COMMENTARY

The DAGs of war

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> The essence of war is fire, famine, and pestilence. They contribute to its outbreak; they are among its weapons; they become its consequences.
>
> —Dwight D. Eisenhower

The past decade has been marked by the emergence and resurgence of infectious diseases, many of which had previously been controlled through public health distancing measures, sanitation infrastructure, and/or immunization. Notable among these have been Ebola virus infection in West Africa and the Democratic Republic of the Congo (DRC) (1); cholera epidemics in Yemen (2), South Sudan (3), and Zimbabwe (4); polio in the Afghanistan–Pakistan border area (5); diphtheria and other diseases in Venezuela (6); and a variety of communicable diseases in Syria in the context of that country's civil war (7). In each of these cases, social disruption, conflict, and violence appear to have been key ingredients in undermining disease control efforts. However, as Wells et al. (8) note in PNAS, "[the] interplay between the conflict and the disease transmission [had not been previously] assessed"; here, they refer to the ongoing Ebola outbreak in the eastern DRC, but the thesis is more broadly applicable. We observe the frequent co-occurrence of conflict, disease resurgence, and societal disruption, but the direction and strength of potential causal pathways are uncertain. Understanding causal pathways is key to disease control efforts: When we understand causal pathways, we can predict disease events and potentially control outcomes (9).

As the authors themselves note, clear delineation of causal relationships that link societal disruption, conflict (manifested in what they term "disruptive events"), and disease spread are likely to be complex and multidirectional. They have combined epidemiological data with qualitative, ethnographic observations regarding the nature and impact of conflict, to parameterize a mathematical model that appears well calibrated to observed disease activity (8). In their model, it is assumed (and based on the evidence they present, reasonably so) that upstream disruptive events impede disease control activities through 2 mechanisms: via diminished effectiveness of vaccination programs, and by disrupting efforts to isolate infectious cases. These disruptive events have been horrific and have included killings of healthcare workers and directed, intentional attacks on Ebola treatment centers. However, they also note that ongoing weak government in DRC effectively set the table for this outbreak due to ineffective disease surveillance efforts. Without disease surveillance, reaction times of those who might control the outbreak are slowed. As the so-called "force of infection" (incidence of disease among susceptible individuals) of a communicable disease is partly a function of the number of infective cases in a population (10), late recognition means that control efforts introduced late in an outbreak are almost certain to be less effective than those introduced early, even in the absence of disruptive events like those described in this paper.

Wells et al. remind us that while mathematical models of infectious disease spread are often parameterized by focusing on a few key parameters that can be measured empirically, including contact rates (measured under peaceful circumstances) (11), infectivity (12), and prevalence of underlying immunity to the infection in question (12), such simple models often misrepresent epidemic processes in human populations for the simple reason that humans are behaviorally complex and may react to, exacerbate, or even initiate epidemic processes in ways that are difficult to anticipate or understand. In an important paper published over a decade ago, Epstein et al. (13) demonstrated that accounting for the contagion of epidemic-inspired fear in parallel with epidemic transmitted disease, with frightened individuals hiding or fleeing, resulted in markedly different epidemic trajectories than are seen in models that ignore the impact of dynamic human behavior; Epstein allowed individuals in his model to be "infected" with fear, upon being confronted with infectious cases or other frightened individuals; frightened individuals could either hide or flee, with resultant maintenance of susceptible

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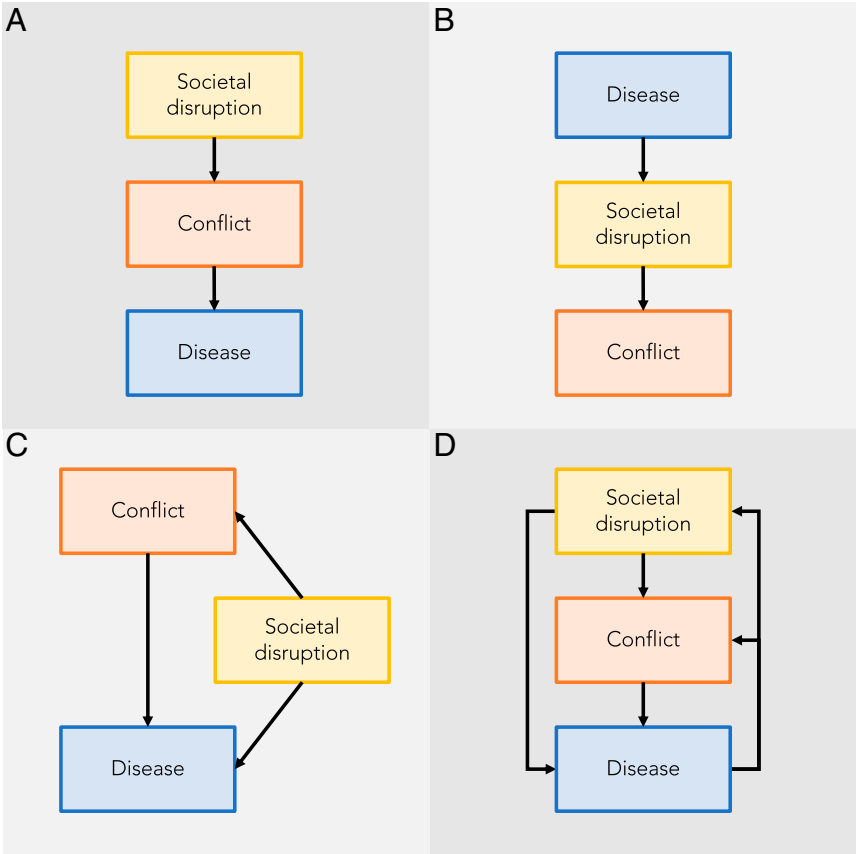

