Lepr Rev (2005) **76,** 127–143

Immunoprophylactic effects of the anti-leprosy *Mw* vaccine in household contacts of leprosy patients: clinical field trials with a follow up of 8–10 years

PANKAJ SHARMA*, RAMA MUKHERJEE*,+++,
G. P. TALWAR*,#, K. G. SARATHCHANDRA*,
R. WALIA*, S. K. PARIDA*,###, R. M. PANDEY*,##,
RAJNI RANI*, HEMANT KAR**,
ASHOK MUKHERJEE***, KIRAN KATOCH +,
S. K. BENARA++, TULSI++ & PADAM SINGH++
**National Institute of Immunology, Aruna Asafali Marg, New Delhi-110067, India*
***Department of Dermatology, Leprosy & Venereology, Dr R.M.L.Hospital, New Delhi-110001, India*
****Institute of Pathology (ICMR), Safdarjung Hospital Campus, New Delhi-110029, India*
+ Central Jalma Institute of Leprosy (ICMR), PO Box 31, Tajganj, Agra-282001, U.P. India
++ Institute for Research in Medical Statistics, Indian Council of Medical Research, Ansari Nagar, New Delhi-110029, India
Present address *+++ Dabur Research Foundation, Sahibabad, U.P., India*
#The Talwar Research Foundation, New Delhi, India
##All India Institute of Medical Sciences, New Delhi, India
###Oxford University, Oxford, UK

Accepted for publication 22 April 2005

Summary We report here a large scale, double blind immunoprophylactic trial of a leprosy vaccine based on *Mycobacterium w* (*Mw*) in an endemic area of Kanpur Dehat, Uttar Pradesh, India. A population of 420,823 spread over 272 villages was screened where 1226 multibacillary (MB) and 3757 paucibacillary (PB) cases of leprosy were detected. A total of 29,420 household contacts (HHC) of these patients were screened for evidence of active or inactive leprosy. After exclusion of 1622 contacts for any of the different exclusion criteria, a total of 24,060 HHC could be

K. K., S. K. B., T. and P. S. were associated only with the third follow-up survey (April 1999 to December 2000); the rest of the authors have been associated with the trial since its commencement until completion of the second mid-term follow-up survey.

Correspondence to: R. Rani, Neuroimmunology Laboratory, National Institute of Immunology, Aruna Asaf Ali Marg, New Delhi-110067, India (Fax: +91 11 26162125; e-mail: rajni@nii.res.in; rajnirani@yahoo.com)

vaccinated for vaccine or placebo under coding (20,194 administered two doses and 3866 received single dose). The vaccine consisted of 1×10^9 heat killed bacilli (*Mw*) in normal saline for the first dose and half of the first dose, i.e. 5×10^8 bacilli for the second dose, given 6 months after the first dose. The placebo consisted of 1/8th dose of the normal dose of tetanous toxoid. Both placebo and vaccine were given under double-blind coding, The contacts were followed up during three surveys at 3, 6 and 9 years after the initial vaccination, for detection of post-vaccination cases (PVCs) and observing any side-effects caused as a result of vaccination. The codes were opened on 24th January 2001, after the analysis of the data following completion of the third and final follow-up survey. When only contacts received the vaccine, *Mw* vaccine showed a protective efficacy (PE) of 68·6% at the end of first, 59% at the end of the second and 39·3% at the end of the third follow-up survey. When both patients and contacts received the vaccine, the protective efficacy observed was 68%, 60% and 28% at the end of the first, second and third surveys, respectively. When patients, and not the contacts, received the vaccine, a PE of 42·9% in the first, 31% in the second and 3% in the third survey was shown. These results suggest that the vaccination of the contacts is more valuable in achieving the objective of immunoprophylaxis than that of patients, and the vaccine effects are noted maximally in children (as compared to adolescents and adults) who constitute the most responsive group The effect of vaccine is sustained for a period of about 7–8 years, following which there is a need to provide a booster vaccination for the sustained protection.

Introduction

The results of immunotherapy with *Mycobacterium w* (*Mw*) vaccine in multibacillary (MB) leprosy patients, used as an adjunct to the standard multi-drug therapy (MDT) regimen have been encouraging.[1–5] The promising outcome of the hospital based clinical trials (launched in 1986) at Urban Leprosy Centres at Delhi, India[4,5] led to further expansion of the trial in a larger population under the field situation. The trial design aimed at finding out the efficacy of *Mw* based anti-leprosy vaccine for its potential beneficial effects as an immunoprophylactic agent. Ghatampur Leprosy Control Unit of District Kanpur in Uttar Pradesh, India, was selected as the area due to high prevalence of leprosy (over 18 per 1000 population) in this area. The vaccine has been administered to MB leprosy patients receiving MDT, and to healthy household contacts (HHC) of both MB and paucibacillary (PB) leprosy patients. The MDT was administered as per the standard regimen prescribed by the National Leprosy Eradication Program (NLEP).[6–8]

This trial was initiated at a time when leprosy was highly endemic in India and several other countries. It was believed that elimination of leprosy might not be possible by MDT alone. Vaccination was combined with immunotherapy to see if this could reduce the transmission of the disease. Under this backdrop, this study was initiated to study the immunoprophylatic efficacy of *Mw* vaccine in imparting protection to the household contacts of the index leprosy cases. It was a double-blind study and the vaccination schedule of the HHCs comprised two doses at 6-month intervals. The vaccination was followed by three (first, second and third) follow-up surveys, for detection of post-vaccination cases (PVCs) among HHCs. The third and final survey was completed by December 2000, and the codes were opened after analysis of the data. Here we report the results of the immunoprophylactic arm of the study.

