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BCG : DO WE HAVE AN ALTERNATIVE

Vaccination is generally used as a form of immunoprophylaxis, so that administration of the vaccine even a long time before exposure to the wild-type infectious organism should afford protection. Since effector T and B cells are short-lived, a prime requisite for a vaccine is to generate immunological memory.[1] In the case of organisms such as mycobacteria which are obligate intracellular pathogens and which elicit granulomatous tissue reactions, artificial immunisation with live bacteria is required to induce protection.[2,3] The only existing vaccine against tuberculosis is the BCG (Bacille Calmette - Guerin), an attenuated strain of *M.bovis* and it is mandatory or officially recommended in 182 countries or territories. Under the Expanded Programme on Immunisation (EPI) started by the Government of India in 1978, BCG is recommended to be given to all infants 3-9 months after birth.[4]

History of BCG Vaccine

The history of BCG vaccination and the trials conducted to assess its effectiveness in humans have been reviewed by many workers.[5-10] BCG, the bile-tolerant, attenuated strain of *M.bovis*, was isolated by Calmette and Guerin.[11] Ox-bile was originally added to these cultures to prevent clumping of bacilli. This led to the fortuitous observation that growth in the presence of bile also resulted in attenuation or gradual loss of virulence. Such attenuated organisms will multiply only to a limited extent in the animal or human body and can bring about an increase in the resistance of the host to a subsequent fully virulent infection by the same or other antigenically closely related organisms. Calmette further attenuated this strain by cultivation of the organism on a potato-glycerol-bile medium for 230 serial transfers between the years 1908 and 1918.

The bacilli resulting from this attenuation have never been cloned. The original strain of BCG has been lost and has been replaced by a variant while it was being transferred serially on artificial culture media at the Pasteur Institute[12] and have since been maintained by many different laboratories, using many different methods. As a result, the BCG strains used today are not bacteriologically identical.[13,14] In 1966, a WHO Expert Committee on Biological Standardisation adopted a series of recommendations for the production of BCG vaccine.[15] These recommendations stated that the vaccine should be freeze-dried, and that the vaccine strain should be maintained by the seed-lot-system whereby no vaccine is produced from a seed more than 12 passages removed from a primary freeze-dried lot. Such a method of maintenance was soon adopted by

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most laboratories and this eliminated the possibility of more attenuated variants in later BCG vaccine lots.[16]

BCG Vaccine Production in India

In India, the BCG Vaccine Laboratory was started in Madras in 1948 for the production of BCG vaccine for use in India and also for supply to some of the neighbouring countries. Since 1966, Danish strain 1331 is being used here for the preparation of both the liquid and the freeze-dried BCG vaccines, based on the seed-lot-system[17].

For preparing the liquid and freeze-dried vaccine, the BCG Laboratory, Madras, uses the method followed at the State Serum Institute, Copenhagen, but using Sauton potato medium for maintaining the BCG strain. The prepared vaccine is tested for purity by Ziehl-Neelsen smear for acid fast bacilli, and by culture on nutrient broth, thioglycollate medium and Sabouraud's agar medium. Total bacterial count and the number of culturable particles in the preparation are estimated. Biological tests are carried out in guineapigs to estimate the degree of virulence of the BCG vaccine, allergenicity and safety. In addition to the above tests, in the case of the freeze-dried vaccine, tests are carried out to estimate residual moisture and heat stability. Both types of vaccines are to be stored at refrigeration temperature, protected from light. Under these conditions of storage, the liquid vaccine can be used for 4 weeks from the date of manufacture while the freeze-dried vaccine can be used for 3 months.

BCG can be administered intracutaneously, orally, by scarification or by multiple puncture. The most widely used method of administration is by intracutaneous injection. The dose is usually 0.1 ml and the site of injection is the upper arm. In the newborn, the dose used is 0.05 ml. The liquid BCG vaccine prepared by the BCG Laboratory, Madras, is to be administered by an intracutaneous injection of 0.1 ml of the vaccine containing 0.075 mg (moist weight) of BCG. The freeze-dried vaccine prepared here is reconstituted by the addition of sterile distilled water or sterile saline to contain 0.1 mg (moist weight) in 0.1 ml of vaccine which is given intracutaneously.

Efficacy of BCG Vaccine

BCG was used successfully in humans for the first time in 1921 by Weil-Halle, a colleague of Calmette and Guerin.[18] Scepticism concerning the safety and efficacy of BCG vaccine, and the Lubeck disaster in which 72 of 240 children vaccinated with BCG died as a result of being fed a batch of vaccine containing virulent tubercle bacilli, delayed the acceptance of BCG. A series of controlled trials were begun in the 1930s. Despite inconsistent results from the trials, WHO encouraged widespread dissemination of BCG vaccines, starting in the 1950s.[7] By the 1970s, BCG became the most widely used vaccine in the world. About 3 billion doses have been given in the last four decades, and more than 70 per cent of the world's children now receive BCG.[5,19]

Between the years 1935 and 1955, at least eight controlled trials were conducted to assess the efficacy of BCG vaccine against tuberculosis. The protective efficacy obtained ranged from none to 80 per cent (Table).[8]

Table: Protective efficacy of BCG vaccine against tuberculosis

Population group	Period of intake	Protective efficacy (%)
North American Indians	1935-1938	80
Chicago infants	1937-1948	75
Georgia school children	1947	None
Illinois children	1947-1948	None
Puerto Rico general population	1949-1951	31
Georgia and Alabama general population	1950	14
British children	1950-1952	78
South Indian rural population	1950-1955	31

The South Indian Trial

A study was started in Chingleput, south India, in 1968 in an attempt to avoid the methodologic errors that might have affected previous trials.[10,20,21] The south Indian BCG trial was organised by the Indian Council of Medical Research (ICMR) in collaboration with the WHO and Centre for Disease Control (CDC), US Public Health Services. The intake for the study started in 1968 and was completed in 1971, including about 2.6 lakh participants out of a population of 3.6 lakhs. The entire population of all ages was eligible and tuberculin reactors were not excluded, in contrast with

previous trials. Two BCG strains, Copenhagen and Paris, were tested at two doses, 0.1 mg and 0.01 mg. Neither of the vaccines, whether in full or reduced dosage, had given any protection against the bacillary form of pulmonary tuberculosis as assessed over a 7.5 year follow up period. No data are available from the study to evaluate protection in children. Very little disease was observed in the period immediately after infection.[22] Incidence peaks were absent in young children and in young adults but the incidence increased logarithmically with age.

