INTERNATIONAL JOURNAL OF LEPROSY

Volume 69, Number 2 (Suppl.)
Printed in the U.S.A.
(ISSN 0148-916X)

SOUTH INDIA IMMUNOPROPHYLAXIS TRIAL AGAINST LEPROSY: REVELANCE OF FINDINGS IN THE CONTEXT OF LEPROSY TRENDS

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South India study. Our group conducted a successful immunoprophylaxis study in South India involving 171,400 volunteers for the study ([1]). The study was launched during 1991 with the following five arms: vaccines = combination of BCG and killed *M. leprae*, ICRC, *Mycobacterium w* (Mw); control preparations = BCG, placebo (normal saline).

It was decided to consider the results from the second resurvey to judge prophylactic efficacy of various vaccines. BCG + killed *M. leprae* provided 64% protection (CI 50.4–73.9), ICRC provided 65.5% protection (CI 48.0–77.0), Mw gave 25.7% protection (CI 1.9–43.8) and BCG gave 34.1% protection (CI 13.5–49.8). In view of the extensive use of BCG and several studies conducted using BCG against leprosy, BCG was used more as a benchmark. The observed efficacy with BCG was in line with our earlier study in an adjacent area, where it was 24.4% (CI 20.9–27.8) ([2]). These findings have been presented in several meetings and have led to very interesting discussions.

Findings from the first resurvey immediately following vaccination showed a consistent negative effect, not statistically significant, with all the vaccine preparations, including BCG. The negative effect was 7.6% with BCG + killed *M. leprae* and 6.9% with ICRC. With Mw it was 11.5% and with BCG 28.7% (Fig. 1). It was possible to judge this negative effect because of comparison with incidence rates in the placebo arm. The negative effect seen in this South India trial not seen for the first time. It had been observed earlier in several other studies, such as South India BCG study against tuberculosis as well as the first resurvey in Burma study ([3–4]). If the trial design had not had a placebo arm, it would be impossible to know the negative effect of the vaccine preparations, as happened in the Venezuela and Malawi studies ([5–6]). Fine suggested that this negative effect could result because of accelerated progression to mycobacterial disease among individuals incubating infection at the time of vaccination ([7]). Some scientists even feel that this precipitation of disease could be considered as possible indication of future vaccine efficacy. The two vaccine preparations which gave the least negative effect in the first resurvey also resulted in the best protective efficacy in the second resurvey. It is, therefore, difficult to consider any definitive explanation for such phenomena.

In view of this almost universal occurrence, at least following mycobacteria vaccines, is it necessary to consider such effect as something new? In the light of these findings, it may not be appropriate to club the results of the two resurveys to provide an overall efficacy for each of the vaccines. We are presently continuing with the third resurvey, and if we find efficacy of the same level as observed in the second resurvey, it would certainly make a strong case for the use of the effective vaccine in the prevention of leprosy.

There were two other interesting features in this study. Trial vaccination with BCG, as judged by the presence of BCG scars, did not affect vaccine efficacy in any considerable manner (unpublished). It was also seen that the efficacy of various vaccines was not affected by age. It appears that in a highly endemic population for leprosy, such as the South India vaccine trial area, efficacy of the vaccines did not depend on prior infec-

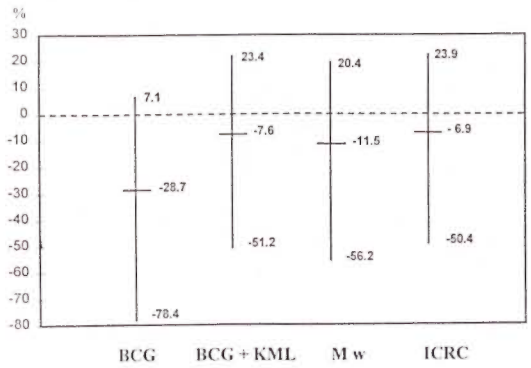

FIG. 1. Results at first resurvey; five arms concurrent comparison (percentage protective efficacy).