Materials and methods

STUDY AREA AND ORGANIZATION OF THE TRIAL

Ghatampur Leprosy Control Unit of rural area of Kanpur Dehat district of Uttar Pradesh, India, had a population of 420,823 (1991 census), the prevalence rate of leprosy was 18–19 per 1000 population during 1988–1990. For the administration of MDT, the Ghatampur Leprosy Control Unit comprised three community blocks of Bhitergaon, Patara and Ghatampur, with a total of 272 village units.

The trial was run by the field unit of National Institute of Immunology (NII) in administrative collaboration with National Leprosy Eradication Program (NLEP) Division of Directorate of Health Services (Uttar.Pradesh, India) until March 1999, the end of second follow-up survey. The NLEP staff primarily carried out distribution of drugs (MDT). The third re-survey was undertaken independently by the Central JALMA Institute for leprosy and the Institute for Research in Medical Statistics (both under Indian Council of Medical Research).

ETHICAL ASPECTS

The protocol of the trial, finalized by the review/advisory committee and scrutinized by the Institutional Ethical committee, was approved by the Drug Controller General of India. Before vaccinating any subject, written consent from the subject and village head was obtained. The use of tetanus toxoid as placebo was approved by the advisory committee. MDT was made available to all the patients and post-vaccination cases (PVCs) by the NLEP staff. The NII teams tried to ensure that all subjects in the trial received monthly doses of MDT and took the treatment regularly.

VACCINE AND PLACEBO PREPARATION, DOSE AND ADMINISTRATION

The vaccine is a suspension of killed *Mycobacterium w* in physiological saline at 10^{10} bacilli per ml. Briefly, *Mw* from master seed stock was initially grown in Lowenstein-Jensen (L-J) medium. Seed lots were expanded in Middlebrook medium (Difco Laboratories, Detroit, Michigan, USA) with bovine albumin, dextrose and casein (ADC) enrichment. The bacteria were harvested during the log phase on day 8–9 of culture. The pellet was centrifuged and washed 3 times with normal saline (0·85% NaCl). The purity of the preparation was assessed in nutrient agar. The bacilli suspended in saline were autoclaved for 15 min at 15 lb $inch^{-1}$ pressure. Complete killing was ensured as assessed by lack of growth of the autoclaved specimens in L-J medium after 2 weeks of culture. The sterility of the vaccine preparation was tested in thioglycolate and soyabean casein digest medium. Thiomersal was added to a final concentration of 0·01% as a preservative.

The first dose of vaccine comprised 1×10^9 autoclaved bacilli in 0·1 ml physiological saline (0·85% NaCl), while the subsequent doses contained half the number of bacilli, i.e. 5×10^8 per dose. The vaccine was administered intradermally in the deltoid region, using a fine-bore 30G hypodermic needle. Tetanous toxoid was used as placebo in both HHCs as well as the patients in 0·1 ml volume.

TRIAL DESIGN

This involved allotment of vaccine and placebo groups and double blind coding. The trial was undertaken as a double blind, controlled study with factorial design under field conditions. The villages in the trial area were stratified and cluster randomized on the basis of prevalence rate of leprosy and population size to ensure that the numbers of subjects under different modes of treatments were comparable. The allocation of subjects to different groups was done by cluster randomization method, considering 'the village' as the one unit, i.e. the whole village belonged to either the vaccine (experimental) or placebo (control) group. The target population of 272 villages on trial (both of patients and the healthy household contacts) was divided into 4 groups. The patients were allotted P1, P2, P3 and P4 groups, while the contacts were allotted C1, C2, C3 and C4 group in such a manner that if the index case got P1, his or her contact got C1, similarly if the patient was given P2, his/her contacts were given C2 and so on. The process of randomization of villages was accomplished at the Institute of Research in Medical Statistics, New Delhi and the vaccine codes were retained by The Director General, Indian Council of Medical Research. The double blind codes of vaccine and placebo administered to the patients and controls were opened after the analysis of the data under codes (Table 1).

RECRUITMENT PROCEDURES AND EXCLUSION CRITERIA

A pre-vaccination survey was undertaken for the purpose of enumeration and identification of MB leprosy cases for induction (Table 2). NLEP unit provided the addresses and baseline data of index cases. The population was screened, looking for eligible prospective subjects, i.e. household contacts of patients for any signs or symptoms suggestive of leprosy, whether active or regressed. All such subjects with evidence of present or past leprosy were excluded from the study. Healthy household contacts were defined as subjects living in the same household under one roof as that of the patient who were free from the disease and other exclusion criteria. In addition, subjects with certain other conditions listed below were also excluded (Tables 2 and 3).