The findings of the south Indian trial were disappointing. The ICMR convened an expert committee meeting to scrutinise the trial methodology, wherein it was agreed that no errors in the conduct of the field operations or in the data processing could have been so serious as to invalidate the results.[10] In the first meeting of the ICMR/WHO Scientific Group[23] it was stated that the data obtained in this trial are unique and of great importance for tropical countries, and should be considered as the starting point for further intensive investigations into the epidemiological, bacteriological and immunological problems related to BCG vaccine and tuberculosis, as well as studies to test certain hypotheses, *eg*, that the immune response of the population was unusual, that the vaccine were inadequate to confer immunity, that the south Indian variant of *M. tuberculosis* acted as an attenuated immunising agent, and that mycobacteria other than *M. tuberculosis* may have partially immunised the study population.

Explanations for the Varying Efficacy of BCG

The explanations and hypotheses for the varying efficacy of BCG have been discussed in detail[5-7]. BCG's varying efficacy due to interactions with the immune responses to other mycobacterial infections still remains one of the most popular explanations. Palmer and associates[24,25] showed in animal experiments, and in studies of US navy personnel, that infections with certain non-tuberculous mycobacteria could impart some protection against infection with the tubercle bacillus and such naturally acquired protection could mask any protection due to BCG vaccination, partially or totally. This explanation was criticised by Hart[26] as being inadequate to explain all the differences between the various BCG vaccine trials. Comstock *et al*[27] also could not find any evidence for lowered protection by BCG in those with intermediate levels of tuberculin reactivity, and this was thought to be due to non-tuberculous mycobacterial infection, in the Puerto Rico trial.

In the 1980s, Rook, Stanford and associates[28-30] proposed that exposure to non-tuberculous mycobacteria (NTM) can result in two types of cell-mediated responses, the 'Listeria type' and the 'Koch type'. Which of these two types of responses is evoked depended, among other factors, on the mycobacterial species inducing the response and the immunomodulating cells and the pathway brought into play. They further proposed that the 'Listeria type' of response enhances the protective effect of subsequent vaccination with BCG while the 'Koch type' response opposes the protective effect of BCG. Once Koch-like responsiveness is present, this blocks subsequent recognition of further species by Listeria-like responses. BCG vaccination of a person with a pre-existing Koch-like response will temporarily boost this response, but completely fail to reconvert to Listeria-like responsiveness or induce protection from pathogenic challenge. According to them, this is likely to have been the situation in the south Indian trial.[31,32]

Investigations carried out since then have been able to produce some evidence supporting the hypothesis that infection with NTM induces a protective response and does not interfere with the immunity produced by BCG. Attempts to demonstrate that prior infection with any of the mycobacteria induced a suppressive effect against BCG have failed.[33-36]

The study population in the south Indian BCG trial was characterised by a very high prevalence of nonspecific sensitivity.[37] Further, nearly 20 per cent of the NTM obtained from sputum samples of subjects in this area belonged to the *Mycobacterium avium-intracellulare-scrofulaceum* (MAIS) complex,[38] and a recent study on the isolation profiles of environmental mycobacteria present in soil, water and dust samples, and sputum samples of symptomatics in this area has shown that isolates belonging to the MAIS complex are predominant in water, dust and sputum samples while organisms of the *M.fortuitum* complex are predominant in soil samples.[39]

The hypothesis that oral immunisation with *M.avium intracellulare* complex might induce tolerance which

might interfere with the immune response to subsequent BCG immunisation was studied at the Tuberculosis Research Centre (TRC)[40] in guineapigs challenged with *M.tuberculosis*, and it was found that there was no interference with the protective immunity induced by BCG. A later study using intradermal route showed that while there was no interference with the immunity due to BCG by prior exposure to NTM on the early course of challenge infection, modulation could be taking place during the later course.[41]

The variation in the efficacy of BCG has also been attributed to the differences between the BCG preparations.[42,43] Another view is that BCG is more effective in stopping haematogenous spread of the bacteria as occurring in primary progressive disease and endogenous reactivation versus exogenous reinfections.[44] Other explanations include the genetic or physiological differences between the trial populations.

More recently, another explanation for the varying efficacy of BCG has been proposed based on the observation that a subgroup of the population may be actually adversely affected by vaccination.[45] Several trials include in the assessment many subject with weak initial tuberculin sensitivity, due either to environmental mycobacterial infection or to infection with *M.tuberculosis*. While it is accepted that vaccine efficacy may be moderately reduced in the former subgroup, it has been postulated that the lattar subgroup may be at risk of reactivation of tuberculosis soon after vaccination perhaps from focal reactions due to enhancement of their weak sensitivity. The low levels of efficacy in several trials, and the early adverse effect in the south Indian trial are broadly consistent with this hypothesis.

In a search for identifying the correlates of vaccine-induced protective immunity, more than 70000 subjects in northern Malawi were skin tested with soluble antigens of the tubercle and leprosy bacilli, and then followed up for 5 years for tuberculosis and leprosy incidence. Incidence rate ratios were calculated to compare subjects with different levels of prior skin test sensitivity.[46] It was found that delayed type hyper-sensitivity to mycobacterial antigens has different implications for tuberculosis and leprosy: low level hypersensitivity, probably attributable to environmental mycobacteria, was associated with protection, but persistent vaccine associated hypersensitivity to mycobacterial antigens was not a correlate of vaccine derived protection against mycobacterial diseases.

BCG Vaccination and HIV Infection

With regard to BCG vaccination in HIV infected individuals, there are reports of BCG abscesses in HIV seropositives, and of disseminated infection due to BCG in at least one case given BCG.[47] However, in all these cases,, the infection could be successfully treated. Since the risks and known consequences of natural infection with tubercle bacilli are likely to be more serious than the risks associated with live attenuated vaccines, the WHO has recommended that all asymptomatic HIV infected children should receive all standard vaccines both live and inactivated; and those with symptoms of AIDS Related Complex (ARC)/AIDS should receive all vaccines other than BCG. However, in developing countries like India, where extensive HIV testing is not possible, the WHO Expert Group has recommended that all infants should continue to receive immunisation against all the major preventable diseases.[48]

