

## Editorial

### VACCINATION AGAINST LEPROSY—THE VIEW FROM 1996

Results of the latest leprosy vaccine trial were reported in the 6 July 1996 *Lancet*<sup>1</sup>. This 'Karonga Prevention Trial' was unusual in several respects: because it combined two diseases (leprosy and tuberculosis), because it evaluated two vaccine comparisons (two versus one BCG, and BCG plus killed *Mycobacterium leprae* versus BCG alone), and because of its size (120,000 individuals randomized, making it the largest trial ever carried out in Africa). The results, based on 5–9 years of follow up, indicated the following:

#### *Concerning leprosy*

The BCG booster reduced the risk of leprosy by approximately 50%. Given that previous studies in this population had indicated that an initial BCG vaccination imparts at least 50% protection,<sup>2,3</sup> these new results indicate that a two-dose regimen imparts on the order of 75% protection in this environment.

The combined BCG plus killed *M. leprae* vaccine showed no convincing evidence of imparting more protection than did BCG alone (a slight excess of leprosy among those who were less than 15 years of age and received only BCG, compared to those who received the combined vaccine, was based upon small numbers, and failed to reach statistical significance).

#### *Concerning tuberculosis*

There was no evidence that either repeated BCG or combined BCG plus killed *M. leprae* imparted any protection against pulmonary tuberculosis. There was some evidence for protection against glandular tuberculosis, but this was based upon small numbers and failed to reach statistical significance.

We thus have yet another surprising result in the history of BCG trials. What do we make of it? First, we note that the results concerning leprosy are consistent with those of the trial carried out a few years earlier in Venezuela.<sup>4,5</sup> Though the Venezuela trial did not formally evaluate repeat BCG in a randomized fashion, it provided observational data which suggested that the practice of repeated BCG vaccination, as has been carried out routinely in Venezuela, was effective in enhancing protection with successive doses.

The Venezuela trial also failed to show evidence that the addition of killed *M. leprae* to BCG enhanced protection against leprosy.

Taken together, these two trials, both originally fostered by the IMMLEP programme of WHO, provide very strong evidence that repeating a BCG vaccination adds protection against leprosy. They thus support the policy of repeat BCG vaccination of leprosy contacts, as has been routinely carried out in Cuba, Venezuela and Brazil.

The trials do not support the addition of *M. leprae* antigens to BCG, to enhance its protection against leprosy. It may even be fortunate that killed *M. leprae* did not prove a useful adjunct as a vaccine—because killed *M. leprae* material is expensive, and difficult to standardize. Instead, we are given assurance that BCG, which is both cheap and readily available everywhere, is increasingly effective in repeated doses against leprosy. This is an important contribution; for although many countries have employed repeated BCG vaccination, these studies provide the first evidence that such a policy is justified—though it must be said that the justification for the second and subsequent doses in most situations has been because of an assumed enhancement of protection against tuberculosis; an effect which has yet to be confirmed.

What do we do with this new evidence? First, we should recognize its implications for leprosy control. The evidence accumulated to date shows that BCG is protective to at least some degree against leprosy in all populations, and that it protects against multibacillary as well as paucibacillary disease (see Figure 1). The protection against multibacillary disease is particularly important, in that it multiplies the impact of BCG on leprosy incidence, by reducing transmission as well as by reducing susceptibility. Given the wide use of BCG in the world, this is surely making an important contribution to the declines in leprosy incidence recorded in many countries<sup>6</sup>. Second, more leprosy programmes should seriously consider utilizing this new evidence on repeat BCG to their advantage. Given that BCG is readily available in almost all vaccination clinics in leprosy endemic countries, leprosy control programmes may wish to consider the possibility of using these routine vaccine services to enhance leprosy control. It may be feasible in some areas to encourage contacts of leprosy patients (who are known to be at highest risk of disease) to attend the local vaccination clinic for BCG vaccination. The only concern with such a policy would be the danger of giving BCG vaccination to individuals who are immunocompromised because of HIV. According to WHO recommendations, BCG is contraindicated for individuals who are immunocompromised with AIDS, but may be given to healthy HIV positives<sup>7</sup>. The HIV concern may raise a problem in some populations—in which case it would be appropriate to restrict the repeat BCG recommendation to leprosy contacts who are below 15 years of age or who are in otherwise low risk groups for HIV. Given the simplicity of implementing such a policy, it would be worth setting up a formal community randomized trial to evaluate its impact.

