

CORRESPONDENCE



Extensively Drug-Resistant Tuberculosis

TO THE EDITOR: Mitnick and colleagues (Aug. 7 issue)¹ have raised awareness about the clinical management and outcomes of extensively drug-resistant tuberculosis in Peru. Although a cure rate of 60% is encouraging, we caution against generalizing these findings to other high-burden settings. Of 95 patients with extensively drug-resistant tuberculosis (of whom about 60% were negative for the human immunodeficiency virus) we identified in Cape Town, South Africa, between 2006 and 2008, only 10% underwent culture conversion, despite intensive inpatient therapy, including capreomycin-based regimens. This difference may be due to higher rates of alcohol and drug abuse, smoking, and malnutrition among our patients, along with differences in strain virulence² and host immunity (including underlying profiles of helper T cells).³ Another factor may be our minimal use of moxifloxacin (which was administered to 72% of the patients in the study by Mitnick et al., as compared with 1% in our cohort). The clinical additive value of this agent requires further

evaluation, and it would be useful to know the level of cross-resistance between the different quinolone subclasses in the Peruvian study. Thus, in an African setting, treatment outcomes for patients with extensively drug-resistant tuberculosis are poor. This underscores the importance of strengthening laboratory capacity, programs for tuberculosis treatment, and the rollout of rapid diagnostic tests.⁴

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TO THE EDITOR: Mitnick et al. emphasize the concept of comprehensive management of extensively drug-resistant tuberculosis for successful outcomes. Each patient received tailor-made therapy that ranged from a highly efficacious drug regimen (obtained after detailed testing of drug susceptibility) to nutritional and psychosocial support. However, the study raises a practical and ethical question: Is it feasible to implement and sustain such aggressive, multilevel intervention under vari-

ous conditions in national tuberculosis-control programs? Another issue relates to the financial implications of executing such a rigorous approach. The estimated costs of treatment of multidrug-resistant tuberculosis range from \$1,979 to \$8,196 per patient, and costs of treatment of extensively drug-resistant tuberculosis range from \$6,843 to \$15,579 (all in U.S. dollars).¹ A further analysis of the study by Mitnick et al. to address the costs per averted death from tuberculosis and per gain in quality-adjusted life-year would throw light on the monetary implications of carrying out such a complex yet coordinated and complete intervention.

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THE AUTHORS REPLY: We agree with Dheda and colleagues about the importance of reinforcing tuberculosis management. New, affordable, and widely available drugs that have proven safety and efficacy against *Mycobacterium tuberculosis* are essential for the treatment of drug-resistant disease — and these drugs include moxifloxacin. Although testing for moxifloxacin susceptibility was not performed in patients in our study, testing for resistance to ciprofloxacin and levofloxacin was common (see Table 3 in the Supplementary Appendix of our article). Nearly all patients who received moxifloxacin had confirmed resistance to ciprofloxacin; 31% had documented resistance to levofloxacin (Table 1 in the Supplementary Appendix of our article). Limitations in the data and susceptibility testing, however, preclude evaluation of the effectiveness of moxifloxacin in these patients. Additional research on cross-resistance among the fluoroquinolones and the clinical implications of such resistance remains critical.

Possible reasons for the difference in patient outcomes between the two settings are myriad and may be related to the strain, the host, the composition of the therapy regimen and other supportive elements, or the environment. The common objective in all sites, however, is the implementa-

tion of the types of therapy and support that yield optimal results. The elucidation of such generalizable approaches can best be accomplished through multisite randomized trials, for which large-scale, long-term financing must be secured.¹

Cheruvu and Bhadriraju question the practicality of replicating the conditions in our study. As noted by Raviglione² in an editorial accompanying our article, the components of the intervention in Peru conform to the standard of care recommended by both the Stop TB strategy of the World Health Organization and the current guidelines for the treatment of drug-resistant tuberculosis.^{3,4} Although more modest approaches have been deemed cost-effective, at least one did not cure even 50% of patients with multidrug-resistant tuberculosis.⁵ In the meantime, the estimated global incidence of multidrug-resistant tuberculosis nearly doubled between 2000 and 2006, and extensively drug-resistant tuberculosis emerged in at least 49 countries. Cost-effectiveness studies that do not evaluate the effect of interventions on further development of resistance through transmission and amplification are of limited value. It would be neither ethical nor practical to rely on a cost-effective approach that does not consider these developments. A cost analysis of the intervention in Peru is under way to permit the “clear planning, financial commitment and adequate resources” that Raviglione recommends for scale-up of these appropriately complex interventions.

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