There is no evidence that BCG activates HIV infection.[49] Further, it has been observed that the incidence of disease due to *M.avium intracellulare* (MAI) in AIDS patients varies from region to region and it has been postulated that this difference is the result of a protective effect of neonatal BCG vaccination.[50] In the USA, 30 per cent of patients with AIDS develop MAI disease in contrast to only 10 per cent of AIDS patients in Sweden. This difference in incidence between the two countries could be due to BCG vaccination: most Swedish patients with AIDS would have received BCG in infancy while those in the USA would be unvaccinated. This is further supported by the fact that over 50 per cent of AIDS patients in Netherlands, where BCG vaccination is not given, developed disease due to MAI or *M.scrofulaceum*. Also, in a limited follow up of HIV infected individuals at the TRC, Madras, it has been found that while a few HIV infected individuals developed disease due to *M.tuberculosis* no case has been encountered so far with disease due to MAI (Tuberculosis Research Centre - Unpublished observations). It has been suggested that MAI disease in AIDS is not due to direct infection but that it arises from long standing silent foci of MAI in the lymphatic tissue of the patient.[51] It is possible that neonatal BCG vaccination prevents overt infection by MAI and may

therefore prevent inapparent persisting infection of lymphoid tissue thus removing the internal reservoir of these bacilli from which AIDS-related MAI disease may arise later in life.[52]

BCG as an Immunopotentiating Agent

The widespread use of BCG has demonstrated its safety and its potent immunogenicity. This has also led to its suggested use as a carrier to vaccinate against other diseases.[53,54] BCG and other mycobacteria are highly effective adjuvants. It is one of the few vaccines that can be given at birth, and with a single dose it induces long-lived immune responses. Till now, nearly 3 billion vaccinations have been carried out using BCG with a long record of safe use in man. There is also a worldwide distribution network with experience in BCG vaccination. The adjuvant properties of BCG and its cell wall components have previously been made use of in experimental vaccines. Mixtures of BCG and schistosomal antigens have been used successfully to protect mice in a model of schistosomiasis.[55] Mixture of muramyl dipeptide, which is one of the mycobacterial cell wall components that contributes to the adjuvant properties, and killed simian immunodeficiency virus (SIV) has been shown to provide partial protection against SIV infection in monkeys.[56] Mixtures of BCG and killed *M.leprae* have been used in large scale trials to assess the efficacy of this leprosy vaccine candidate.[57]

Recombinant BCG and BCG as a Multiple Vaccine Vehicle

Recently developed genetic engineering techniques for mycobacteria have provided the means for the introduction and expression of foreign genes in BCG.[53,58] Recombinant BCG vaccine vehicles can induce immune responses to foreign proteins produced by the bacillus, indicating that BCG can act simultaneously as an adjuvant and as a vehicle to produce and deliver specific antigens to the immune system. A BCG recombinant may provide a longer lasting immunity to a pathogen than a simple mixture of BCG and the antigen because the antigen continues to be produced by BCG multiplying in the host.

There is no ready answer for the question whether there is an alternative for BCG vaccine for protection against tuberculosis. It is possible to improve the protective efficacy of the existing BCG vaccine against tuberculosis by using the tools of genetic engineering even though very little has been achieved in this direction to date. Such an approach requires a full understanding of the factors important in the virulence of *M.tuberculosis*, pathogenesis of tuberculosis, and protective response against tuberculosis. Genetic deletion or modification of mycobacterial virulence factors or the addition of appropriate mycobacterial antigens important for protection might improve the effectiveness of BCG as an antituberculosis vaccine.

CONCLUSION

Fine and Rodrigues[7] state that several factors, especially the differences in BCG strains and regional differences in mycobacterial ecology, in addition to differences in trial methods, have all contributed to the observed variation in BCG's efficacy. They conclude that despite our inability to predict its precise effect, BCG is still judged worthwhile in many countries because there is a possibility that the vaccine might provide reasonable levels of protection against childhood forms of the disease in most populations.[7] Recent retrospective studies of BCG vaccine efficacy among newborns and children have reported a protective effect against all forms of tuberculosis ranging from 17 to 90 per cent, and protection against tuberculous meningitis and against cavitary, miliary and bone and joint tuberculosis has been estimated to be 75 per cent or greater.[59-61] BCG vaccine, when effective, apparently does not prevent infection but interferes with the haematogenous spread of tubercle bacilli, thus reducing the risk of severe primary disease and its complications.[60] A meta-analysis of 14 trials and 12 case-control studies showed that the protective effect of BCG against tuberculosis was 51 and 50 per cent respectively.[62] Combining data from 7 trials reporting on deaths from tuberculosis, the relative risk for death among the vaccinated was 0.29 (71% protective effect). Five case-control studies reporting on tuberculous meningitis showed a 64 per cent protective effect, and 3 case-control studies reporting efficacy of BCG in preventing disseminated tuberculosis showed a 78 per cent protective effect. The conclusion was that BCG reduces the risk for active tuberculosis on an average by 50 per cent, and the risk for tuberculosis death, meningitis and disseminated tuberculosis. The fact that

BCG provides variable though significant protection against leprosy increases its value in those countries with high prevalence of leprosy.[63]

It has been concluded that vaccination alone, at least with the present vaccine, cannot substantially influence the epidemiological situation but should be continued for children when its use is justified for prevention.[64] BCG vaccination of the newborn usually protects against serious forms of tuberculosis, is safe and cheap and should be used in developing countries, including India, where tuberculosis is more prevalent. In such highly endemic areas, due to the frequent occurrence of exogenous reinfection and also due to the waning of protective effect over the years after vaccination, BCG vaccination of the newborn may not offer protection in the later years of life when revaccination, perhaps at the school going age, may have to be considered. In developed countries with low prevalence of tuberculosis, BCG should be given to high risk groups such as immigrants, their newborn, contacts of patients with tuberculosis and hospital staff.[65]

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GOI - BCG/TB policy

DIRECTORATE GENERAL OF HEALTH SERVICES
NIRMAN BHAVAN, NEW DELHI 110 011

No.T-18020/6/80-TB 26th Aug.,1980

From: The Director General of Health Services

To : All Directors of Health Services
of States/Union Territories

Sir,

Sub: The new policy of BCG vaccination in the National Tuberculosis Control Programme

As you are aware, the BCG vaccination programme has been in operation in our country for the last 30 years. The vaccination was initially offered to all persons negative to tuberculin tests and later to all persons in the 0-19 years age group without any tuberculin test. The strategy of BCG vaccination programme was to cover the entire susceptible population initially by a mass campaign and thereafter to maintain the protective effect of BCG vaccination in the community by covering the young population added by new births regularly through the general health services.

To make BCG vaccination routinely available in the general health service, therefore, the BCG vaccination policy of the country was revised about three years back and it was decided that: 1977

1) The mass BCG vaccination teams should be disbanded and the technicians of these teams should be posted in Primary Health Centres and sub centres for training of all the para-medical workers in the rural areas in the technique of BCG vaccination.

problem during ① Mass campaign ② Transition ③ Omitted

2) In future, BCG vaccination will be performed by the multipurpose health workers like basic health workers, ANMs, etc. in their respective areas of responsibility under the expanded programme of immunization.

