Francisco, CA: Jossey-Bass, 2009.
- 8 Mendenhall E. Syndemic suffering: social distress, depression, and diabetes among Mexican immigrant women. Walnut Creek, CA: Left Coast Press, 2013.
- 9 Strickland G. Liver disease in Egypt: hepatitis C superseded schistosomiasis as a result of iatrogenic and biological factors. *Hepatology* 2006; **43**: 915–22.
- 10 Blanton L, Mendell N, Walker D, Bouyer D. “Rickettsia amblyomii” induces cross protection against lethal Rocky Mountain spotted fever in a guinea pig model. *Vector Borne Zoonotic Dis* 2014; **14**: 557–62.
- 11 González-Guarda R. The syndemic orientation: implications for eliminating Hispanic health disparities. *Hisp Health Care Int* 2009; **7**: 114–15.
- 12 US Department of Health and Human Services, Centers for Disease Control and Prevention. U38 addressing syndemics through program collaboration and integration, CDC-PS10-10175. 2010. <http://www.federalgrants.com/Addressing-Syndemics-Through-Program-Collaboration-and-Service-Integration-28146.html> (accessed Dec 30, 2016).
- 13 Singer M. A dose of drugs, a touch of violence, a case of AIDS: conceptualizing the SAVA syndemic. *Free Inq Creat Sociol* 1996; **24**: 99–110.
- 14 Bourgois P. In search of respect: selling crack in El Barrio. New York, NY: Cambridge University Press, 1995.
- 15 Wallace R. Urban desertification, public health and public order: ‘planned shrinkage’, violent death, substance abuse and AIDS in the Bronx. *Soc Sci Med* 1990; **31**: 801–13.
- 16 Waterson A. Street addicts in the political economy. Philadelphia, PA: Temple University Press, 1993.
- 17 Stall R, Mills TC, Williamson J, et al. Association of co-occurring psychosocial health problems and increased vulnerability to HIV/AIDS among urban men who have sex with men. *Am J Public Health* 2003; **93**: 939–42.
- 18 Sullivan KA, Messer LC, Quinlivan EB. Substance abuse, violence, and HIV/AIDS (SAVA) syndemic effects on viral suppression among HIV positive women of color. *AIDS Patient Care STDS* 2015; **29** (suppl 1): S42–48.
- 19 Gilbert L, Raj A, Hien D, Stockman J, Terlikbayeva A, Wyatt G. Targeting the SAVA (substance abuse, violence, and AIDS) syndemic among women and girls: a global review of epidemiology and integrated interventions. *J Acquir Immune Defic Syndr* 2015; **69** (suppl 2): S118–27.



- 20 Ostrach B, Singer M. At special risk: biopolitical vulnerability and HIV syndemics among women. *Health Sociol Rev* 2012; **21**: 1532–69.
- 21 Stall R, Friedman M, Catania J. Interacting epidemics and gay men's health: a theory of syndemic production among urban gay men. In: Wolitski RJ, Stall R, Valdiserri RO, eds. *Unequal opportunity: health disparities affecting gay and bisexual men in the United States*. Oxford: Oxford University Press, 2007.
- 22 Weiser SD, Leiter K, Bangsberg DR, et al. Food insufficiency is associated with high-risk sexual behavior among women in Botswana and Swaziland. *PLoS Med* 2007; **4**: 1589–98.
- 23 Weiser SD, Young SL, Cohen CR, et al. Conceptual framework for understanding the bidirectional links between food insecurity and HIV/AIDS. *Am J Clin Nutr* 2011; **94**: 1729S–39S.
- 24 Ellison G, Parker M, Campbell C. *Learning from HIV and AIDS*. New York, NY: Cambridge University Press, 2003.
- 25 Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet* 2007; **370**: 851–58.
- 26 Kilmarx P, Mock P, Levine W. Effect of *Chlamydia trachomatis* coinfection on HIV shedding in genital tract secretions. *J Sex Transm Dis* 2001; **28**: 347–48.
- 27 McClelland RS, Lavreys L, Katingima C, et al. Contribution of HIV-1 infection to acquisition of sexually transmitted disease: a 10-year prospective study. *J Infect Dis* 2005; **191**: 333–38.
- 28 Kjetland EF, Ndhlovu PD, Gomo E, et al. Association between genital schistosomiasis and HIV in rural Zimbabwean women. *AIDS* 2006; **20**: 593–600.
- 29 Strictland G. Liver disease in Egypt: hepatitis C superseded schistosomiasis as a result of iatrogenic and biological factors. *Hepatology* 2006; **43**: 915–22.
- 30 Rousseau CM, Learn GH, Bhattacharya T, et al. Extensive intrasubtype recombination in South African human immunodeficiency virus type 1 subtype C infections. *J Virol* 2007; **81**: 4492–500.