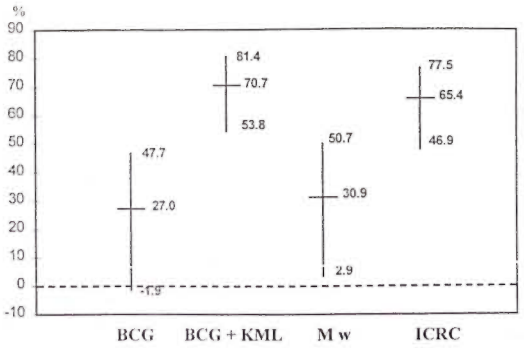

FIG. 2. Results at second resurvey; five arms concurrent comparison (percentage protective efficacy).

tion status with either *M. leprae* or some other environmental mycobacterial.

Both ICRC and Mw are killed vaccines and both have produced statistically significant levels of protection (Fig. 2). This is against the widely held belief of the necessity of live vaccines to produce protective efficacy ([7]). Presently, the exact nature of the ICRC vaccine is not very clear. It is necessary to undertake studies to characterize the ICRC vaccine at the earliest. Various vaccines in the present study, except BCG, would come from lots and not batches. Studies on characterization of these vaccines would provide the necessary quality control mechanisms.

At the time of launching the study, we expected a higher level of incidence rates than we actually observed. The observed incidence rate with multibacillary (MB) forms of leprosy was rather low and, therefore, it was not possible to study the prophylactic efficacy of any of the vaccine preparations against these serious forms.

A prophylactic efficacy of 65% to 70% can certainly be considered as a promising result from the public health point of view. The vaccine BCG + killed *M. leprae* is unlikely to be available in view of the nonavailability of armadillo-derived *M. leprae* in sufficient quantity for vaccine preparation. ICRC seems to be a strong possibility as a prophylactic agent for the future. This would certainly call for urgent steps for characterizing ICRC and possible Phase IV studies with this candidate vaccine.

There could be some possibilities regarding second-generation vaccines against leprosy. To conduct a vaccine trial against leprosy one would need a population with a high level of endemicity and a higher level of incidence. It would not be possible to conduct placebo-controlled vaccine studies in the future since there are at least two good candidate vaccines which could meet public health needs. The vaccine trial itself would be a very time-consuming and financially demanding exercise. As such, there are very bleak prospects for conducting any fresh antileprosy prophylactic study. However, there could be opportunities to make observations for leprosy as well in a second-generation tuberculosis vaccine trial.

Is there any need for vaccines against leprosy? Leprosy prevalence has shown considerable decline since the implementation of multidrug therapy (MDT) strategy worldwide. As of September 1999, the global prevalence of leprosy was around 1.4 per 10,000 population ([8]). However, new case detection rates have not shown a perceptible decline at the global level. In a workshop conducted by the Indian Association of Leprologists in Chennai, India, in 1993, several data sets from the country were examined. Very interesting patterns for recorded prevalence and new case detection rates emerged from these studies (Fig. 3) ([9]). It was clearly seen that in the face of rapid decline in prevalence following MDT, the new case detection rate remained quite steady. Our study on leprosy case detection trends for several countries clearly demonstrated that MDT did not result in a precipitous decline of new case detection rates ([10]). There is a steady and al-

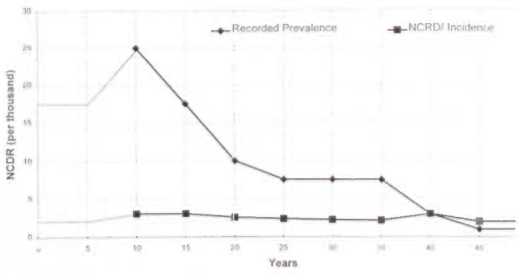

FIG. 3. Effect of dapsone and MDT interventions on prevalence and incidence of leprosy.

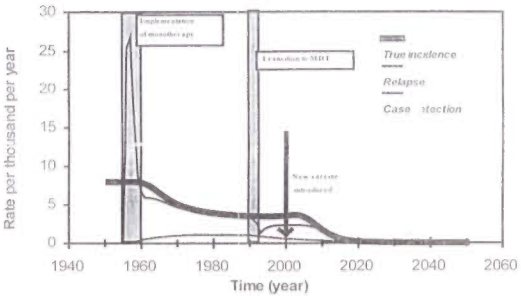

FIG. 4. Model predictions for the immunoprophylaxis experiment.

most imperceptible declining trend of new case detection. Since single-patch leprosy cases cannot find a place in prevalence of leprosy because of single-dose therapy, and the fixed-duration therapy regimens are short enough, prevalence levels are expected to remain at low and constant levels. It is possible to consider strengthening antileprosy programs in an integrated manner which would help in clearing the still existing backlogs in leprosy prevalence. However, the presently observed trends do not suggest leprosy would be eliminated or eradicated in the near future in a true sense. It is therefore possible to make a strong case for the use of prophylactic leprosy vaccines to control or eradicate leprosy.