3) The multipurpose workers will cover the infants within 3-9 months of their birth rather than immediately after birth, as tuberculin conversion after vaccination immediately after birth has been found to be unsatisfactory and BCG vaccination within 3-9 months after birth is operationally convenient for the multipurpose workers in the EPI, as this can be performed at the time of giving any of the three doses of DPT vaccine.

4) In urban areas where BCG vaccination of the new borns immediately after birth has been in operation for a number of years because the new borns are available in the maternity institutions immediately after the mother's confinement, and once the mother leaves the hospital, it is difficult to contact the child, new born vaccination immediately after birth may continue.

The recently published results of the BCG trial of the ICMR in the Chingleput district have created some doubt in the minds of various members of the profession about the use of BCG vaccination. The results have shown that BCG vaccination failed to prevent emergence of infections pulmonary tuberculosis cases in the vaccinated group in the trial. However, the direct benefit of BCG vaccination is in the reduction of the incidence of clinical forms of tuberculosis diseases following upon primary infection, like miliary tuberculosis, meningeal tuberculosis, bone and joint tuberculosis, tuberculosis lymph adenitis, etc. The Chingleput study has not provided any definite evidence, one way or the other, regarding effectiveness of

BCG in preventing such clinical diseases after primary infection, whereas other scientific BCG studies suggest that enough protection is indeed conferred by BCG vaccination against these types of clinical tuberculosis manifestations that are mostly prevalent in infants and children.

Our revised policy of BCG vaccination therefore continues unchanged. All the para-medical workers in the rural areas who are going to be the multipurpose workers under the Expanded Programme of Immunization(EPI), should be expeditiously trained in the technique of BCG vaccination. The training methodology has already been circulated vide Government of India letter No.18011/1/77-PH dated 24.5.1977. During training, the trainess are to perform the vaccination in the thicker skins of higher age groups first and gradually go down to the very thin skin of the new borns. This has been done with the purpose of properly training the para-medical workers for intradermal vaccination in the very thin skins of the new borns and infants and also in the process of such training, to cover the backlog of unvaccinated population in the 0-19 years age group that is still available in the rural areas.

When the expanded programme of immunization is implemented in any district, the target age group to be covered under the programme should be all the infants within 3-9 months of their birth as per the recommended immunization schedule.

In urban areas where new born BCG immunization immediately after birth is being practical for a long time, the same may be continued for operational convenience.

The age groups to be covered under BCG vaccination in urban and rural areas have in fact been clearly explained in this Directorate circular No.12-16/75-TB dated 21.2.78, that has been circulated to all the AMOs, TB Officers and Directors of Training and Demonstration Centres in all the States and U.Ts.

One BCG vaccination performed properly within the first year of life is considered to be adequate, as the protection afforded lasts for several years. Revaccination at subsequent years of life is therefore not being considered at present.

I would request you to kindly bring the above instructions to the notice of all persons engaged in BCG vaccination and others responsible for implementation of the EPI in your State including paediatricians, District and State TB and EPI Officers, PHC Medical Officers, etc.

Yours faithfully,

sd/-
(Dr B. Sankaran)
Director General of Health Services

NTI Lib Ref

TB very much a set: 1) The blind man & the elephant

(1)

DGHS Bulletin for Sept. 1952

- Devoted to the Prevention of TB.

Issued by TB Section DGHS, MOH, GOI

Report of TB Subcommittee of the Health Panel of the Planning Commission is

- emphasised value of preventive measures in anti TB progr. - expected to yield maximum results for min. funds in shortest possible time

BCG - used extensively in western countries & has proved its value - reliance on what has supposedly worked before Gupta & (ie 1948) Mikkelsen work is given top priority.

BCG campaigns in India started in assistance of Joint Calcutta & now assisted by WHO/UNICEF. Despite some controversy in earlier stages, BCG now demanded by Dr's, public men & social service inst. overcame local resistance

Progress record of BCG campaigns encouraging - 8 States - UP, Punjab, Madras Board, Bombay, Travancore-Cochin, HP, Behar, Ajmer & Bhopal carrying on mass vaccin campaigns. five States

States of Mysore, WB, Hyderabad & Bihar expected to start similar campaigns during the year (ie 1952) while the rest will have mass campaigns started by end of next year.

BCG vaccine lab of GOI has expanded considerably & is producing all the vaccine upto the campaign. 87 Trained teams in 71 Dts & 408 the personnel engaged in field work. Till end June '52 >89 L persons Tted & >28 L BCG vaccinated.

Col. Lakshmanan DGHS said at BCG Conference last year that BCG vaccin is to materially influence epidemiology of TB in India it is necessary to vacc. all / majority of tuberculin-ve cases in shortest time. This is the essence of the BCG campaigns

Est 170 mill people < 20 yrs - majority should be Tted & BCGed in next 5-7 yrs. Its major effect in reducing the

+ effective HE progr, + efficient planning, organi: & execution of progr. on the State BCG workers' rests the layer responsibility of making the campaign a success & bring true enslavement of in effecting the epidemiology of TB in India

Report

BCG 1st place in list of priorities "prevention measures would yield the best return for the limited resources now available."

"TB is a major health prob in India -- apart from being a communicable dis, it has great repercussions on economic & social life. In the economic field it attacks wage earners at a period of their greatest productivity. In social life it devastates families causing incalculable suffering for the indi & the family ..."

"There are abt 500,000 deaths every year in India d/o TB & 25,00,000 are suffering from active disease

no signs of realistic ness!

Conds favourable for the spread of infection & high mortality are all too common. Std of living is low, housing conditions are poor & inadequate. There is malnutrition. Hygienic conds are far from what they should be.

"Economic implic's of these figures broadly stated in terms of man days lost is abt 900 - 1000 mill. days, accepting a very conservative estimate of loss of 1 year per sufferer. The loss in terms of money will be incalculable."

Radical measures to combat TB :— The improvement of the general std of living, provision for the isolation + Rx of the sufferer, + introduction

of preventive measures, are the Bumps. measures needed for controlling TB. As TB is an infectious dis & is transferred from the diseased person to the healthy, the best way to deal with the problem is to isolate all infectious pts i.e. TB instn. But the attainment of this objective has not been achieved in any country of the world & this India existing trends negate the possibility of attempting satisfactorily isol of even a reasonable proportion of our infectious cases. . . .

Priorities evolved by the committee

The committee recommended a list of priorities In order these are — (1) BCG vaccin (2) Chest & Domiciliary Services (3) Tng & Demonstr. Centres (4) Beds for resl'y Rx (5) After Care & (6) Research.