- 31 Kijak GH, McCutchan FE. HIV diversity, molecular epidemiology, and the role of recombination. *Curr Infect Dis Rep* 2005; **7**: 480–88.
- 32 Jefferys RJ. Evidence for HIV weakening over time. *Proc Natl Acad Sci USA* 2015; **112**: E2118.
- 33 Tscherne DM, Garcia-Sastre A. Virulence determinants of pandemic influenza viruses. *J Clin Invest* 2011; **121**: 6–13.
- 34 Mehle A, Dugan VG, Taubenberger JK, Doudna JA. Reassortment and mutation of the avian influenza virus polymerase PA subunit overcome species barriers. *J Virol* 2012; **86**: 1750–57.
- 35 Ahmed S. HIV trial halted. *Nat Rev Immunol* 2007. <http://www.nature.com/nri/journal/v7/n11/full/nri2211.html> (accessed Dec 30, 2016).
- 36 Pybus OG, Drummond AJ, Nakano T, Robertson BH, Rambaut A. The epidemiology and iatrogenic transmission of hepatitis C virus in Egypt: a Bayesian coalescent approach. *Mol Biol Evol* 2003; **20**: 381–87.
- 37 Latkin C, Srikrishnan A, Yang C, et al. The relationship between drug use stigma and HIV injection risk behaviors among injection drug users in Chennai, India. *Drug Alcohol Depend* 2010; **110**: 221–27.
- 38 Earnshaw V, Chaudoir S. From conceptualizing to measuring HIV stigma: a review of HIV stigma mechanism measures. *AIDS Behav* 2009; **13**: 1160–77.
- 39 Wright RJ, Steinbach SF. Violence: an unrecognized environmental exposure that may contribute to greater asthma morbidity in high risk inner-city populations. *Environ Health Perspect* 2001; **109**: 1085–89.
- 40 Clougherty J, Levy J, Kubzansky L, et al. Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology. *Environ Health Perspect* 2007; **115**: 1140–46.
- 41 Hatzembuehler ML. How does sexual minority stigma “get under the skin”? A psychological mediation framework. *Psychol Bull* 2009; **135**: 707–30.
- 42 Sheth PM, Sunderji S, Shin LY, et al. Coinfection with herpes simplex virus type 2 is associated with reduced HIV-specific T cell responses and systemic immune activation. *J Infect Dis* 2008; **197**: 1394–401.
- 43 Wongsrichanalai C, Murray CK, Gray M, et al. Co-infection with malaria and leptospirosis. *Am J Trop Med Hyg* 2003; **68**: 583–85.
- 44 Shaikh MA, Singla R, Khan NB, Sharif NS, Saigh MO. Does diabetes alter the radiological presentation of pulmonary tuberculosis. *Saudi Med J* 2003; **24**: 278–81.
- 45 Baker MA, Harries AD, Jeon CY, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC Med* 2011; **9**: 81.
- 46 Leatherman T, Goodman A. Expanding the biocultural synthesis toward a biology of poverty. *American J Phys Anthropol* 1998; **101**: 1–3.
- 47 Mok H, Lin D. Major depression and medical comorbidity. *Bull Can Psychiatr Assoc* 2002; **December**: 25–28.
- 48 Beliles K, Stoudemire A. Psychopharmacologic treatment of depression in the medically ill. *Psychosomatics* 1998; **39**: S2–19.
- 49 Fortin M, Dionne J, Pinho G, Gignac J, Almirall J, Lapointe L. Randomized controlled trials: do they have external validity for patients with multiple comorbidities? *Ann Fam Med* 2006; **4**: 104–08.
- 50 Reddy M, Gill SS, Kalkar SR, Wu W, Anderson PJ, Rochon PA. Oral drug therapy for multiple neglected tropical diseases: a systematic review. *JAMA* 2007; **298**: 1911–24.
- 51 Rye DB. Sleepiness and unintended sleep in Parkinson's disease. *Curr Treat Options Neurol* 2003; **5**: 231–39.
- 52 Summers W. Bacteriophage therapy. *Ann Rev Microbiol* 2001; **55**: 437–51.
- 53 Lu T, Koeris M. The next generation of bacteriophage therapy. *Curr Opin Microbiol* 2011; **14**: 524–31.
- 54 Merabishvili M, Pirnay JP, Verbeken G, et al. Quality-controlled small-scale production of a well-defined bacteriophage cocktail for use in human clinical trials. *PLoS One* 2009; **4**: e4944.
- 55 Wright A, Hawkins CH, Anggard EE, Harper DR. A controlled clinical trial of a therapeutic bacteriophage preparation in chronic otitis due to antibiotic-resistant *Pseudomonas aeruginosa*; a preliminary report of efficacy. *Clin Otolaryngol* 2009; **34**: 349–57.
