WORKSHOP 9: LEPROSY VACCINE TRIALS

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The participants for the Workshop came from a wide range of disciplines and included epidemiologists, statisticians, and immunologists. The participants had rich experience in large-scale vaccine trials. The group discussed the results from the four major BCG vaccine trials to generate information that could be useful to the ongoing and future leprosy vaccine trials.

BCG trials

Burma. Some 26,000 healthy children were included in the trial; half of them received BCG, the other half served as controls. Two batches of Glaxo freeze-dried vaccine were used. Very little protection (10%) was observed with the first batch, and as much as 30% with the second batch. Although the second batch was a little more potent, both batches had acceptable potency. Combining the results from both batches, it was concluded that the protection conferred by BCG was of a very modest level.

Uganda. A trial of BCG vaccine against leprosy among 19,000 children in Uganda, all contacts or relations of known cases, began in 1960, using the Glaxo strain of BCG. The efficacy of BCG against early forms of tuberculoid leprosy during the first 8 years was 80%, with evidence of continued protection up to 23 years. The degree of protection was independent of age, sex, and the child's exposure to infection.

South India. A BCG prophylaxis study against tuberculosis in South India included the leprosy component, 5 years after the large-scale study involving 200,000 persons began (intake 1968–1971). An overall 25% protection against all forms of leprosy has been recorded in 5–12.5-year period. Two different strains of BCG (French and Danish) gave similar results. With a lower dose of BCG (0.01 mg) there was a lower level of protection, and with the higher dose (0.1 mg) there was higher level of protection seen against different types of leprosy in all age and sex groups.

Papua New Guinea. The intake period for the trial was about 1 year in 1963–1964 and involved about 5000 persons. At the end of 9 years of follow up, the efficacy rate of BCG was 46%. This trial was carried out in an area virtually free of tuberculosis and environmental mycobacteria.

Reasons for the differences. The differing results of the trials of BCG vaccine in leprosy were similar to the experiences with BCG against tuberculosis. Possible explanations include: a) differential exposure of the population to *Mycobacterium leprae* and other mycobacteria; b) differences in immunogenetic characteristics of the population; c) different strains of *M. leprae*; and d) BCG strains could vary with respect to their protective effect.

Animal models

The limitations of the mouse model in experimental situations to judge vaccine efficacy were highlighted. Conflicting results have been reported by different investigators. The participants suggested that additional animal models should be developed.

Ongoing trials

Venezuela. A large-scale trial was started in Venezuela in 1985, to test the ability of a vaccine based on a mixture of killed *M. leprae* and live BCG to protect against leprosy. Participants in the trial were selected from among the household contacts and

other close contacts of prevalent leprosy patients in three states of Venezuela. After initial skin testing with PPD and leprosy soluble antigens (LSA), about 30,000 contacts (aged 6–64 years) were randomized in a double-blind fashion to receive either BCG or BCG plus *M. leprae*. The trial population is being followed through annual surveys for the occurrence of leprosy; each year a sample of the participants are skin tested with PPD and LSA. To date, the incidence of leprosy in the trial population has been about 0.75 cases per 1000 per year, and no side effects to vaccination have been observed other than those normally associated with BCG. The skin-test studies show no differences in response to PPD between the two randomized groups, but large and significant differences in responses to LSA up to 3 years postvaccination (the maximum follow-up time to date). It is expected that sufficient cases will have occurred within the next 2 years to evaluate the initial protective effect against leprosy.

Malawi. The Karonga Prevention Trial is a randomized controlled trial of BCG and BCG plus killed *M. leprae* vaccine against leprosy (and tuberculosis). Among individuals without a BCG scar prior to entry into the trial, the protective efficacy of BCG plus killed *M. leprae* will be assessed against vaccination with BCG alone. In individuals with a BCG scar, the protective efficacy of repeat vaccination with either BCG or BCG plus killed *M. leprae* vaccine will be assessed, the initial vaccination with prior BCG being mostly several years ago. The intake phase started in December 1985, and is expected to be completed at the end of 1989. The first follow-up survey will take place from 1991 to 1994. First results can be anticipated by 1995.

ICRC vaccine. The ICRC bacilli, a group of leproma-derived cultivable mycobacteria, exhibit crossreactivity with *M. leprae* with reference to both B- and T-cell antigens. This forms the basis of their use in the vaccine preparation. It has been demonstrated that the ICRC vaccine brings about lepromin conversion in a proportion of lepromatous leprosy patients and in 95% of contacts. It also possesses immunotherapeutic potential. The vaccine is currently (from February 1987) undergoing a large scale immunoprophylactic trial in Maharashtra, India. It is a randomized, double-blind and controlled trial. The target population consists of 40,000 healthy household contacts of leprosy patients (all forms) between 1–65 years of age and of both sexes. The trial has two arms, a) receiving 1×10^9 radiation-attenuated ICRC bacilli and b) receiving one fifth the standard dose of BCG—the control arm. Lowering the incidence of the disease (all forms of leprosy) will be used as the criterion of the vaccine efficacy. The trial is expected to last 10 years. To date, about 20,000 contacts have been vaccinated. In addition, a separate large-scale study on immunotherapeutic efficacy is underway. Simultaneously, a vaccine containing a very high molecular weight (approximately 10^6) cell wall component of the ICRC bacilli is now undergoing Phase-I and Phase-II clinical studies.