Committee further recommended & these be supplemented by (a) all organisns employing large no of workers, providing facilities for the care of their TB pts by adding beds to existing institutions / starting new institutions (b) ESI extending its scope to cover Rx of employees dis. TB (c) Universities & educ instns laying a small fee for medical relief & earmarking part of this for students & TB (d) encouraging non-official org's to establish & run TB instns & Govt giving them grants for bldg & maintenance, provided these institutions are run on sound lines & on a non profit basis.

Report clearly emphasises that BCG alone cannot control TB. But it is however true that if the BCG scheme is pushed forward — it can substantially & progressively ↓ the future bed. reqts.

State planners interests ← national level resource use, needs etc
patients interests idl / human level
? Subsidising - need to be championed by other organisations

Source: Bulletin: devoted to the prevention of tuberculosis, Vol I No 2
Tuberculosis Section, DGHS, MOH, GOI, N Delhi. Sept. 1952.

GOI - BCG/TB policy

WITH B.C.G. THERE IS HOPE

(Excerpt from the Paper read at the Commonwealth Medical Conference, Calcutta, by P.V. Benjamin, M.B.B.S., T.D.D.)

Why B.C.G. Vaccination has been allotted such a high priority in the scheme (of Planning Commission) is a legitimate question, especially because this is not used extensively in the United Kingdom or America or in some of the more advanced countries of the Commonwealth. Tuberculosis has been controlled without B.C.G. in many countries and some eminent epidemiologists have even questioned the wisdom of giving so much importance to B.C.G. Vaccination as this may, in their opinion, distract attention from other important measures which have proved their value and without which tuberculosis cannot be controlled. At the outset it may be stated that those who advocate B.C.G. Vaccination in India do not consider that B.C.G. alone can control tuberculosis. They do not overlook the fact that B.C.G. is only one of the measures for tuberculosis control and that the other accepted methods such as the provision of institutions for diagnosis, treatment and isolation are essential and should not be neglected.

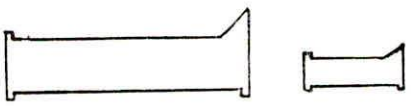
What India needs by way of tuberculosis institutions is 3,000 to 4,000 clinics and 500,000 beds. As against this need we have only 110 clinics and about 10,400 beds. It is estimated that about 450 crores of rupees will be required for the establishment of the minimum number of institutions and about 60 crores of rupees a year to run them. The present annual expenditure in the whole of India for tuberculosis work is not more than 2 crores of rupees. It is against this background that the question of B.C.G. Vaccination in India is to be viewed. We are proceeding on the assumption that if B.C.G. Vaccination programme is carried out extensively and systematically, that is, if at least 80% of the tuberculin negative individuals in the country are vaccinated during the next five to seven years, a reduction in the tuberculosis morbidity and mortality in the country to 1/2 to 4/5 of what is at present can be anticipated in about 20 years' time. But it should be emphasised that it would be too much to expect that B.C.G. alone can make any appreciable effect on the epidemiology of tuberculosis unless it is carried out on a mass scale and in the shortest possible time. Where infection is widespread and the conditions for its transference from one person to another are widely prevalent, vaccination of a few thousands here and there cannot materially change the trend of tuberculosis mortality in the country as a whole, though it will, undoubtedly, have some effect on the small groups vaccinated. Even in England and America it is now recognised that B.C.G. Vaccination should be offered to groups especially exposed to tuberculous infection such as medical students, nurses and those children living in tuberculous homes. In India, as could be judged from the tuberculin reactions, practically the whole population especially those who live in the cities and urban areas are exposed to tuberculous infection.

Dr. P.V. BENJAMIN

The author of this contribution is the Adviser-in-T.B. to the Government of India and Technical Adviser to the Tuberculosis Association of India, New Delhi.

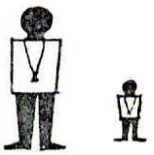
It is estimated that in India there are about 170 million persons below the age of 20 and about 17 to 20 millions of these are in the urban and semi-urban areas. The Planning Commission has accepted the principle of mass vaccination and has directed that the initial effort should be made in the urban and semi-urban areas and extended whenever possible to rural areas. To carry out this programme the Government of India is providing the advisory and co-ordinating staff, tuberculin and B.C.G. vaccine and the budget provision for this purpose for 1952-53 is Rs. 4 lakhs. The UNICEF is providing the necessary equipment and the WHO the foreign personnel needed. They have already allotted or spent $ 760,000 on this account. The State Governments have to provide the necessary local staff and the running expenses in their areas and it is estimated that 19 to 20 lakhs of rupees per year have to be spent by all the States on this programme. If B.C.G. Vaccination is carried out on a mass scale and if the programme of building institutions is pursued simultaneously it will give the country the immediate benefit of reducing the incidence of the disease, thereby lessening the number of institutions required in the country by about 50 to 70%. This will also give time to build up the necessary institutions. Without B.C.G. Vaccination the prospect of tuberculosis control in India under the present circumstances is very depressing, but with B.C.G., there is hope of achieving it within a measurable time.

BEDS

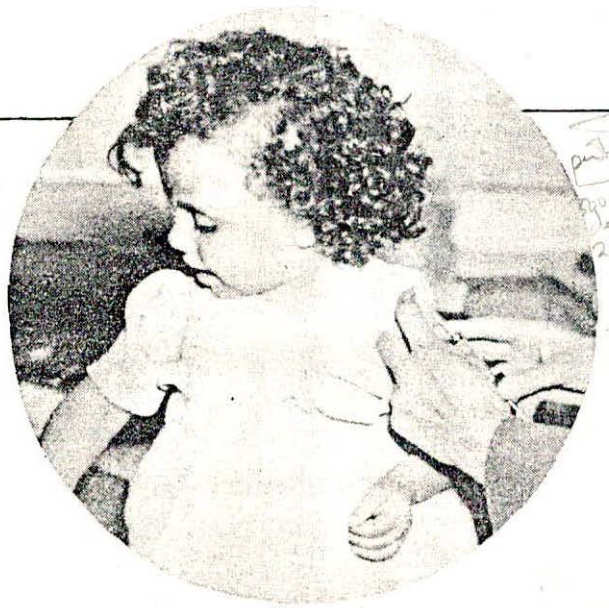


India requires 5 lakh beds for isolation & treatment of its 5 lakh T.B. patients. As against this only 10,400 beds are available.

DOCTORS



To man the required number of T.B. institutions India requires 15,000 qualified Doctors. As against this only 150 are available.



treatment now-a-days. This is specially so, because greater advances in the medical care of scuh people have helped much in the salvaging and even in the permanent cure of patients who at one time would have considered themselves doomed if they had been infected by the T.B. germ. Now, if proper treatment and precautions are taken in time, not only is the patient helped to recover but his assistance is taken so that the disease is not communicated to others. Thus the erstwhile rapid spread is soon prevented.