- Age above 65 years and below 1 year
- Tuberculosis and other chronic debilitating conditions
- Malnourishment and debility
- Mental disorders
- Pregnancy

Table 1. Double blind codes of the vaccine and placebo groups (as elicited after opening of codes)

Group code	Patients	Contacts
P1C1	MDT + Placebo	Vaccine
P2C2	MDT + Vaccine	Placebo
P3C3	MDT + Placebo	Placebo
P4C4	MDT + Vaccine	Vaccine

Table 2. Pre-vaccination survey of the trial area (January to March 1990). HHCs = household contacts

Group code	No. of villages	Population	No. of HHCs screened	Leprosy cases detected		
				MB	PB	Total
P1C1	65	103,389	7562	287	1016	1303
P2C2	72	91,674	7161	308	889	1197
P3C3	73	114,064	6933	322	932	1254
P4C4	62	111,696	7764	309	920	1229
Total	272	420,823	29,420	1226	3757	4983

PROCEDURES DURING FOLLOW-UP SURVEYS

Immediately after the pre-vaccination survey, the initial coverage involving the administration of the first vaccine dose to the household contacts was started in March 1990 and completed in August 1993. The booster dose coverage (at 6-month intervals) to the contacts was started in Sept.1990 and completed in July 1994.

The first mid-term survey started at an interval of 36 months from the commencement of the trial, so as to ensure a period of 36 months to elapse after administration of initial dose. For example, the patient and HHC of the 1st village covered in March 1990, was surveyed in March 1993. This completed the first mid-term survey by March 1996. The second mid-term survey commenced in April 1996 (in first village of the trial) and was completed in March 1999. The third mid-term survey, after conclusion of the second survey, was entrusted to an outside agency (Indian Council of Medical Research) for an independent evaluation. This third survey started in April 1999 and concluded in December 2000.

During clinical examination of the subjects, the double blind nature of the study was ensured by the person accompanying the examiner covering the vaccination site by putting a piece of green cloth over the subject's arm. In this way, the examiner was kept blind regarding the vaccination status of the subject. The confirmation of diagnosis was based primarily on clinical examination, aided by histopathological evaluation.

STATISTICAL ANALYSIS

The numbers of incident cases in each survey were counted to include the numbers observed in the previous survey/s giving a cumulative number of cases observed till that particular

Table 3. HHCs excluded from induction in the study (as per exclusion criteria) during initial screening

Criteria	P1C1	P2C2	P3C3	P4C4	Total
PB leprosy	261	195	211	225	892
MB leprosy	7	8	5	7	27
Pregnancy	29	32	15	24	100
Over-age (>60 years)	60	51	37	43	191
Under-age (<1 year)	103	82	85	114	384
Tuberculosis	3	2	4	9	18
Mental disorders	1	–	1	3	5
Acute illness	–	3	–	–	3
Total	464	373	358	425	1620

survey, i.e. the number of PVCs in the second survey includes those detected in the first survey also. The number of PVCs in the third survey also includes the PVCs detected in the first and second survey. This was done to assess the total impact of vaccine efficacy at different time-points.

Chi-square (χ^2) test was used to study the significance of difference in incidence of new post-vaccination cases between the two groups, for example P4C4 vs P3C3 or P1C1 vs P3C3, and so on, using 2 × 2 tables with the help of Epistat software, which also gave the odds ratios and 95% confidence intervals. Protective efficacy of the vaccine was calculated as (1-odds ratio) × 100, as described by Orenstein *et al.*[9]

Results

After presentation and discussion of the analyzed data with respect to incidence of leprosy in HHCs in all the four vaccination groups, the vaccine codes were opened on January 24, 2001.

During screening of the population of 420,823 spread in 272 villages, 4983 cases of leprosy (1226 MB and 3757 PB) were detected and a total of 29,420 HHCs of these patients were screened for evidence of disease (Table 2). Of these, 1620 HHCs were excluded from induction due to different reasons for having past or present leprosy, or other conditions listed in the exclusion criteria (Table 3). Of these, 24,060 HHCs received vaccine/placebo (20,194 two doses and 3866 single dose. Table 4 shows the percentage distribution of HHCs with respect to initial status of subjects' age, sex and their relationship to the Index case of the family. The numbers in the different groups of MB and PB leprosy index cases show that the number of HHCs in the four vaccination groups P1C1, P2C2, P3C3 and P4C4 were comparable to start with. We have been able to follow up 78·5% HHCs in the first follow-up

Table 4. Comparison of the four vaccination groups at the time of initiation of the trial (% distribution of contacts by age, sex and relationship to the index case)