M. w vaccine. *M. w* is a nonpathogenic, fast-growing, soil mycobacterium similar but not identical to mycobacteria listed in Runyon's Group IV. It shares several antigens with *M. leprae,* but has also additional cell-mediated immune-reactive antigens not present in *M. leprae.* An immunotherapeutic trial with this vaccine was initiated in December 1986 in two hospitals in Delhi. The patients were classified as having the LL, BL and BB types of leprosy and are bacillary positive, lepromin negative. All 89 patients reported to date received MDT; 52 of them were given, in addition, immunotherapy with the *M. w* vaccine. The first dose consisted of 10^9 autoclaved *M. w* bacilli. Repeat doses of 5×10^9 bacilli are to be given at 3-month intervals, up to 8 injections. Preliminary results are promising.

Proposed trial

South India. The Central JALMA Institute of Leprosy (ICMR) Field Unit, Madras, proposes to carry out a vaccine trial against leprosy to test the efficacy of three candidate vaccines: a) BCG plus armadillo-derived killed *M. leprae,* b) the ICRC vaccine, and c) the *M. w* vaccine. This trial would include 260,000 individuals from the Chingleput district, an area known to be hyperendemic for leprosy.

Laboratory support

Presently, there are no proxy indicators available to judge the efficacy of a vaccine.

The only method available would be to measure the protective efficacy in terms of reduction in the incidence of clinical disease. Recently, several *M. leprae*-specific antigens/epitopes have been studied as candidates for tools for the detection of infection with *M. leprae*. The ongoing, large-scale, leprosy vaccine trials provide ideal, well-characterized "population laboratories" for the evaluation of candidate assays. The initial observations suggest that several assays may have epidemiological value.

PGL-I antibody. Findings from Venezuela indicate a high relative risk of developing clinical disease in individuals with high levels of antibodies for the phenolic glycolipid. However, this type of survey would not be useful as a screening test to identify high-risk individuals since a large proportion of cases came from individuals with low levels of antibody response. Findings from Malawi, which are of a cross-sectional nature, do not indicate any predictive value for the PGL antibodies; the levels are similar in contacts as well as noncontacts.

Skin-test antigens

M. leprae-derived soluble antigens, particularly the Rees and the Convit antigens, are being used for research purposes. Results from Venezuela show that the Convit antigen indurations are positively and strongly correlated to the Mitsuda antigen late reactions. However, results from Malawi and India bring out the deficiencies with these antigens in terms of reproducibility, sensitivity, and specificity.

Development of second-generation subunit vaccines

The recent application of recombinant DNA technologies, together with the availability of *M. leprae*-specific monoclonal antibodies and the ability to derive *M. leprae*-specific T-cell clones, has led to the identification and characterization of at least six major protein antigens from *M. leprae*. Based on this approach, the identification of those antigens which are capable of evoking an appropriate cellular immune response in man should contribute to the development of a new generation of leprosy vaccines. Several groups are actively engaged in attempts to introduce genes coding for mycobacterial antigens into various potential vaccine vehicles, including vaccinia virus, BCG, and Salmonella. In addition, several recent reports suggest that *M. leprae* cell-wall-associated antigens may be candidates for a subunit vaccine.

Methodological and design issues

Like most vaccine trials, those for leprosy should, in general, include: a) prior evidence of protection as, for example, from animal studies, sensitization studies, etc.; b) selection of trial area, trial groups and determination of sample size; c) choice and definition of "control" and vaccine groups and dose of vaccine; d) revaccination criteria, when indicated; e) procedures for avoiding bias, such as randomization, coding, "blinding," etc.; f) exclusion criteria; g) standardization of leprosy diagnosis; h) quality control of vaccines and field procedures; i) resurveys and provision to monitor adverse effects; j) information system, including data processing; and k) duration of trial and rules for stopping.

Additional epidemiological information from vaccine trials

While the trial should, in principle, concentrate on its specific objectives, the population base and the resources deployed permit, in general, the gathering of critical epidemiological information (such as trends in incidence rates) with very little additional effort. Such information is generally of value in interpreting the trial results. Care should be taken that this extra effort is kept separate and does not interfere with the conduct of the vaccine trial.

Conclusions

Vaccine trials should be carried out simultaneously in different areas of the world with uniform methodology which includes procedures, vaccines and doses.

At least one large-scale trial should compare the three candidate vaccines currently available, BCG plus killed *M. leprae,* the ICRC bacillus, and the *M. w* bacillus.

Serious consideration should be given to immunotherapeutic and immunoprophylactic trials in view of their importance to control programs.