Fig. 1. (*A–D*) Graphs representing possible causal pathways linking societal disruption, conflict, and disease. Arrows represent direction of causal effects.

populations that fueled subsequent epidemic waves, or geographic spread of epidemics (13).

While it would be desirable to incorporate changes in human interaction that occur during, or are driven by, epidemics themselves, empirical collection of such data is difficult, and often requires the application of both qualitative and quantitative methods as in the work of Wells et al. For example, mobile phone movement data have been used to map population movement following natural disasters, but these efforts may be of limited generalizability if only more affluent individuals possess phones, or if natural disasters or conflicts result in destruction of communications infrastructure (14). In the paper by Wells et al., a senior physician contributing to the Ebola response by Médicins Sans Frontières is able to provide direct observations about the attitudes and concerns of local populations as conflict and violence emerged. However, it is easy to see that the collection and reporting of such information from a conflict zone is exceptional.

The complex relationships between conflict, societal collapse, and epidemic disease are well captured in the quotation from US President Eisenhower (above). We might posit a number of different causal pathways that link these phenomena; for each distinct pathway, optimal disease control strategies might differ. Conceptualizing complex causal relationships is challenging, and epidemiologists often embrace directed acyclic graphs (DAGs) as tools for mapping causal pathways (9). These tools have their origins in computer science but have proven useful for evaluation of confounding, for identification of situations where adjustment introduces bias, and for the use of such statistical tools as structural equation modeling. By definition, DAGs are not recursive; they represent causal pathways as a series of phenomena without positive or negative feedbacks. Construction of a series of simple DAGs (Fig. 1) shows us that, even in the limited context of outbreaks and epidemics mentioned in this Commentary, a variety of plausible causal pathways are possible. We will use the term "societal disruption" as a catchall to represent failed institutions, dysfunctional governance and poor government services, and/or weakened social cohesion. For example, DAG (*A*) would be a reasonable representation of the impact of societal disruption (precipitated by a devastating earthquake) that resulted in the introduction of peacekeepers to Haiti, who themselves likely introduced cholera to the country (15). It might also be a reasonable representation of Yemen's slide into civil conflict, in which degradation of sanitary infrastructure (e.g., intentional aerial bombardment of sewage treatment plants) helped precipitate a cholera epidemic (2). However, societal disruption and conflict may themselves be precipitated by disease outbreaks, a phenomenon well described in such historical epidemics as the "Black Death" in 14th-century Europe (16) [Fig. 1, DAG (*B*)]. We might consider DAG (*C*) to be a possible model of the current situation in the DRC, with societal disruption leading to conflict, while both societal disruption and conflict have independent impacts on disease transmission. In this latter model, the effects of conflict on disease are potentially confounded by societal disruption such that observed associations may not represent true causal effects. Finally, in DAG (*D*), we have modified DAG (*C*) such that it is not a DAG anymore, as recursive (dashed) arrows have been added, to represent potential positive-feedback effects of disease outbreaks on societal disruption and conflict. Such

feedback loops are common in infectious disease epidemiology and can be captured by dynamic systems models, like that used by Wells et al. Other causal pathways might also be proposed, but we end here for the sake of brevity.

Why is this important? Wells et al. implicitly endorse a causal pathway that involves conflict as a potentiator of disease. If this is correct, flare-ups of conflict become predictive of worsening disease activity, and control or resolution of violence becomes an important component of the epidemic response. Highly effective tools, including vaccination and social distancing, become far less effective in the face of violence and conflict. If other causal pathways are operative, violence and conflict should be less predictive of surges in disease transmission, and their control may not impact disease transmission. Ultimately, the ideas expressed above echo the suggestion of the 19th-century pathologist Rudolf Virchow, who noted the congruence between disease in individuals and societal ills that manifest in large-scale problems, and that need to be solved politically ("medicine on a grand scale") (17). While we might consider political dysfunction, conflict, and epidemics as distinct scourges, Wells et al. remind us that their causes and control may be intertwined.

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