group, and we think that further case-control studies to assess BCG efficacy in leprosy should consider this alternative in their design.

—Sergio de Andrade Nishioka, M.D., M.Sc.
Isabela Maria Bernardes Goulart, M.D.

Centro de Ciências Biomédicas
Universidade Federal de Uberlândia
Av. Pará 1720
38400-902 Uberlândia, M.G., Brasil

REFERENCES

1. Fine, P. E. M., Ponnighaus, J. M., Maine, N., Clarkson, J. A. and Bliss, L. Protective efficacy of BCG against leprosy in northern Malawi. Lancet **2** (1986) 499–502.
2. Muliyil, J., Nelson, K. E. and Diamond, E. L. Effect of BCG on the risk of leprosy in an endemic area: a case control study. Int. J. Lepr. **59** (1991) 229–236.
3. Noorden, S. K. The epidemiology of leprosy. In: *Leprosy*. Hastings, R. C., ed. Edinburgh: Churchill Livingstone, 1985, pp. 15–30.
4. Rodrigues, M. L. O., Silva, S. A., Neto, J. C. A., Andrade, A. L. S. S., Martelli, C. M. T. and Zicker, F. Protective effect of intradermal BCG against leprosy: a case-control study in central Brazil. Int. J. Lepr. **60** (1992): 335–339.

Drs. Muliyil, *et al.* Reply to the Letter from Drs. Nishioka and Goulart

To the Editor:

Drs. Nishioka and Goulart feel that, since cases were at higher risk for leprosy than the controls, the results regarding the protective efficacy of BCG found in our study could be misleading. They base their concern on the fact that the proportion of subjects with household contact with leprosy is higher among cases than controls. In our study we adjusted for the effect of household contact, both with "infectious" and "non-infectious" cases in the household. In addition, we adjusted for the effect of having a family member with leprosy outside the household. Despite these analytic procedures, Drs. Nishioke and Goulart remain skeptical of our interpretation of our results. They suggest matching cases and controls according to exposure in the households.

We agree that matching controls to cases by their exposure to leprosy in the household would be a possibility that might better control for exposure. However, this matched design would create other problems. Intrafamilial contact can act as a confounder only if it is also associated with BCG vaccination. In areas where contacts of leprosy cases are being selectively vaccinated with BCG, a case-control study which ignores this policy can result in an underestimation of the protective effect of BCG. The reverse would be the case if contacts of cases generally tend to have lower BCG coverage than the general population being studied.

In our study, we selected controls matched for age, sex and the geographic locality. The locality matching resulted in a good balance between cases and controls with respect to a number of socioeconomic variables. These socioeconomic factors could have had a significant influence on the chance of exposure of BCG, the risk of leprosy and the chance of being diagnosed as having leprosy by the health care system. In fact, we did attempt to select an extra control for each case who had intrafamilial contact with another case from among healthy contacts of other known index cases of similar severity. In doing this, we had to give up matching for locality. In South India, the BCG coverage varies with localities as does the emergence and diagnosis of new cases of leprosy. Apart from the difficulty in finding a suitable number of age- and sex-matched controls with a similar history of intrafamilial contact, we also faced the difficult task of adjusting for the effect of different geographical areas when we attempted to match for household exposure. Therefore, we feel that the method of selection of controls and data analysis

we selected is preferable to the procedure recommended by Drs. Nishioka and Goulart.

—Jayaprakash Muliyil, M.D., M.P.H.
Department of Community Medicine
Christian Medical College
Vellore, India

—Kenrad E. Nelson, M.D.
Earl Diamond, Ph.D.
Department of Epidemiology
Johns Hopkins University
School of Hygiene and Public Health
Baltimore, Maryland, U.S.A.

Rodrigues, *et al.* Reply to Letter from Drs. Nishioka and Goulart

TO THE EDITOR:

We appreciate the comments of Drs. Nishioka and Goulart regarding the choice of controls for case-control studies on leprosy. This has been recognized as a controversial subject, especially with respect to the evaluation of a possible protective effect of BCG ([4, 5]). As a general rule, in case-control studies controls should be selected from a reference population with an opportunity of exposure similar to the cases and with the equivalent probability of having been included in the study if they develop the disease of interest. Adjustment for differences in these aspects may be done by matching cases and controls on selected variables at the design stage of the investigation or by conducting a stratified or multivariate analysis.

In our study ([3]), controls were age-, sex-, and geographically matched to cases. The selection of classmates from cases also assured that they had a similar socioeconomic background and were representative of the population at risk, from which the cases came. As far as we can anticipate, the balance of these characteristics between cases and controls is required to obtain comparable groups regarding BCG coverage and the risk of developing clinical leprosy. We agree with Drs. Nishioka and Goulart's comment that cases are likely to be more exposed to *Mycobacterium leprae* infection than controls because cases are more likely to have a household contact than controls. We would say that this difference, if not taken into account, would overestimate the protective effect of the vaccine. Some authors consider that the methodological issue about vaccine efficacy and effectiveness is not whether cases and controls have the same "amount of exposure," but if there is "comparability of exposure to infection" between vaccinated and unvaccinated individuals ([1, 2]).

We would have liked to match cases and controls with regard to having or not having a leprosy contact in the household. This would resolve the problem of opportunity to exposure to infection. Controls would have been selected either from the community or from within the case's household, depending on whether the case had or did not have a household contact. To be more exact, the clinical form of the index leprosy contact also should be taken into consideration. This turned out not to be feasible, considering the matching required on age and sex, which may also relate with the length of exposure and the 3:1 ratio between controls to cases adopted in the study. The selection of household controls other than the contacts of the cases, as suggested by Drs. Nishioka and Goulart, seems, in the same way, not feasible.

In order to control for a possible bias related to a difference in household contact among cases and controls, we carried out a stratified analysis of our data. The results indicated that among case/control sets (matched analysis) with a leprosy household contact the BCG protective effect was 90.7% (95% C.I. = 72.4%–96.9%). Among sets with no leprosy contacts, the BCG protective effect against leprosy was estimated to be 77.3% (95% C.I. = 34.3%–92.2%). There-