The current pandemic of type 2 diabetes mellitus (DM) is accelerating [1, 2] in a world where approximately one-third of the population is latently infected with Mycobacterium tuberculosis [3]. DM affects 230 million persons worldwide, and this number is anticipated to reach 366 million by 2030, at which time 80% of those affected will be living in low- and middle-income countries, where active tuberculosis (TB) is widespread [4, 5]. Eight of the 10 countries with the highest incidence of DM worldwide [5] are also classified as high-burden countries for TB by the World Health Organization [6]. The consequences of these converging epidemics are likely to be substantial.

The association between DM and TB was documented by Avicenna (who lived from 980 through 1027). During the early 20th century, it was said that a patient with diabetes who did not die in a diabetic coma was likely to die of TB, particularly if the patient was poor [7, 8]. The discovery of insulin in the 1920s and the later discovery of effective antibiotics led to the eclipse of the combination of these life-threatening diseases. Nevertheless, large surveys conducted prior to the 1960s indicated that TB was 2–4 times more prevalent in individuals with DM than in those without DM [7–10]. The patients’ characteristics (e.g., onset of DM at young age and insulin use) suggested that at least one-half of the patients had type 1 DM [7, 9]. Today, with type 2 now accounting for 90%–95% of all cases of DM, we are “rediscovering” the association between TB and DM [11–21].

The current literature about TB and DM is sometimes contradictory and difficult to interpret. Most reports have limitations that are inherent in retrospective studies, lack confirmation of DM, or provide no measures of blood glucose control. Many contain data only on hospitalized patients, with bias towards the most seriously ill. Nevertheless, in the aggregate, the studies point to a significant impact of DM on TB, and these reports cannot be ignored. For example, data consistently reveal that the OR of patients with active TB who have type 2 DM ranges from 1.3- to 7.8-fold [14, 16, 18, 22–24], indicating that DM clearly increases the risk of TB. Although, at the individual level, the risk of TB associated with DM is less than the risk of TB associated with AIDS (113- to 170-fold) [25, 26], the sheer number of patients with DM means that the associated risk of TB is likely to have an equal or greater effect on the population and at the public health level. In at least 1 region of the United States, the number of excess cases of TB that are attributable to DM has already reached the number of TB cases attributable to HIV infection [14].

What is more difficult to interpret from the current literature is the effect of type 2 DM on the clinical presentation and treatment response during TB. Although results are sometimes conflicting, several studies, including our own, indicate that patients with TB who have DM present a higher bacillary load in sputum [17, 27], delayed mycobacterial clearance [27, 28], and higher rates of multidrug-resistant infection [12]. These results imply that patients with TB who have DM may be more seriously ill and may pose higher risk for spread of (drug-resistant) mycobacteria in the community. Thus, these issues require urgent attention.

In this issue of Clinical Infectious Diseases, Alisjahbana et al. [29] present prospective data from a cohort of patients with TB in Indonesia, where the prevalence of confirmed DM among patients with TB is 14.8%, compared with 3.2% in the general population [18]. Their study contrasts with the mostly retrospective reports cited above, because it provides detailed prospective data (including HIV documentation and exclusion), clinical manifestations, DM classification, and mi-
crobiological findings at diagnosis and at 2 and 6 months after TB treatment for at least 543 patients. The most significant conclusion in the study by Alisjahbana et al. [29] was that, after 6 months of treatment, patients with DM were 7.65-fold more likely to have positive culture results in a multivariate model that controlled for age, sex, study site, body mass index, chest radiograph findings, and culture conversion at 8 weeks.

This careful and complete prospective study provides strong evidence of the deleterious effect of DM on TB treatment and its potential impact on control of TB. Will similar findings be observed in other areas where DM and TB are prevalent? We can only know this when we have more prospective studies. In the meantime, we can speculate on why we might see variations between reports. For instance, in contrast to other studies [17, 27], Alisjahbana et al. [29] were not able to detect differences in the prevalence of positive sputum smear results at the start of treatment between TB patients with and without DM. Sputum smears are highly insensitive, and because a positive smear result is the defining criteria for the diagnosis of TB in Indonesia, as in many developing countries, differences in smear positivity can only be reported in programs in which diagnosis is based on clinical criteria, cultures, and smears.

The detectable impact of DM on TB in a given population will depend on the characteristics of patients with TB without DM. In places where AIDS is highly prevalent, the immunosuppression induced by this infection is likely to be so strong that it will probably “mask” the impact of DM. A similar scenario, but to a lesser degree, may be encountered with other risk factors for TB, such as incarceration and alcohol or drug abuse. Thus, a critical component of data analysis is proper modeling on the basis of understanding the role of risk factors for TB as possible confounders or effect modifiers. In the study by Alisjahbana et al. [29], the effect of DM on TB was detected in a population in which <1% of the patients with TB were HIV positive (and were excluded), and none reported a history of incarceration or alcohol or substance abuse.

Notably, by the end of TB treatment in the study in Indonesia, there were still 38 of 322 patients with TB and DM who remained culture positive. This delayed clearance may be related to drug resistance. The authors report no association between multidrug-resistant TB and DM at diagnosis, but no further evaluation of drug resistance was conducted during the course of treatment. This is an important consideration, because multidrug-resistant TB may be more frequent among patients with TB and DM from certain populations, including the population of the United States and Mexico border that we studied (S. P. Fisher-Hoch, J. B. McCormick, and B.R., unpublished data) [12], but whether this is because of primary or acquired resistance remains unknown. Studies in Indonesia by the same research team have, in fact, indicated that plasma levels of rifampin were 53% lower in patients with TB who have DM than in patients with TB who do not have DM [19]. It may well be that the metabolism of rifampin is affected by DM, rendering it less effective and predisposing patients to acquisition of resistance to rifampin during treatment.

In summary, the findings by Alisjahbana et al. [29] highlight the need for further research aimed at understanding how the current global epidemic of type 2 DM is affecting TB control and prevention. Many questions are yet unanswered: what is the magnitude and impact of these converging epidemics worldwide? Should every patient with DM be screened for latent TB infection, and if the results are positive, how should TB progression be monitored or prevented? Should patients with TB and DM be treated with a different drug regimen than the regimen used to treat those with TB alone? What is the biological basis of the association between TB and DM? What is the most cost-effective measure to assess DM among patients with TB? In the meantime, simple and economically realistic approaches can be immediately implemented at every TB clinic worldwide. These include documenting self-reported DM in every new patient with TB and, where feasible, performing a finger stick glucometer assay for random blood sugar. For any patient with DM and active TB, readings will likely be very high. These patients can then be flagged for potential treatment failure and be accorded special attention.

Acknowledgments
I thank Drs. Susan Fisher-Hoch, Joseph B. McCormick, and Hossein Rahbar, for critical review of the manuscript.

Financial support. National Institute of Allergy and Infectious Diseases (R21 AI056207), National Institutes of Health National Center on Minority Health and Health Disparities (EXPORT grant MD000170), and the General Clinical Research Center (GCRC) from the University of Texas at Houston (M01- RR 02558 [GCRC] and UL1 RR024148 [Clinical and Translational Science Award]).

Potential conflicts of interest. B.R.: no conflicts.

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