INTERNATIONAL JOURNAL OF LEPROSY

Volume 61, Number 3
Printed in the U.S.A.

CORRESPONDENCE

This department is for the publication of informal communications that are of interest because they are informative and stimulating, and for the discussion of controversial matters. The mandate of this JOURNAL is to disseminate information relating to leprosy in particular and also other mycobacterial diseases. Dissident comment or interpretation on published research is of course valid, but personality attacks on individuals would seem unnecessary. Political comments, valid or not, also are unwelcome. They might result in interference with the distribution of the JOURNAL and thus interfere with its prime purpose.

Assessment of BCG Protective Efficacy by Case-Control Studies

TO THE EDITOR:

Two case-control studies assessing the efficacy of BCG on the prevention of leprosy were recently published by the INTERNATIONAL JOURNAL OF LEPROSY ([2, 4]). Rodrigues, *et al.* ([4]) found that BCG had a protective efficacy of 81% in a population of adolescents and children in central Brazil. A study from India by Muliyil, *et al.* ([2]), although not showing an overall protection, suggested a shift toward paucibacillary cases in vaccinated persons, also an important finding because a decrease in multibacillary cases should, theoretically, decrease the transmission of the disease.

Although the results of these studies are perfectly coherent with the findings of previous cohort and case-control studies and field trials ([1]), therefore giving consistency to the hypothesis that BCG has a prophylactic effect against leprosy, we would like to address a methodologic issue that we believe is important.

In case-control studies used to assess the efficacy of a treatment or a preventive measure on a disease, cases and controls ideally must have had the same risk of developing the disease. The efficacy of the studied measure is shown or not by whether the odds of the disease differ significantly among those exposed and nonexposed to it.

In the Brazilian study, the controls were chosen among schoolchildren from the same areas as the cases. There was no information about the prevalence of leprosy in people living in the same household of the cases and controls, but it is predictable that the cases were more likely to have had a household contact than the controls and, therefore, were more exposed to the disease. It is well known that the risk of developing leprosy is higher in family clusters, although it is debatable whether this happens by genetic predisposition or because the transmission of the disease requires intimate and prolonged contact, or for both reasons ([3]). In Muliyil's study, where the cases and controls came from the same population, the risk of having a household contact was measured and was 11.7- and 2.7-fold higher in the case group for contacts of multibacillary and paucibacillary cases, respectively.

The question is: Were the control groups in both studies good controls? Although the results agreed with those of other, theoretically, stronger cohort studies and field trials, we believe that the choice of controls as it was made could have been misleading. In the study by Muliyil, *et al.*, the presence of a case in the household was actually taken into consideration and adjusted for a multivariate analysis. Nevertheless, we believe that appropriate controls should have had the same exposure as the cases: household controls would be best, but in this situation the prevalence of previous BCG vaccine probably would not differ in cases and controls. Members from households of patients with leprosy other than the contacts of the cases would make an interesting control

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

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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