Six Degrees of Separation: Use of Social Network Analysis to Better Understand Outbreaks of Nosocomial Transmission of Extensively Drug-Resistant Tuberculosis

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(See the major article by Gandhi et al, on pages 9–17.)

Extensively drug-resistant tuberculosis (XDR-tuberculosis), a form of tuberculosis resistant to the most effective tuberculosis drugs, is typically lethal among patients coinfected with human immunodeficiency virus (HIV) [1–3]. Although HIV-uninfected patients in whom XDR-tuberculosis is diagnosed promptly and managed comprehensively experience treatment success rates of 40%–60%, these rates are far from good [1, 4]. Furthermore, the treatment regimens used for XDR-tuberculosis are often as long as 2 years and are associated with numerous toxic effects, assuming patients survive long enough to complete treatment. In areas where both XDR-tuberculosis and HIV infection are prevalent, it is therefore essential to prevent person-to-person transmission. Unfortunately, ongoing reports of nosocomial transmission of drug-resistant tuberculosis in tuberculosis-endemic settings document the unacceptable risk of infection faced by healthcare workers and patients hospitalized for drug-susceptible tuberculosis and other illnesses [5–7].

It is recognized that the greatest risk of tuberculosis transmission is from patients with unsuspected tuberculosis during no therapy or from known tuberculosis patients with unsuspected drug resistance during ineffective therapy [8–14]. Active case finding and rapid diagnosis of drug resistance are therefore critically important to stop transmission. In some South African settings, the proportion of multidrug-resistant tuberculosis (MDR-tuberculosis) cases attributable to transmission is as high as 50%–80% [15]. Given the serious consequences of MDR and XDR-tuberculosis infection, a better understanding of the factors that facilitate transmission is essential for informing and expanding intervention strategies.

In this regard, the tools of classic and molecular epidemiology have greatly advanced our understanding of tuberculosis transmission. Genetic fingerprinting, for example, has helped suggest or establish linkages between seemingly unconnected patients in outbreak investigations, including those of MDR and XDR-tuberculosis transmission in hospital wards and prisons in areas of endemicity [16–18]. But even though molecular epidemiologic data have improved our ability to map the transmission of Mycobacterium tuberculosis strains within populations, such linkages cannot provide detailed understanding of how human interactions, behaviors, and patterns of movement impact transmission. This is where social network analysis can play a role.

Social network analysis is a method rooted in social science, mathematics, statistics, and anthropology [19]. It has been used in contexts where the interconnectedness of people—their relationships and networks—is relevant to the disease being studied [19]. Over the past decade, for example, it has been used in advancing the understanding and dynamics of HIV transmission [20]. More importantly, social network analysis can help strengthen context-specific, environmental, or behavioral interventions. To date, its use in research on tuberculosis transmission has been less common than for other diseases, but when used, it has enhanced the epidemiologic evaluation process. For example, investigators of a 3-year-long tuberculosis outbreak in British Columbia, Canada, used social network analysis to reveal that the outbreak had its origins rooted within an increase in crack cocaine use in the community that brought infectious and susceptible people together, resulting in
transmission [21]. This risk factor might not have been identified without the use of social network analysis. Similarly, social network analysis of a highly mobile population in which many members were infected with the same strain of M. tuberculosis illustrated that they had all had lived in a homeless shelter together [22]. The network analysis identified an opportunity to improve infection control in shelters to reduce future outbreaks.

In this issue of the Journal, Gandhi et al demonstrate the usefulness of integrating social network analysis with traditional molecular epidemiologic methods, in their study of a protracted outbreak of XDR-tuberculosis among patients who had been hospitalized in a Tugela Ferry, South Africa, district hospital. Since 2005, Tugela Ferry, an area within the Kwazulu-Natal province, has had a staggeringly high incidence of XDR-tuberculosis of 52 cases per 100 000 population [6]. In their retrospective, observational study, the authors report the results of a transmission network analysis of one large cluster (51 patients) of the ST60/KZN strain found among the patients.