	Multibacillary index cases				Paucibacillary index cases			
	P1C1	P2C2	P3C3	P4C4	P1C1	P2C2	P3C3	P4C4
Age (years)								
1–10	38·7	34·4	35·4	37·8	39·1	37·8	36·3	40·7
11–20	23·2	24·3	23·2	21·5	21·9	22·4	23·2	21·5
21–30	15·2	17·5	16·5	16·4	16·3	15·5	16·6	14·5
31–40	10·2	10·2	10·8	11·4	9·7	11·0	10·2	11·0
41–50	7·4	6·6	6·6	6·2	7·0	8·2	7·8	7·2
51–60	4·8	6·1	6·9	6·2	4·9	4·1	5·2	4·3
>60	0·7	0·9	0·6	0·5	0·8	0·9	0·7	0·6
Sex								
Male	49·9	53·1	52·7	51·1	52·4	51·5	51·9	49·9
Female	50·1	46·9	47·3	48·9	47·6	48·5	48·1	50·1
Relationship to index case								
Spouse	8·4	9·3	9·0	9·5	8·3	8·1	9·2	7·4
Child	20·8	28·7	25·4	26·4	25·8	24·9	27·3	23·6
Parents	3·4	4·2	6·7	5·4	9·4	9·4	9·4	8·5
Grandchildren	26·7	21·1	19·6	21·9	10·2	12·2	11·1	11·2
Others	40·7	36·7	39·3	36·9	46·3	45·4	43·1	49·3

survey, 80·5% in the second and 87·9% HHCs in the third survey, for appearance of new cases of leprosy and any other side effects or complications related to vaccination (Table 5).

No major untoward effects were seen during and after vaccination, and both patients and HHCs received the vaccine/placebo without ill-effects. In some cases, the skin at the site of vaccination showed induration and ulceration within 15 days, with oozing of seropurulent discharge for 1–2 months. In most cases it lead to self-healing within 8–10 weeks, leaving a scar. Only 0·16% of contacts had a complaint of delayed healing. These patients were found to have malnourishment or recent systemic infections or chronic infections such as amoebiasis, and living under unhygienic conditions. Twenty-six HHCs (0·11%) had axillary lymphadenitis, one HHC had axillary as well as supraclavicular lymphadenitis, and 29 HHCs (0·12%) developed local abscesses at the site of vaccination. In 15 HHCs, hypertrophic scars and keloids were noticed and some of them were found to have a tendency to develop keloids. Only one HHC developed a exanthematous rash on the next day of vaccination and that got cured with antihistaminic and oral steroid therapy.

Table 6 shows the incidence of leprosy cases in post-vaccination HHCs at the end of first follow-up survey at 3–4 years period and second follow-up survey at the end after 6–8 years of vaccination stratified on the bases of index case being multibacillary or paucibacillary. The number of PVCs mentioned include those from both categories, those having received two doses as well as a single dose. Since there was no statistically significant difference in the number of HHCs getting the disease between single dose and double dose contacts within each group, the data on the single and double dose contacts were combined for each group. Moreover, incidence of leprosy in the HHCs of multibacillary and paucibacillary patients also did not show any significant difference within any of the groups, hence the data of MB and PB cases were combined to calculate the protective efficacies. Early post-vaccination cases detected within 1 year period following vaccination (data not shown) have not been

Table 5. Coverage in the three surveys after vaccination

Category	P1C1	P2C2	P3C3	P4C4	Total
Target contacts	6010	6048	6087	5915	24060
First survey deaths	89	73	85	83	330
Net target	*5921*	*5975*	*6002*	*5832*	*23730*
2 dose contacts	3840	4172	4031	3981	16024
1 dose contacts	711	514	584	789	2598
1 + 2 dose contacts	4551	4686	4615	4770	18622
Coverage (% to net target)	76·9	78·4	76·9	81·8	78·5
Second survey deaths	145	114	129	131	519
Net target	*5865*	*5934*	*5958*	*5784*	*23541*
2 dose contacts	3962	4318	3968	3969	16217
1 dose contacts	774	564	587	810	2735
1 + 2 dose contacts	4736	4882	4555	4779	18952
Coverage (% to net target)	80·7	82·3	76·5	82·6	80·5
Third survey deaths	205	186	208	200	799
Net target	*5805*	*5862*	*5879*	*5715*	*23261*
2 dose contacts	4621	4390	4509	4010	17530
1 dose contacts	789	579	679	879	2926
1 + 2 dose contacts	5410	4969	5188	4889	20456
Coverage (% to net target)	93·2	84·8	88·2	85·6	87·9

Table 6. Newly detected cases with leprosy among household contacts of the index cases stratified with respect to multibacillary (MB) or paucibacillary (PB) status of index cases observed in the first two surveys