The successful rehabilitation of the patient when he is ready for it requires all the skill and care of the Social Workers concerned. On them finally rests the future happiness of people who have faced tragedy, but have also been assisted to over-come it. This they can accomplish only if they get the full co-operation of the community and the government of the country concerned.

The Ministry of Health at the Centre and some at the local levels, also the T.B. Association in India, have done much to rouse consciousness about the social aspects of this disease both through dissemination of pertinent facts and the training of appropriate personnel. They have to their credit, as being almost one of the first Public Welfare Departments in India that has recognised the importance of a team approach to the prevention and cure of Social problems.

In the promotion of a sound Health programme which is their major responsibility, they have also included the contributions that can be made by social workers, both by training them and appointing them as funds allow. It is hoped that other Departments will soon follow their example and accept the fact that Man is a social animal and therefore cannot be served in water-tight compartments. He has many more needs than the merely physically and materially visible ones. These social and emotional needs can only be adequately tended to by social workers who are equipped with special knowledge and skill to do so.

Lt. Col. C.K. Lakshmanan, the new Director General of Health Services, Government of India.

"It is obvious that India cannot find for many years to come the finances or the personnel needed for the anti-tuberculosis measures of the type which has been used and found successful in the more advanced countries of the world. We have to take advantage of every possible preventive measures which can be introduced in our country without much capital outlay and which will not need a large number of highly qualified doctors and nurses. This is the time when B.C.G. has come to its own and is being widely used as a preventive measure in many countries in the world. This is a method which can be introduced fairly quickly and at comparatively little cost. The country has now the experience of over 3 years in tuberculin testing and B.C.G. Vaccination by different groups in the various parts of India. There is a general awareness of the seriousness of the tuberculosis problem in the country and there is constant demand for introduction of anti-tuberculosis measures. The response for B.C.G. Vaccination has been very good, and in fact we are at present not in a position to cope with the demand as quickly as we would wish, though there had been criticism and objection to this vaccination from certain quarters."

C.K. LAKSHMANAN,
Lieut. Colonel

B.C.G. IN THE PREVENTION OF TUBERCULOSIS*

A.C. UKIL, M.B., M.S.P.E. (Paris), F.C.C.P.,
F.S.M.F.B., F.N.I., F.A.S.

Apart from general and health education and improvement in the standard of living including housing, a sound plan for the control of tuberculosis should have the following objectives, viz., (1) the prevention of spread of tuberculosis from known infectious cases; (2) the protection of groups highly exposed to tuberculosis and most likely to get the disease; and (3) the furthering of all other preventive and curative measures including after-care and rehabilitation.

The application of protective vaccination is meant to meet the second of the above objectives. The isolation of infective cases may be the most important method in checking the spread of tuberculosis; but, being a costly programme, it may not be possible for an under-developed country like India to provide a sufficient number of beds for the purpose within a short period. Hence. we have to think of a method which does not involve a large expenditure and which can be fairly rapidly carried out. The use of a suitable protective vaccine against tuberculosis naturally arises in our mind. The only practical way so far known for producing specific resistance against tuberculosis, even if this resistance is not absolute, is B.C.G. Vaccination. However, the full effectiveness of B.C.G. Vaccination will be achieved only if it is carried out as part of a general programme of tuberculosis control.

After working persistently for over 13 years, Drs. Calmette and Guerin, two French bacteriologists working at the Pasteur Institute in Paris, were able to prepare a vaccine with a living but weakened variety of tubercle bacillus which has proved to be permanently harmless for man and animals, at repeated trials extending over 20 years. The term B.C.G. is derived from the first letters of the name of the vaccine, which was Bacillus of Calmette and Guerin. The speaker, having been a former associate of Professor Calmette, personally tested the harmlessness of the bacillus and the efficacy of the vaccine and the findings were published in a series of papers between 1927 and 1946. At the present time, the methods of preparation and standardisation have been so perfected by skilled workers in special laboratories solely devoted to this work that its harmlessness is assured. In India, the vaccine is being manufactured according to international standards in a special laboratory at the King Institute of Preventive Medicine, Madras.

Dr. A.C. UKIL

The author of this contribution is a Consulting Physician for Chest Diseases to the Medical College Hospitals, Calcutta and Chairman of Bengal Tuberculosis Association.

* From a broadcast talk given before the A.I.R., Calcutta, June 7, 1952.

To those who are already naturally infected with the tubercle bacillus, usually from an infective person in the community, it confers a certain amount of resistance but the dose of germs which enter the body cannot be measured in this process. Such persons do not require to be inoculated with the B.C.G. Vaccine. B.C.G. Vaccine has the merit of being given in a measured dose and whether it has "taken" or not can be tested after 6-8 weeks. If there is a case of tuberculosis in the house it is better to isolate the child during this period. In case the vaccine takes successfully, the tuberculin test becomes positive at the end of this period. If it proves negative, the vaccine has to be given again. A preliminary tuberculin testis, therefore, needed before the vaccine is given, except in new-born babies during the first few days after birth. Those who have already been infected, i.e., in whom the tuberculin test proves positive, need not and should not be vaccinated. The vaccine is suitable for those who have not been infected, i.e., in whom the intra-dermic tuberculin test, done by introducing a measured quantity of the products of growth of the tubercle bacilli (known as tuberculin) into the superficial layers of the skin, proves negative.

Immunity or resistance conferred by the B.C.G. Vaccine is akin to the immunity produced by an attack of, for example, syphilis, i.e., the immunity lasts so long as the human body harbours even a small quantity of the specif c germ or virus. Work done in various countries in the world shows that resistance conferred by the B.C.G. vaccine lasts for 3-5 years during which period, if the tuberculin test proves negative, the vaccine should be re-administered. In the U.S.S.R., to which I paid a visit recently, the vaccine is given thrice before adolescence is reached, namely, once after birth, again at the end of the Kindergarten stage, and lastly at the commencement of the teen age, provided, of course, the tuberculin test proves negative in such cases.

The protective power of the vaccine has been tested in many countries during the last 25 years or so. It has been generally found that the disease rate in susceptible groups of population has been reduced to at least one-fifth among those receiving this vaccination, as compared to groups which did not receive it. This naturally contributes to a lowering of the general mortality rate.