By using hospital admissions dates and length of stay information as well as a set of rules to epidemiologically link patients, Gandhi et al constructed a plausible transmission network over the 2-year study period. The network analysis illustrated how the spread of the ST60/KZN strain in the Tugela Ferry district hospital occurred over several generations. Patients not only became infected with XDR-tuberculosis in the hospital but became sources of ongoing spread of XDR-tuberculosis to others during subsequent hospitalizations. It is alarming to see how highly connected patients were to each other through overlapping hospital stays during their infectious and susceptible periods. One male patient, for example, was “linked” to 11 other male patients, while one female patient was “linked” to 10 other females on the ward.

The Tugela Ferry district hospital transmission network highlights the way in which long lengths of stay, large congregate wards with inadequate infection control, and delays in diagnosis of XDR created a dangerous environment in which such transmission was not only possible but inevitable and cyclic. Patients were hospitalized for a median of 15 days (interquartile range, 10–25 days) while they were potentially infectious [6]. Furthermore, on most days (91%) of the 2-year study period, there was at least 1 yet to be diagnosed (eg, unrecognized) XDR-tuberculosis patient occupying the ward [6]. Are these conditions unique to this district hospital? Unfortunately, the answer is no. Far too many hospitals in high-burden settings have conditions that are ripe for repeated XDR-tuberculosis transmission. As the article by Gandhi et al reinforces, it is imperative to work toward ameliorating these conditions. Patients with highly drug-resistant forms of tuberculosis must quickly receive their diagnosis, start an effective regimen (ie, one that includes several drugs to which their infecting strains are susceptible), and managed in settings where they are less likely to expose susceptible individuals until they initiate an effective treatment regimen. Although increasing degrees of drug resistance may make it more difficult to find effective regimens to convert an infectious patient into a noninfectious one before sputum conversion, there is preliminary evidence to suggest that this may still be possible for MDR-tuberculosis [23], as it is for drug-resistant tuberculosis. This should allay concerns about ongoing transmission in the community following treatment initiation for drug-susceptible tuberculosis and MDR-tuberculosis. It also follows that hospitalization of only the sickest patients is warranted, while those who are less ill can and should be treated in their community.

What should be done when dealing with XDR-tuberculosis? In settings where healthcare facilities have poor infection control, inadequate isolation capacity, or inability to quickly diagnose XDR-tuberculosis, hospitalization should be as short as needed to reduce exposure of hospital staff and patients. An important way forward, however, is to improve hospital infection control and isolation capacity in settings where XDR-tuberculosis patients are treated, to reduce the risk of transmission to others, especially since it is not known whether or how quickly treatment renders XDR-tuberculosis patients noninfectious.

Although not the focus of this study, social network analysis of XDR-tuberculosis transmission in the community would be an important next step to advance our understanding of the factors that contribute to epidemic level spread. Given the limited efficacy of currently available treatment regimens for XDR-tuberculosis and evidence that transmission outside the hospital is clearly a problem [24], future studies using social network analysis to investigate the environmental, behavioral, and social factors contributing to transmission outside of healthcare facilities will be helpful in strengthening community level interventions against transmission.

Until the use of better and faster diagnostic tools for drug-resistant tuberculosis is more widespread and tightly linked to timely initiation of effective therapy, healthcare facilities must be diligent about creating and maintaining environments that are safe for their patients and staff. As the article by Gandhi et al shows, social network analysis can be combined with molecular epidemiologic tools to highlight the conditions that facilitate XDR-tuberculosis transmission. Their work also serves as a blueprint for using this tool in other contexts where XDR-tuberculosis transmission occurs, thereby allowing those involved in tuberculosis control to come one step closer to more effectively developing context- and setting-specific interventions that will reduce transmission.

Notes

Acknowledgments. I thank Edward Nardell and Carole Mitnick for their helpful comments and critique in preparation of this editorial.
Financial support. This work was supported by the National Institutes of Health (K23 AI084548).

Potential conflicts of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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