		First survey (3–4 years)				Second survey (6–8 years)			
Group	Leprosy type	Contacts examined (*n*)	No. of PVCs*	% of new cases	MB vs PB comparison** (*P*)	Contacts examined (*n*)	No. of PVCs*	% of new cases	MB vs PB comparison** (*P*)
P1C1	MB	1376	6	0·436	0·587	1437	14	0·974	0·485
	PB	3175	9	0·283		3299	24	0·727	
	Total	4551	15	0·330		4736	38	0·802	
P2C2	MB	1396	11	0·788	0·371	1438	27	1·808	0·066
	PB	3290	17	0·517		3444	38	1·103	
	Total	4686	28	0·597		4882	65	1·311	
P3C3	MB	1371	17	1·240	0·476	1359	29	2·134	0·547
	PB	3244	31	0·956		3196	58	1·815	
	Total	4615	48	1·040		4555	87	1·910	
P4C4	MB	1374	7	0·509	0·296	1387	16	1·081	0·171
	PB	3396	9	0·265		3392	22	0·649	
	Total	4770	16	0·335		4779	38	0·774	

* No. of PVCs: shows the total cumulative number of newly detected incident cases (i.e. post vaccination cases with actual disease) until the survey mentioned, i.e. the number of PVCs in second survey includes those detected in the first survey also i.e., the number of new cases detected in first survey + the number of cases detected in the second survey. The number of PVCs in third survey includes the PVCs detected in first and second survey also. This is done to assess the total impact of vaccine efficacy at different time-points.

MB vs PB (*P*)**: comparison between case incidence in the household contacts of MB and PB leprosy index cases in the four vaccination groups. None of the comparison showed statistically significant difference in any group.

considered for analysis, as they probably represent the manifestation of disease due to modulation of immune response in the vaccine recipient who did not show the manifestations of an overt disease, however, were harbouring the infection. Table 7 shows the combined incidence of leprosy in contacts of both MB and PB cases after first, second and the third surveys It may be noted that the numbers for the second survey in the table are cumulative numbers, i.e. numbers observed in the first survey plus the numbers observed in the second survey. Similarly, the figures of third survey include the numbers of PVC's in first and second survey as well plus the numbers observed in the third survey, in a cumulative manner.

Table 8 shows the impact of vaccine, on protection imparted against the development of active disease following vaccination.. The results have been compared in three sets (P4C4 vs P3C3, P1C1 vs P3C3 and finally P2C2 vs P3C3). It should be noted that the maximum protective effect of the vaccine is seen in the first two sets of comparison (where contacts have received the vaccine), the protective efficacy (PE) is 68–68·6% in the first, followed by 59–60% in the second survey. In the third survey, PE has declined to 28–39·3% in the two comparisons where the absolute placebo group is compared with the two groups where the contacts received the vaccine. The difference was highly significant statistically in the first and the second surveys ($P < 0{\cdot}00005$) but not so significant in the third survey ($P < 0{\cdot}01$). In the third set of comparisons (where the contacts did not receive the vaccine in any group but the patients received the vaccine in P2C2), the PE was 42·9% in the first, 31% in the second and 3% in the third survey; the differences were statistically significant in the first and second surveys. P4C4 vs P1C1 did not show any statistically significant difference. P4C4 vs P2C2 showed significant differences only in second survey (data not shown).

Table 9 shows the distribution of PVC's with respect to age at the end of second survey. The subdivision of PVC's into three age groups, i.e. pediatric (1–12 years), adolescent (13–17 years) and adult (18 years and above) shows that the incidence of PVCs is lower in the pediatric age group in groups P1C1 and P4C4 (0·381% and 0·543%, respectively) and higher in groups P2C2 and P3C3 (1·25% and 1·43%). Among adults, the incidence rate was 1·12%, 1·213% and 0·857% in P1C1, P2C2, and P4C4, respectively, and 1·72% in the P3C3 group.

Table 10 shows the statistical difference between the three vaccination groups as observed within the three age groups mentioned earlier. The statistical difference is most marked in the 1–12 years age group. The maximum contribution to the overall protective value of the vaccine is because of reduction of new incident cases in this group. In adults the difference between the similar comparisons are significant only when absolute vaccine group is compared with absolute placebo group, i.e. P4C4 vs P3C3 as shown in the table. However, P2C2 vs P3C3 did not show any statistically significant differences in children or adults, though a marginally significant difference was observed in the adolescents.

The break up of new cases showed a predominance of paucibacillary type (indeterminate, TT and BT) of leprosy (data not shown) in all the four groups in all the three follow-up surveys and very few cases belonged to pure neuritic type. The incidence of MB leprosy among the PVCs varied from 5% to 19% in different groups.