If it is possible to mobilise a campaign of inoculating the whole tuberculin-negative population in a country, priority should be given to (1) new born infants, particularly in slums and tuberculous households, (2) children in creches, schools, orphanages etc., (3) pupils and medical and auxiliary personnel who are exposed to infection in nursery schools, medical schools, hospitals or lunatic asylums, (4) the general population, particularly of younger age groups, from among whom recruitment is made for the Police, Army, Navy and Air services, and the factories, coal fields and plantations, and (5) refugees and those who come from rural areas to large centres of population for residence, study or employment. In Denmark, a concerted campaign of B.C.G. vaccination has brought about a phenomenal reduction in tuberculous meningitis and miliary tuberculosis in children, in a sharp decline in the number of older children admitted to the children's sanatoria and in the tuberculosis mortality rate.

The campaign was inaugurated in India in 1948 with the aid of the International Tuberculosis Campaign which is a joint enterprise by UNICEF, WHO, the Scandinavian Voluntary Organizations and the Government of the country concerned and since July 1951 with the aid of UNICEF/W.H.O. Already nearly 2½ millions people have been vaccinated. It is hoped to cover 80% of the tuberculin-negative population in urban and semi-urban areas within a period of 7 - 10 years, if all the constituent States and the public cooperate with the campaign. This is likely to lead, as has happened in other countries, not only to a reduction in tuberculous disease and deaths but will probably effect a great saving for the Government in limiting the number of tuberculosis institutions in the country. It is a perfectly safe method of vaccination which does not adversely affect the health of the individual vaccinated.

DIVERSIONAL THERAPY FOR T.B. PATIENTS

By Divya Bhatt, B.A., M.Sc., (Boston)

RFK's personal interest

Sir William Osler once said that the fate of a T.B. patient depended more onwhat he had in his head than what was in his chest. This fact is increasingly recognized today in the treatment of tuberculosis. A tuberculous patient usually passes through a long period of heavy emotional stress arising from socio-economic factors like social stigma, separation from the family, problems of job, education of the children, his own treatment, etc. This affects the course of his treatment. Diversional Therapy deals with this tremendous impact of mind on body, and has for its main purpose the relieving of boredom and helping in the recovery of the patient by keeping him as happy as possible, during his treatment. This has been accepted by medical authorities in advanced countries as an essential part of treatment. It helps the patient to divert his mind from the disease, makes him a happy and well-adjusted person in the hospital and thus ultimately contributes towards his early recovery. In our country also, the need for introducing Diversional Therapy work is now being gradually realized and a small beginning has been made.

Diversional Therapy work in its initial stages consists of introducing light, easy recreation and crafts or games. The patients as a rule are usually grown up men and women with set patterns of life; and so some of them may become more rigid because of this sudden on-set of a terrible disease. Hence, one has to be very careful in introducing such a programme. The need, aptitude and interest of every patient has to be understood first. His suggestions have to be taken into consideration. Even for teaching small things he has to be treated as a grown up person, otherwise, it may, at times, become difficult to get him interested in small things. There should be a thorough understanding of what the patient is and what he would like to do before the programme is introduced. A quick survey of the patient's interests should be conducted before introducing any new programmes and activities.

Another factor which sometimes comes in the way of making this programme a success is the patient's fear of physical movement. The need for physical rest is so much emphasised that a patient gets almost obsessed with the fear of movement, and even though he may be getting physically better, he remains a mental invalid with the consequent result that he returns to the hospital in a state of relapse. No doubt, rest is essential but something also must be done to keep his mind away from dark and depressing thoughts while he is under treatment to bring him back to normal life by the time he leaves the hospital. Through the Diversional Therapy work the patient can be

Mrs. DIVYA BHATT

The author of this contribution is a Lecturer in Medical Social Work at the Delhi School of Social Work. She is also the Field Work Supervisor Incharge of Diversional Therapy Centre at the Silver Jubilee Tuberculosis Hospital, Delhi.

helped gradually to over-come this fear complex and be prepared for future life. What the patient needs is self-confidence which gives him a feeling of getting better. Even the making of a little paper flower or the playing of a game of carrom will have a more salutory effect on his recovery than a hundred consoling words of the doctor.

While planning a programme it should be kept in mind that it has to be conducted by a trained social worker. Diversional Therapy work should be closely integrated with social service programme. While teaching some crafts or conducting literacy classes, the worker will be presented by the patient with many personal problems. But once the relationship between the patient and the worker is established, the patient will not hesitate to seek a solution of these from the worker. Only a trained social worker can competently handle these. Unless the basic social services are rendered, mere teaching of crafts or introduction of any other diversional activity will not succeed. This is so because the patients must be helped in the solution of their own problems first before they can be expected to take any interest in the Diversional Therapy programme.

It may however be mentioned that although this programme is generally started with the object of diverting the minds of the patients from their disease by providing recreational activities and light crafts, which may keep them happy and well-adjusted, and thus contribute towards their early recovery, it can also be developed into a vocational rehabilitation centre. In fact as the Diversional Therapy work develops and as the patients take more and more interest, regular vocational training should be provided. Tuberculosis always entails the problems of rehabilitation and Rehabilitation Centres will meet a long felt demand.

DIVERSIONAL THERAPY CENTRE, DELHI.

Diversional Therapy programme was started by the Delhi School of Social work in co-operation with the Ministry of Health, Govt. of India in Silver Jubilee T.B.Hospital, Kingsway, Delhi. Initially, this programme was aimed at providing some activities for the patients and thus helping them break the tedious monotony of the mechanical hospital routine.

Before introducing any activity, contacts are made with each patient. A rapid survey is made. The patients are asked to fill in the forms indicating their interests, aptitudes, previous occupational experience and lastly, their inclinations.

It will be interesting to note that this survey itself acted as a first item on the Diversional Therapy Programme. It was for the first time in the history of this hospital that somebody took individual interest in the patients and gave them an opportunity to express themselves. The patients wrote pages for one enquiry! They were so happy and excited!

After analysing the data, the following activities were started for bed and ambulatory patients:-

(i) A small library was established and books were distributed in the wards.
(ii) Paper flower-making was introduced.
(iii) Language classes were started.
(iv) Straw-string bag making and leather work were introduced.
(v) Embroidery, knitting and painting etc. were also started.

To the above mentioned crafts, various light games were added. These few activities along with relayed music really caused a change in the hospital atmosphere and in due course helped in the development of more activities like health competitions among the patients, exhibition of articles they were learning to make, group games and game competition, composition of poems and celebration of festivals.

Whenever a patient was discharged from the hospital, paper flower garlands were made and offered. Farewell speeches were also given. Whenever there was a festival, wards were decorated with the various things, the patients had learnt to make, and on Diwali day patients kept busy preparing greeting cards for sending to their friends in and outside the hospital. These and many other similar activities developed an initiative in patients for learning and creating something good. It also created interest in their surroundings and in other

people. For the first time they found their minds off the disease. They became sociable. Excitement and smiling faces were seen all over the hospital. Monotony was broken.

