

Immunoprophylaxis of leprosy: Current status and future prospects

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Immunoprophylaxis of leprosy continues to intrigue medical scientists even today. Due to this continuing interest, in spite of the merits and demerits of bacillus Calmette-Guérin (BCG) vaccine, its routine use has been postulated to benefit the outcome of the World Health Organization's (WHO) anti-leprosy strategy. Moreover, the BCG vaccine containing heat-killed *M. leprae* (HKML) has been shown to offer some immunity against the invasion of *M. leprae*. Its reported efficacy ranges from 34% to 80% in different countries^[1-3] across the globe. Despite the variable efficacy, BCG vaccination is still widely recommended for use in leprosy-endemic countries. Nevertheless, it is still a matter of speculation^[4-6] as to who should be vaccinated, when and how often, in order to achieve optimum protection.

BCG VACCINE

Although the BCG vaccine was initially developed for protection against *M. tuberculosis*, it was deemed to be able to protect against *M. leprae* as well. The efficacy of the second dose of the BCG vaccine in the general population was found to differ from 0 to 50% in Brazil and Malawi respectively.^[1-3,7] The protective efficacy of the first dose of BCG vaccine was found to be 14 per cent in the general population and 80 per cent in household contacts of leprosy cases in India.^[3,7]

The enhancement of cell-mediated immune response following BCG vaccination was demonstrated earlier in Argentina^[8] among contacts of leprosy patients. However, it was argued^[9] that BCG along with killed *M. leprae* is a better combination in enhancing the immune response. Animal studies have also demonstrated that BCG is protective against

M. leprae.^[10] Shepard *et al.*^[11] have shown that BCG was most protective under two circumstances: just before the challenge with *M. leprae* and just before the logarithmic multiplicative phase of *M. leprae* in mice. Although some studies found BCG to be more protective in leprosy than in tuberculosis,^[12] a meta-analysis of the experimental studies demonstrated an overall protection of 26% in leprosy, which was lower than the average protection of 50% seen in tuberculosis.^[13]

META-ANALYSIS OF BCG VACCINE DATA

A meta-analysis of data pertaining to the utility of the BCG vaccine in leprosy^[14] has concluded that there is sufficient evidence of a protective effect of BCG vaccine against leprosy, based on data of trials, cohort studies and case-control studies. However, results of a similar meta-analysis done in the past by another group of workers have been less optimistic.^[7] They found that in experimental studies, BCG vaccination offered an average protection of 26% (95% confidence interval (CI) 14-37%) against leprosy with significant heterogeneity amongst the trials ($P < 0.00001$). However, the overall protective effect of BCG was estimated to be 61% (95% CI 51-70%), also with significant heterogeneity in these observational studies ($P < 0.00001$).^[10]

Thus they concluded that the observational studies overestimated the protective effect of BCG vaccine in leprosy. The protection was better for multibacillary (MB) leprosy than for paucibacillary (PB) leprosy. However, whereas the experimental studies demonstrated a protective effect of 31% for indeterminate (I) leprosy; the observational studies showed an increased risk for it.

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As with all meta-analyses, like the one published in this issue,^[14] the optimistic findings may be influenced by three important factors—heterogeneity among studies, bias and publication bias. Some other issues not addressed in the article relevant to bias are the role of environmental and geographic factors, knowledge of immunization status of the trial participants and last but not the least, a misclassification, a major hazard of leprosy eradication and/or elimination.

ONGOING TRIALS

It is, therefore, high time to take careful note of a comparative blinded vaccine trial of all vaccines showing any efficacy in leprosy.^[15] A multi-arm trial of anti-leprosy vaccines was initiated in South India in January 1991. From a population of about 300,000, 171,400 individuals were recruited to take part in the trial. The trial had five arms-BCG alone, BCG+HKML, *Mycobacterium welchii* (M. w), ICRC bacillus and placebo. Preliminary findings from the third re-survey conducted between August 1999 and December 2002 showed the overall vaccine efficacy to be 67% for BCG + HKML, 51% for ICRC, 41% for M. w. and 22% for BCG alone. Vaccine efficacy for contacts was: BCG+HKML 88%, M. w. 87%, BCG 11% and ICRC 11%. Interestingly, the placebo group showed a significant decline in leprosy incidence during the three re-surveys—from 23.6 per 10,000 during the first, to 12.8 per 10,000 during the second and 6.1 per 10,000 during the third re-survey.

The important findings from this vaccine trial, the largest in recent times, are that the two extensively studied vaccines (BCG alone and M. w) have been found to be less protective and that the highest protective efficacy of 67% for BCG+HKML is still not adequate for commercial use.^[15]

LACUNAE IN LEPROSY VACCINE STUDIES

It is worthwhile to define the lacunae in the vaccines currently proposed for prevention of leprosy.

1. Very few well-performed double blind randomized controlled trials with proper follow up.^[1,2,7]
2. The largest vaccine trial to be conducted in recent times, has found a maximum efficacy of 67% (BCG+HKML) which still does not meet the criteria of usage.^[15]
3. Scientific analysis of data has shown that observational studies overestimate the efficacy of vaccines.^[7]

Hence, in view of the enormous progress being made towards elimination of leprosy by the widespread application of MDT,^[16] the role of vaccines is becoming increasingly less

relevant and less cost-effective^[1,2,17] although they continue to engage academic minds. Thus, on reviewing the available scientific data, we concur with the WHO view^[17] that the leprosy vaccine in any form is currently not a practical alternative for the prevention of leprosy.^[1]

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