Discussion

We report here a large-scale immunoprophylactic trial of an anti-leprosy vaccine in an endemic area with high prevalence rate (over 18 per 1000 population) using *Mycobacterium w* vaccine. An account of trial design and details of vaccination coverage in 224 villages was

Table 7. Newly detected cases with leprosy among household contacts of the index cases irrespective of the type of disease in the index cases, at the first second and third follow-up surveys

	First survey (3–4 years)			Second survey (6–8 years)			Third survey (9–10 years)		
Group	No. of contacts examined (*n*)	No. of post-vaccination cases	% of new cases	No. of contacts examined (*n*)	No. of post-vaccination cases	% of new cases	No. of contacts examined (*n*)	No. of post-vaccination cases	% of new cases
P1C1	4551	15	0·33	4736	38	0·8	5410	87	1·61
P2C2	4686	28	0·60	4882	65	1·33	4969	126	2·53
P3C3	4615	48	1·04	4555	87	1·91	5188	136	2·62
P4C4	4770	16	0·33	4779	38	0·79	4889	93	1·9

Table 8. Protective efficacy (PE) of the vaccine observed in the three surveys (overall cumulative protection observed over a period of 10 years of post-vaccination follow-up)

		First survey (3–4 years)			Second survey (6–8 years)			Third survey (9–10 years)		
Group	Vaccine status	*P*-value	Odds ratio (95% CI)	PE (%)	*P*-value	Odds ratio (95%CI)	PE (%)	*P*-value	Odds ratio (95%CI)	PE (%)
P4C4 vs P3C3	Vaccine for both patient and contacts vs placebo for both	0·00005	0·32 (0·17–0·58)	68	0·000003	0·4 (0·275–0.613)	60	0·01	0·72 (0·547–0·948)	28
P1C1 vs P3C3	Vaccine for contact only vs placebo for both	0·00006	0·314 (0·618–0·579)	68·6	0·000006	0·41 (0·278–0·619	59	0·0003	0·607 (0·458–0·804)	39·3
P2C2 vs P3C3	Vaccine for patient vs placebo for both	0·02	0·571 (0·349–0·934)	42·9	0·03	0·69 (0·495–0.969)	31	0·833	0·97 (0·75–1·24)	3

PE = protective efficacy = (1 − odds ratio) × 100.
95% CI = 95% confidence interval.

Table 9. Age-wise break-up of the newly detected post-vaccination cases at the end of second follow-up

		Age distribution (years) and PVC (no. of HHCs examined)					
		1–12		13–17		18 and above	
Group	PVC	No.	%	No.	%	No.	%
P1C1	38	9 (2362)	0·381	5 (454)	1·101	24 (2147)	1·118
P2C2	65	27 (2157)	1·252	11 (495)	2·22	27 (2226)	1·213
P3C3	87	28 (1945)	1·439	22 (461)	4·722	37 (2147)	1·723
P4C4	38	12 (2208)	0·543	8 (467)	1·713	18 (2100)	0·857

HHC: number of household contacts examined in the survey in parenthesis.

reported earlier.[10] However, now we present the complete data on 272 villages with the details of the population covered mentioned in the result section.

These results show the protection imparted by the *Mw* vaccine against development of leprosy among household contacts of leprosy patients. During the three surveys at about 3, 6 and 9 years time lapse since vaccination, the effect of vaccine was consistent until the initial 7–8 years period and then waned subsequently. This effect is observed best (when the 'absolute vaccine' group is compared with 'absolute placebo' groups, as explained earlier) by 68% protective efficacy during the first, 60% during the second and 28% during the third follow-up-survey. Similar results have been observed in the other comparison of P1C1 (where the contacts, and not the patients, received the vaccine) with absolute placebo group. The figures for the protective efficacy in this comparison in the three follow-up-surveys are 68·6%, 59% and 39·3%, respectively. These findings suggest two important points, first, that there may be a need to give a booster dose of vaccine after 7–8 years following initial vaccination and second, that when contacts receive the vaccine, the additional benefit of vaccinating the index cases along with the contacts becomes negligible as far as protective efficacy is concerned; however, this may help the index case getting cured faster.[3] Incidence of leprosy in HHCs of multibacillary and paucibacillary patients did not show any statistically significant difference within any group, although we did see that the incidence was lower in HHCs of PB cases as compared with those of MB cases, which is expected considering the bacillary load carried by MB cases. Due to the lack of statistical significance as calculated using χ^2 test, we combined the incidence of leprosy in HHCs of MB and PB cases to calculate the protective efficacy of the vaccine. Although logistic regression analysis of all groups together may have revealed an overall significant effect, it could not be done due to the limitations of the present study. The PVCs detected within the first year following vaccination have not been considered for analysis, as they probably represent the manifestation of disease, which could be due to modulation of immune response in the vaccine recipients. As proposed by Fine, the precipitation of disease following antigenic challenge is more likely to be the result of acceleration of progression of incubating sub-clinical mycobacterial infection, rather than the infection occurring soon after vaccination.[11] Not unexpectedly in our study also, the incidence of such cases is more (nearly 3 times higher) in the vaccine groups (0·81% and 0·63%) as compared to that in placebo group (0·23% and 0·24%).

