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Prevention of Multidrug-Resistant Tuberculosis in Close Contacts Back to the Future?

Enormous infectious disease pandemics have bracketed my career in medicine to this point. I entered medical school in the fall of 1981. Just a few months earlier, the first cases of a strange syndrome of previously rare infections began to affect mostly gay men and intravenous drug users in cities in the United States. So began the HIV epidemic. For the first 15–20 years of my career in medicine, AIDS was the dominant infectious disease challenge in the hospitals in which I worked and in many others around the world. Today, for people fortunate enough to have access to medication, treatment provides excellent control of the virus and a satisfactory quality of life for decades. As of this writing, we are in the midst of another infectious disease pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus that has so far killed close to 500,000 persons in 2020. Several phase 3 trials of novel and repurposed drugs have been initiated and even completed. At least two vaccine candidates are already in or nearing phase 3 trials, mere months after the first cases of coronavirus disease (COVID-19) were reported.

Throughout this whole period, tuberculosis (TB) has persisted, a stubborn and deadly presence in many countries in the world, mostly in low- and middle-income nations. In 2020, TB will still likely kill more people than any other infectious disease caused by a single pathogen. Effective prevention and treatment of TB has existed for nearly 70 years. That TB remains as a leading cause of

morbidity and mortality is a scandal of a particular sort. Even worse, multidrug-resistant strains of TB came to worldwide attention almost 30 years ago (1), but the challenge of multidrug-resistant TB (MDR-TB) is nowhere near under control (2). We are still struggling to discover the best ways to prevent and treat this particular form of the disease—to identify the best combination of antibiotics, dosages, and duration of therapy.

In this issue of the *Journal*, Huang and colleagues (pp. 1159–1168) report a most interesting and curious finding (3). They analyzed data from a prospectively organized cohort of patients in Peru who were exposed in the household to someone with TB and who, if under the age of 19 years, were treated with isoniazid (INH) according to Peruvian national guidelines. Of 4,216 contacts under the age of 19 years, half received INH. This treatment, unsurprisingly, was effective in reducing the overall incidence of active disease that developed in contacts. However, in a very surprising finding, INH also seemed to reduce the incidence of active TB in persons who had been exposed to an index case with MDR-TB, which is by definition resistant to INH. How could this be?

There have been prior reports of the effectiveness of INH in prevention of TB in MDR-TB-exposed persons (4–8), but none of those cohorts were as large or as rigorously analyzed as that in the present study. Two possible explanations immediately come to mind. The first is that the MDR-TB strains to which contacts were exposed exhibited only low-level INH resistance, and even standard preventive doses of INH were able to prevent reactivation in latently infected persons, who harbor a very small organism burden. The authors discount this possibility because they saw no difference in rates of subsequent cases related to INH minimal inhibitory concentrations in the isolates taken from the index case. A second possibility is that before being exposed by the index cases

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identified in this study, contacts had already been exposed to drug-susceptible TB and had latent infection on that basis. The authors discount this second possibility because the secondary cases that did develop in the cohort usually were caused by strains that genetically matched the index cases and were themselves drug resistant. This is not entirely persuasive, as the cases of interest are really the cases that did not develop, not the ones that did.

This paper generated quite a bit of discussion among the reviewers and editors precisely because of a lack of an apparent plausible mechanism that could explain the results. When all was said and done, however, the rigor of the observations and the detailed analysis of them convinced us that what the investigators have described is real, even if the reasons for it are not readily apparent.

The major limitation of an observational study, even one as carefully conducted and as well analyzed as this one, is unmeasured confounding. It is possible that unmeasured or residual confounders affected the results of this study. The best way to deal with the problem of unmeasured or residual confounding is, of course, to conduct a randomized controlled trial. The number of randomized controlled trials for latent or active TB remains embarrassingly low. Although the challenges of conducting controlled trials in TB are not trivial—most cases occur in resource-limited settings that often lack a clinical trial infrastructure; TB trials take an inordinately long time because of the nature of the disease itself; there is little industry sponsorship available to support trials; and given its importance, TB is vastly underfunded by government agencies relative to other illnesses—there will be little chance for dramatic progress without them.

In recent years, rifamycin-based regimens have come to the forefront for the treatment of latent TB (9–11). In comparison with INH alone, these regimens have been shown to be noninferior, generally shorter in duration, and better tolerated, particularly regarding hepatotoxicity. Whether rifamycin-based regimens will have a similar effect in contacts to MDR-TB cases will be an important question to answer.

This study has important value for current programmatic activity in countries with a high burden of MDR-TB and in the conduct of future clinical trials examining treatment for latent TB in persons exposed to multidrug-resistant index cases. The proper and ethically acceptable control group in such studies has been difficult to identify. The paper by Huang and colleagues provides an excellent rationale for using INH as a control arm in trials of patients exposed to MDR-TB index cases as opposed to placebo (12, 13). This is in itself a very useful contribution. The challenge of MDR-TB must be met. ■

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