- 56 Farmer P. Challenging orthodoxies: the road ahead for health and human rights. *Health Hum Rights* 2008; **10**: 5–19.
- 57 Farmer P, Leandre F, Mukherjee J, Gupta R, Tarter L, Kim JY. Community-based treatment of advanced HIV disease: introducing DOT-HAART (directly observed therapy with highly active antiretroviral therapy). *Bull World Health Organ* 2001; **79**: 1145–51.
- 58 Farmer P, Nizeye B, Stulac S, Keshavjee S. Structural violence and clinical medicine. *PLoS Medicine* 2006; **3**: e449.
- 59 Singer M, ed. *A companion to anthropology and environmental health*. San Francisco, CA: Wiley-Blackwell, 2016.
- 60 Krieger N. Theories for social epidemiology in the 21st century: an ecosocial perspective. *Int J Epidemiol* 2001; **30**: 668–77.
- 61 Tesh S. *Hidden arguments: political ideology and disease prevention policy*. New Brunswick, NJ: Rutgers University Press, 1988.
- 62 Himmelgreen DA, Romero-Daza N, Turkon D, Watson S, Okello-Uma I, Sellen D. Addressing the HIV/AIDS-food insecurity syndemic in sub-Saharan Africa. *Afr J AIDS Res* 2009; **8**: 401–12.
- 63 Ministerio do Desenvolvimento Social e Combate a Fome. *Matriz de informação social*. 2013. [http://aplicacoes.mds.gov.br/sagi/mi2007/tabelas/mi\\_social.php](http://aplicacoes.mds.gov.br/sagi/mi2007/tabelas/mi_social.php) (accessed Sept 6, 2013).
- 64 Rasella D, Aquino R, Santos CAT, Paes-Sousa R, Barreto ML. Effect of a conditional cash transfer programme on childhood mortality: a nationwide analysis of Brazilian municipalities. *Lancet* 2013; **382**: 57–64.
- 65 Himmelgreen D, Romero-Daza N. Bytes of note. *Environment* 2010; **52**: 6–8.
- 66 Billingsley R, Mothunyane M, Thabane M, McLean S. Lessons from Lesotho: how ‘joined-up’ approach, centred on keyhole gardens, is tackling linked issues of hunger, nutrition and poverty. Hunger, nutrition, climate justice, a new dialogue: putting people at the heart of global development. Dublin, 2013. <http://www.mrfcj.org/wp-content/uploads/2015/09/2013-04-16-Lesotho.pdf> (accessed Sept 8, 2016).
- 67 Puett C, Salpeteur C, Lacroix E, Zimunya SD, Israel AD, Ait-Aissa M. Cost-effectiveness of community vegetable gardens for people living with HIV in Zimbabwe. *Cost Eff Resour Alloc* 2014; **12**: 11.
- 68 Goodrich S, Ndege S, Kimaiyo S, et al. Delivery of HIV care during the 2007 post-election crisis in Kenya: a case study analyzing the response of the Academic Model Providing Access to Healthcare (AMPATH) program. *Confl Health* 2013; **7**: 25.

- 69 Inui TS, Nyandiko WM, Kimaiyo SN, et al. AMPATH: living proof that no one has to die from HIV. *J Gen Intern Med* 2007; **22**: 1745–50.
- 70 Singer M, Bulled N, Ostrach B. Syndemics and human health: implications for prevention and intervention. *Ann Anthropol Pract* 2012; **36**: 205–11.
- 71 Littleton J, Park J. Tuberculosis and syndemics: implications for Pacific health in New Zealand. *Soc Sci Med* 2009; **69**: 1674–80.
- 72 Tsai AC, Burns BF. Syndemics of psychosocial problems and HIV risk: a systematic review of empirical tests of the disease interaction concept. *Soc Sci Med* 2015; **139**: 26–35.
- 73 Diedrich CR, Flynn JL. HIV-1/mycobacterium tuberculosis coinfection immunology: how does HIV-1 exacerbate tuberculosis? *Infect Immun* 2011; **79**: 1407–17.
- 74 Serrano E, Millan J. What is the price of neglecting parasite groups when assessing the cost of co-infection? *Epidemiol Infect* 2014; **142**: 1533–40.
- 75 Harries AD, Lin Y, Satyanarayana S, et al. The looming epidemic of diabetes-associated tuberculosis: learning lessons from HIV-associated tuberculosis. *Int J Tuberc Lung Dis* 2011; **15**: 1436–44.
- 76 Nichter M. *Global Health: Why cultural perceptions, social representations, and biopolitics matter*. Tucson, AZ: University of Arizona, 2009.