In the present study in the P4C4 (the absolute vaccine group where both patients and contacts received the vaccine), the incidence of new cases is 0·33%, 0·79% and 1·9%

Table 10. Protective efficacy of the vaccine observed in the three subgroups of age (in the figures for the second survey)

		1–12 years			13–17 years			18 years and above		
Group	Vaccine status	*P*-value	Odds ratio (95% CI)	PE (%)	*P*-value	Odds ratio (95% CI)	PE (%)	*P*-value	Odds ratio (95% C.I.)	PE (%)
P4C4 vs P3C3	Vaccine for both patient and contacts vs placebo for both	0·005	0·374 (0·179–0·768)	62·6	0·01	0·348 (0·141–0·832)	65·2	0·01	0·493 (0·269–0·896)	50·7
P1C1 vs P3C3	Vaccine for contact only vs placebo for both	0·0003	0·261 (0·115–0·581)	73·9	0·002	0·222 (0·073–0·626)	77·8	0·122	0·644 (0·372–1·112)	35·6
P2C2 vs P3C3	Vaccine for patient vs placebo for both	0·699	0·868 (0·494–1·524)	13·2	0·04	0·454 (0·204–0·993)	54·6	0·2	0·7 (0·413–1·185)	30·0

PE: protective efficacy (1 − odds ratio) × 100.

(cumulative figures for the three surveys) in the first, second and third surveys, respectively, under field conditions. We had earlier reported an incidence of 5·4% leprosy in lepromin negative household contacts who were administered *Mw* vaccine in the hospital based clinical trials in the urban leprosy centres of Delhi.[12] The difference of 5·4% and the lower figures in present study could be attributed to different types of subjects in the two studies. The HHCs chosen for the former study were lepromin negative contacts, who are an immunologically labile group, more prone to contracting the MB form of the disease due to anergic status of the immune response towards *M. leprae*. The index cases of these contacts were smear positive, active MB leprosy patients. However, even among these lepromin negative contacts, the development of disease was of mainly PB type, rather than MB type, which they might have developed if their immune system had not been stimulated with *Mw* vaccine. In the present study, however, all the HHCs of both PB and MB cases, irrespective of their lepromin status (both negatives and positives), were administered the vaccine and we find a general lower incidence of leprosy of below 2% as shown above. In the P3C3 (the absolute placebo group where both patients and contacts received placebo), we observe an incidence of new cases of 1·04%, 1·91% and 2. 62% (cumulative figures for the three surveys) in the first, second and third surveys, respectively. In the comparative trial of South India, the incidence of leprosy in the placebo arm was around 0·4%, which could be understood by virtue of different nature of subjects comprising members of general population, not necessarily the contacts of leprosy patients and irrespective of their lepromin status.[13]

BCG has been used for immunoprophylactic purposes for several years, however, earlier studies[14–17] had problems with respect to design issues, the sample size used to be small and control arms were not properly selected.[18] The later trials with BCG conducted by several investigators in different regions of the world showed varied protective efficacies ranging from 24% to 81%.[19–27] However, Convit *et al.* (1992) observed that the data on number of BCG scars found on each contact screened suggested that BCG alone confers substantial protection against leprosy with a vaccine efficacy of 56%, suggesting that several doses of BCG offered additional protection.[28] In our trial, the BCG vaccination marks were noted at the time of recruitment of contacts. In analysis we found an overall BCG positivity of 8·29% in our contacts (9·71%, 7·78%, 6·63% and 9·05% in the four vaccination groups). We also compared the incidence of new PVCs with respect to contact's BCG positivity and found no significant difference between the BCG positive and negative groups within all the four vaccine groups.

We also analysed the data to assess the age specific protection offered by the vaccine. At the end of the second survey, the minimal rates of incidence were observed in the 1–12 years age group in P1C1 and P4C4 vaccination groups (Table 9), where the contacts had received the vaccine. The rates in the pediatric age group in P2C2 and P3C3 groups (where contacts received the placebo) are comparable to those observed in the other age groups of adolescents and adults). This observation points to the suggestion that children form the better responsive group to the immuno-modulatory intervention, in comparison to adolescents and adults. This is further exemplified by the observation of higher rise in the incidence rate in the pediatric age group, during the third re-survey when we observe the vaccine effect to be waning. Hence, it would not be improper to propose that in a leprosy control program, the outcome of vaccination measures against development of leprosy, are likely to be more rewarding and should be more vigorously directed at children. A similar observation was noted in BCG prophylaxis study in South India where 25% protective efficacy was noticed and the efficacy

was best seen in the youngest age group, which substantially waned over a period of 15 years.[18]