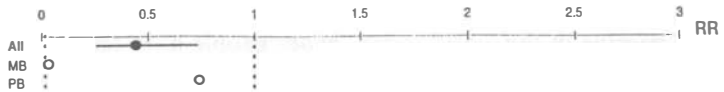
We close by noting three ironies. First, it has sometimes been said that there is no vaccine against leprosy<sup>8</sup>. Nothing could be farther from the truth! Not only is there a

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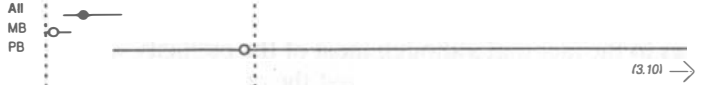
**Figure 1.** BCG protection against leprosy. Summary of published estimates of BCG protection (one or more doses) against leprosy, by classification, location, and study design (trial, case control study or cohort study).<sup>2,3,5,9-18</sup> For each study, the solid circle represents the estimate for all leprosy and the open circles represent estimates by clinical classification. Protection is expressed as the relative risk (*RR*) of disease among vaccinees compared to that in nonvaccinees. A relative risk of less than one thus indicates protection (the conventional protective efficacy statistic is defined as  $100(1 - RR)\%$ ). Horizontal lines are 95% confidence intervals.

**SOUTH AMERICA**

Venezuela (CC)  
(Merida etc.)



Brazil (CC)  
(Golanía etc.)



**AFRICA**

Uganda (T)  
(Teso)



Malawi (COH)  
(Karonga)



Malawi (CC)  
(Balaka)



Kenya (CC)  
(Western)

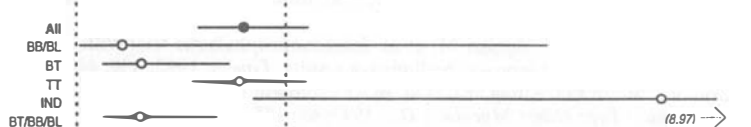


**ASIA**

South India (T)  
(Chingleput)



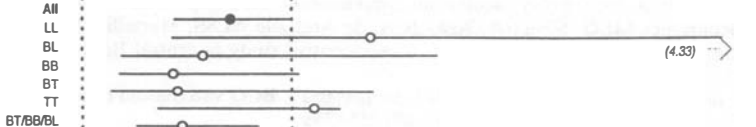
South India (CC)  
(Vellore)



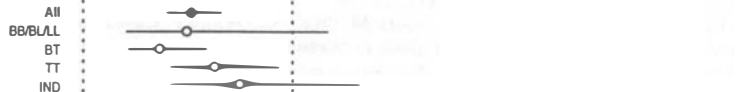
Burma  
(Singu)



Vietnam (CC)  
(Ho Chi Minh)



New Guinea (T)  
(Karimui)



Indonesia (CC)  
(South Sulawesi)



vaccine against leprosy, but it is actually being given to more individuals than is any other vaccine in the world today. More people have received BCG than have received any other vaccine. The second irony is the recognition that although BCG is generally considered a vaccine against tuberculosis, and its use is rationalized on that account, it has been shown to be more consistently protective against leprosy. And the third irony relates to the fact that although most of the publicity which surrounded the Malaŵi and Venezuela vaccine trials emphasized the combined BCG plus killed *M. leprae* product, both studies have found that a simpler alternative, merely repeating BCG, is of greater benefit against leprosy. It is important to recognize that neither trial would have been carried out if their only rationale had been to test repeat BCG. It was the enthusiasm generated by the WHO/IMMLEP programme which created these trials, and that programme (along with LEPRA and the other ILEP organizations which support the Malaŵi trial, and the Venezuelan Ministry of Health which supported the Venezuela trial) deserves credit for their important contributions to leprosy control.

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