We have developed a simulation model against leprosy in collaboration with Erasmus University, Rotterdam, The Netherlands ([11]). Our further work with this model helped us to introduce an intervention with a prophylactic vaccine against leprosy which could provide 65% protective efficacy (Fig. 4) ([12]). Introduction of vaccine intervention could bring about a dramatic decline in leprosy incidence and, at least in the context of model, it is possible to conceive leprosy eradication.

What do leprosy trends mean? Observed time trends for various health conditions are affected by variations in measurement procedures as well as by operational factors. Definitions for the conditions may not be constant and, hence, these projections could not always be very consistent. Thus, the observed trends are affected both by biological and operational factors. Data that are available for leprosy trends usually come from national-level programs or, in some situations, from cohort studies and field practice areas of some institutions. In any study, the initial estimates for leprosy incidence are generally inflated because of backlog clearances and, hence, could not be realistic. There are also various operational factors, such as case-finding methods either active or passive, status of an antileprosy program vertical or integrated, political commitments and decentralization of the program. Also allotment of targets for case detection results in wide fluctuations for case detection rates.

One also needs to consider the fact that in order to conduct various clinical trials for antileprosy drugs, it is becoming necessary to resolve to multicentric studies. Studies against MB leprosy are particularly difficult since sufficient numbers of cases are not available. Hence, the question necessarily comes whether the observed trends for case detection are real or inflated. A consistently very high level of new case detection following sample surveys in leprosy-endemic regions in India increases the complexity of these observations. It is high time that these confusions are resolved quickly and objective decisions are made to achieve substantial low levels of leprosy incidence which should ultimately lead to eradication of leprosy.

REFERENCES

1. GUPTE, M. D., VALLISHAYEE, R. S., ANANTHARAMAN, D. S., NAGARAJU, B., SREEVATSA, BALASUBRAMANYAM, S., DE BRITTO, R. L. J., ELANGO, N., UTHAYAKUMARAN, N., MAHALINGAM, V. N., LOURDUSAMY, G., RAMALINGAM, A., KANNAN, S. and AROCKIASAMY, J. Comparative leprosy vaccine trial in South India. Indian J. Lepr. **70** (1998) 369–388.
2. GUPTE, M. D. Field trials of antileprosy vaccines. (Editorial) Indian J. Lepr. **70** (1998) 363–367.

3. Tuberculosis Prevention Trial Madras. Trial of BCG vaccines in South India for tuberculosis prevention. Indian J. Med. Res. **72** (1980) 1–74.
4. Lwin, K., Sundaresan, T., Gyi, M. M., *et al.* BCG vaccination of children against leprosy: fourteen-year findings of the trial in Burma. Bull. WHO **63** (1985) 1069–1078.
5. Convit, J., Sampson, C., Zuniga, M., *et al.* Immunoprophylactic trial with combined *Mycobacterium leprae*/BCG vaccine against leprosy: preliminary results. Lancet **339** (1992) 446–450.
6. Karonga Prevention Trial Group. Randomized controlled trial of single BCG, repeated BCG or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. Lancet **348** (1996) 17–24.
7. Fine, P. E. M. South Indian leprosy vaccine trial: important lessons for mycobacterial immunology. Lepr. Rev. **70** (1999) 247–249.
8. WHO. Weekly Epidemiol. Rec. **74** (1999) 313–320.
9. Gupte, M. D. Elimination of leprosy: forecasts and projections. Indian J. Lepr. **66** (1994) 19–38.
10. Meima, A., Gupte, M. D., van Oortmarssen, G. J. and Habbema, J. D. F. Trends in leprosy case detection rates. Int. J. Lepr. **65** (1997) 305–319.
11. Meima, A., Gupte, M. D., van Oortmarssen, G. J. and Habbema, J. D. F. SIMLEP: a simulation model for leprosy transmission and control. Int. J. Lepr. **67** (1999) 215–230.
12. Gupte, M. D., Kishore, K. B., Elangovan, A. and Arockiasamy, J. Modelling epidemiology of leprosy. Indian J. Lepr. **72** (2000) 305–316.