From the epidemiological point of view, it would be pertinent to deduce from the results that to attain the control of disease transmission, vaccination of the susceptible contact is of much more importance than vaccinating the index patient. This is demonstrated by the PE of 42·9%, 31% and 3% in the comparison of P2C2 vs P3C3 group (in the P2C2 group, the vaccine was given to the patients and not the contacts) in the first, second and third surveys, respectively. Also, there is no statistically significant difference between P1C1 (where only HHCs got the vaccine) and P4C4 (where both HHCs and patients received the vaccine). In addition, a comparison of P4C4 with P2C2 gives a protective efficacy of 44·1%, 40·7% and 25·5% in the first, second and the third surveys, suggesting that vaccinating both the patients and their household contacts provides much better protective efficacy, as it reduces the infectiousness of the disease as well. A large-scale trial covering the entire population with a prevalence of leprosy of 8/1000 was undertaken in south India. It had four limbs and the subjects in each limb were given ICRC (10^9 bacilli per 0·1 ml), *Mw* vaccine (10^9 bacilli per 0·1 ml), BCG + killed *M. leprae* (6×10^8 bacilli) or BCG, which started in January 1991 and ended in September 1998.[13,30] The results of the second survey of this study have shown that BCG + killed *M. leprae* and the ICRC have sufficiently high levels of PE at around 65%, and BCG alone and *Mw* showed protective efficacy of around 30%. This study, however, differed considerably from the present study in terms of trial design and kind of subjects. The former was done on the subjects comprising members of general population, whereas the subjects in the present study were the household contacts of leprosy patients, where the chances of getting disease are more due to proximity with the patients. The results of the present study indicate that at the end of second survey, *Mw* in the present study is comparable to ICRC in the South Indian study.

As has been stated in the results, no significant difference was observed in the incidence of new cases in the HHCs receiving one or two doses of vaccine within each group. A prophylactic efficacy of 65–70% may certainly be considered a promising result from the public health point of view.[29] From that point of view, the PE of 68% and 60% at the end of the 4- and 8-years period, respectively, following two doses of vaccination, seems to be quite a satisfactory outcome. It would be pertinent to mention that it is important to vaccinate the contacts but vaccination of MB leprosy patients along with the PB leprosy patients would be a step in achieving increased clearance of bacilli from the population. It would be advisable to give a booster vaccination after 7–8 years to enhance and sustain the vaccine effect on the cell-mediated immunity towards *M. leprae*.

The issue as to whether there is any need for having a vaccine against leprosy in the post-MDT scenario has attracted considerable debate among different schools of leprologists. The prevalence of leprosy has declined considerably, since the worldwide implementation of multi drug therapy (MDT) to an extent of 1·4 per 10,000 population according to World Health Organization Report published in 1999. However, if the data from the endemic areas are considered, it is clear that new case detection rates remain quite stable and have not decreased suggesting that transmission of *M. leprae* infection will continue for some time.[29,30] Even in the present study, we find a higher number of leprosy patients during the third survey (at about 9 years after the initial dose of the vaccine/placebo), which shows that there is not only a need to give vaccine to the HHCs, but also to give a booster after a time period of 7–8 years.

Acknowledgements

The phase III clinical trials were supported by a Financial grant from Department of Biotechnology, Ministry of Science and Technology, Government of India. The authors are grateful to Dr N. K. Saxena, the leprosy medical officer of Ghatampur L.C.U., Dr Trivedi, the District Leprosy Officer, Kanpur City, and Dr R. P. Mall and Dr Kannaujia, both of whom served as the State Leprosy Officers of U.P., for their continued help and support. The meticulous hard work of paramedical workers Mr Suresh Kumar (also working as data entry operator), Mr Krishan Pal and Mr Parmal Singh in carrying out the day-to-day work of the trial is gratefully acknowledged. The role of drivers of the team Mr Mahinder Singh, Mr Kesar Jung and Mr Jamuna Prasad cannot be underestimated; they were untiring in driving the field unit to the deep difficult interiors of the villages under any circumstances and any conditions of roads and weather. The authors also thankfully acknowledge the guidance provided by the Review/Advisory Committee, which included Professor P. N. Tandon, Consultant, Task force on Medical Biotechnology, DBT, New Delhi, Dr Manju Sharma, Secretary, DBT, Dr N. K. Ganguly, Director General, ICMR, New Delhi, Dr N. S. Dharmshaktu, Deputy Director General (Leprosy), DGHS, New Delhi, Dr R. S. Misra, Consultant & Head (Rtd.) Dept of Dermatology, Venereology and Leprology, Safdarjung Hospital, New Delhi, Dr Ashok Mukherjee, Deputy Director, Institute of Pathology (ICMR), New Delhi and Dr D. Porricha, Senior Pathologist, Medical Centre Parliament Annexe, New Delhi. The other noted leprologists to whom the authors wish to express their gratitude for the assessment of the trial and helpful advice from time to time include Dr G. Ramu, Dr V. Ekambaram. Dr H. Srinivasan, Dr M. D. Gupte, Dr V. K. Vinayak, Advisor DBT, Dr R. Ganpati, Director Bombay Leprosy Project, Mumbai, Dr R. Revankar, Deputy Director, Bombay Leprosy Project, Mumbai, Dr K. V. Desikan, Chairman, M. G. Institute of Medical Sciences, Wardha, Maharashtra and Dr S. K. Basu, Director National Institute of Immunology. The authors would also like to acknowledge all the help given by the administrative staff of NII, especially Mr. B. Bose, the Senior Manager, who helped in the smooth running of the trial, located at a distance of nearly 500 km from the NII head quarters. And finally above all, the investigators feel immensely indebted to the people of Ghatampur who very actively participated in the trial; without their co-operation, such a long study would not have been possible.

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