suggested that immunodeficiency is the most important determinant. Our definition of disseminated BCG disease, in contrast to that of previous authors [2], did not select for immunocompromised hosts. We required only a positive BCG culture, involvement of two or more sites beyond the region of vaccination, and systemic illness. Nonetheless, 33 of the 37 patients we identified had serious underlying immunodeficiencies [1].

Arya inquires about the BCG substrains implicated in disseminated disease. Although numerous reports have suggested that the BCG strain and dose influence the rate or severity of regional complications of vaccination, such as ulcers or lymphadenopathy [3, 4], these factors have not yet been demonstrated for disseminated disease. The existence of phenotypic and genotypic differences among the BCG substrains is well recognized. Calmette and Guérin subcultured a virulent Mycobacterium bovis strain more than 200 times to develop the attenuated BCG strain in 1921. This parent BCG strain was distributed widely, and the distributed strains were maintained by various subculturing methods [5]. These substrains have been subcultured as many as 1,500 times and may have become further attenuated in the process [6].

All BCG substrains share a 10-kb deletion (RD1), which may explain the attenuation of the BCG parent strain [7, 8]. If BCG substrains vary in virulence, as suggested by the variable incidence of adverse reactions [4], then elucidating the mutations responsible for these variations may lead to the identification of virulence factors in mycobacteria. Unfortunately, substrain information was not available for most of the cases we reviewed.

Although there is much to be learned by comparing substrains, a crucial question is whether any BCG strain should be used in populations with high rates of both HIV infection and tuberculosis. We demonstrated a high mortality among patients with AIDS and disseminated BCG disease, but we could not determine the rate of this complication. In contrast, in some countries up to half of patients with AIDS develop tuberculosis. If BCG vaccination is even moderately efficacious in preventing tuberculosis in patients with AIDS, then the benefits will outweigh the risks. One population-based study showed that the risk of disseminated BCG disease is low for adults with AIDS who were vaccinated as children and that childhood BCG vaccination is associated with protection against Mycobacterium tuberculosis bacteremia [9]. We are currently participating in an international study to further address this question.

M. tuberculosis still causes the deaths of more adults than any other infectious agent. BCG is our only tuberculosis vaccine, but it has limited efficacy and causes important complications. The development of an improved tuberculosis vaccine is a pressing public health priority.

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References


Factors Influencing Time to Sputum Conversion Among Patients with Smear-Positive Pulmonary Tuberculosis

Sir—The editorial by Iseman [1] raises important issues about the duration of respiratory isolation for patients hospitalized with tuberculosis. However, his response to our article had little to do with the data we presented and much more to do with his objections to the 1994 Centers for Disease Control and Prevention (CDC) guidelines for the prevention of nosocomial transmission of tuberculosis [2]. The point of our paper was to quantify the time to sputum conversion, which the title clearly indicates, and, by implication, quantify the number of hospital days required to meet CDC guidelines [3]. This paper was not intended, explicitly or implicitly, to be a public policy paper, and we never suggested that the guidelines be adopted by other physicians in different clinical settings.

Although there is much in Iseman’s editorial that we agree with, given the greatly improved situation in 1997 in New York City with respect to tuberculosis control, the situation several years ago was very different. The analysis we presented was based on data for the period April 1993 through March 1995, a time of great concern about both nosocomial and community transmission of tuberculosis, especially multidrug-resistant tuberculosis (MDRTB) [4].

The staff at our institution in the South Bronx had to deal with a situation that Iseman mentions as “arguably” justifying adoption of the CDC guidelines: a community with “wholesale recent transmission of tuberculosis in hospitals...or in communities”; high rates of drug-resistant tuberculosis (23 of 101 patients in our series had drug-resistant tuberculosis, and 11 had MDRTB); and high rates of HIV infection and AIDS (>20% of our hospital beds were...
occupied by patients with AIDS, and 59 (80%) of the 74 patients in our series for whom HIV status was known were infected with HIV. In 1992, the year before our study period, 24 (20%) of 121 cases of tuberculosis in our hospital were MDRTB [5].

We agree with Isman that our results for patients with MDRTB were surprising, and he is correct that this should have been elaborated on in the discussion section of our paper. In fact, we have documented much longer sputum conversion times in two earlier studies of both HIV-infected and non-HIV-infected patients with MDRTB [6, 7]. The differences between this current study and the larger earlier studies may be explained by both instability of estimates (only 11 patients had MDRTB in this current report) and the treatment that patients with MDRTB may have received before their initial sputum specimen was obtained for this study. A history, both recent and remote, of tuberculosis was more common among patients with MDRTB than among those who were infected with susceptible isolates (7 of 11 vs. 9 of 77, respectively). Although appropriate treatment before study entry could not be confirmed in many instances, we hypothesize that, in fact, antituberculous therapy was provided and resulted in a misleading estimate of the time to sputum conversion.

In the editorial, Isman indicates that his comments refer to current rather than prior circumstances and that our implementation of the CDC guidelines may have been inappropriate because of "some unusual circumstances that rarely apply today." As previously stated, it was not our intent in the article to discuss the merits of the guidelines but rather to present data on the factors influencing the time to sputum conversion. We do believe, however, that the rigorous standards applied at that time were appropriate and that reconsideration of those standards is now reasonable. In fact, since completion of our study in March 1995 and abatement of the crisis, especially relating to MDRTB, we no longer strictly adhere to the 1994 CDC guidelines for many patients. Although we do not use the "2-week icon" suggested by Isman, other determinants of discontinuation of isolation are used. These determinants include clinical response to therapy; known susceptibilities of isolates; patients' willingness to adhere to an antituberculosis regimen as outpatients, ideally by attending a directly observed therapy program after discharge from the hospital; no significant close contact with patients who are immunocompromised; and not being discharged to a chronic care facility or congregate shelter for the homeless.

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References

Reply

SIR—Telzak et al. are correct: I have no quarrel with their study or with their practices during the height of the epidemic of multidrug-resistant tuberculosis in the Bronx [1]. Indeed, I tried to make this point clear in my editorial [2]. To the extent that these authors or others perceive me to be criticizing either the conduct or the reporting of this study, I failed to make my objectives clear.

My apprehension was that some persons or institutions, failing to recognize all of the complex issues involved with this situation, would uncritically adopt the practice of hospital isolation of patients with tuberculosis until negative results of three cultures are obtained. It was not my suggestion that Telzak et al. were trying to make public health policy based on their study. Rather, it was my fear that some readers might draw inappropriate inferences from their data.

‘‘That was then, this is now.’’ The information developed in this study is certainly interesting and relevant in various ways. However, given that budgets for tuberculosis control programs are limited everywhere, I hope that in the future expenditures for hospital care will be minimized and assets for directly observed therapy programs will be increased.

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References

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Clinical Infectious Diseases 1998;26:775–6
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1058-4838/98/2603-0052$03.00

1058-4838/98/2603-0052$03.00