As the Diversional Therapy programme became more popular, need was felt for a Centre where equipment could be housed and the patients enabled to get together in order to learn, to enjoy and to have their social functions. The Ministry of Health, Government of India, kindly provided two nice rooms for this purpose and this, together with an increased grant, have enabled us to form a full fledged Diversional Therapy centre at the S.J.T.B. Hospital, where now the patients learn tailoring, cutting, leather work, typing, shorthand, embroidery, knitting work, string bag making and painting. Here also they listen to music, read newspapers and books, play games, attend classes to learn various languages, and hold discussion groups - thus, to laugh and chase away their blues. Further developed, such a Centre could very well become a good Vocational Training Centre. Thus, for example, an ex-patient who at first was a student at this very Centre has been given the job of a tailoring teacher. The services of the Centre have also been extended to the Wards where the bed patients are provided equipment for light crafts, books, paintings and other desired material which brings to one's mind the case of a patient of this hospital suffering from tuberculosis of the Spine and put in a plaster cast for 2 years. He is not able to sit up at all as the cast covers him from the arm-pits down to the hips. This patient was provided with drawing and painting materials and it is amazing to see the beautiful pencil sketches he makes the while he takes his treatment! He finds a tremendous joy in his recreation. His gloomy expression has disappeared and his face glows with happiness and pride in his work. This, then, is what the Diversional Therapy work can do to a T.B. patient. Joy, happiness and, may be, a quick recovery, as well.

Before concluding, it may be mentioned that this programme would not have been possible without the keen and continuous interest shown by Rajkumari Amrit Kaur, Minister for Health. She has really taken to her heart the needs of the T.B. patients and has helped very much in developing this Diversional Therapy work.

B.C.G. in Assam tea Estates

By Alan Gilroy, O.B.E., M.B.B.S., D.T.M.& H.

An awareness of the increasing incidence of Tuberculosis amongst tea estate workers found expression at a meeting of the Assam Branch of the British Medical Association early in 1949, when the importance of tuberculin-testing and B.C.G. vaccination was brought to the notice of both Medical Officers employed in the Tea Industry and the Indian Tea Association. When it was learnt that the International Tuberculosis Campaign (ITC) was organising a nation-wide B.C.G. campaign, the decision to have the advantages for tea estate populations was promptly made. The Calcutta Committee of the Indian Tea Association readily agreed to finance the campaign and the Ross Institute of Tropical Hygiene, advisers on preventive medicine to the tea estates, agreed to organise and supervise the work. Government agreed to allow the I.T.C. Scandinavian team, already in Assam, to train teams for tea estates and agreed further to a free supply of vaccines and equipment. Three teams were recruited in December 1949 and were trained by Dr. O. Hagan, leader of the I.T.C. team. A fourth team was added in June, 1950.

Each team consisted of two vaccinators, an Assistant Medical Officer as leader, and a Compounder. Personnel received the Indian Tea Association scale of salary and allowances and, in addition, a generous field allowance to compensate for constant travelling.

Names of 4 Teams and Record Clerk.

Team No. 1:	Dr. R.B. Roy, L.M.F.
	Mr. K.P. Paul Choudhury, Compounder.
Team No. 2:	Dr. N. Dey, L.M.P.
	Mr. Ali Hussain, Compounder.
Team No. 3:	Dr. J.K. Mach, L.M.P.
	Mr. M. Sangdem Ao, Compounder.
Team No. 4:	Dr. S.K. Phukon, L.M.P.
	Mr. Dilawar Hussain, Compounder.
Record Clerk:	Mr. S.G. Banerjee.

In addition to a thorough technical training, Dr. Hagen imbued the men with enthusiasm for their work. The teams' pride in the smooth running of the campaign, in the large number of Mantoux tests per team and in the small number of absentees was retained throughout. Even the earthquake of 1950, in spite of disrupted communications and the natural anxieties of the teams concerning their homes, did not delay the campaign by as much as a day.

The tea estate population of I.T.A. member-estates numbers about 9 lakhs. It was decided to include all persons over the age of 1 year. It was realised that there might not be much to be gained in vaccinating aged dependents but to have excluded them would have led to misunderstandings.

Record cards, one for each person, were distributed to estates well before the arrival of the teams.

The campaign had to be planned to cause a minimum of interference with estate work especially in the monsoon months when all available labour is required for leaf plucking. The teams agreed to start the day's work early, and by 8 a.m., each team had given the Mantoux test to 1000 persons and upwards.

The Estate Managers had been advised on a choice of site for the teams and had been asked to put up bamboo fences so that persons approached the vaccinators in single file and did not overcrowd them.

Dr. ALAN GILROY

The author of this contribution is the Principal of the Ross Institute of Tropical Hygiene, India and Pakistan Branch, Cinnamara (Assam).

The campaign commenced in the Sibsagar and Cachar Districts simultaneously, 3 teams working in the former and 1 in the latter. The schedule was planned to take advantage of the dry season to visit districts where communications would be difficult in the rainy season.

The Progress

The campaign lasted almost exactly 2 years and was completed in December 1951 by which time 8.4 lakhs of the estimated total population of 9 lakhs had been tested.

To 31.12.1951.	*Persons*
Mantoux-tested	837,613
Positive	426,953
Vaccinated	361,401

Of persons taking the Mantoux test only 5.9% failed to have the test read.

The average number of Mantoux tests per team (of 2 vaccinators) per month was 9,854. For months on end the average per team exceeded 13,000.

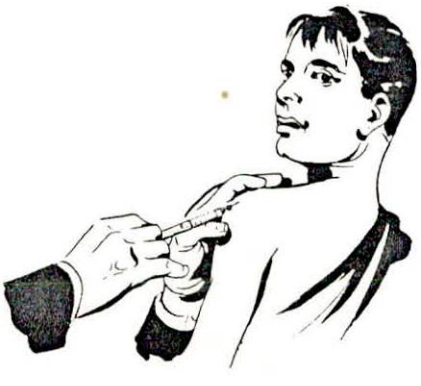
Records

The completed record cards are returned to the Headquarters of the Ross Institute in Assam for analysis where this very onerous and tedious job is carried out by one clerk, employed for the purpose by the I.T.A. and whose part in the campaign has been most important.

The Future

Although the population of tea estates in Assam is a stable one, nevertheless a certain number of "short term" recruits arrive each year. Mantoux tests for these people and for the infants who pass their first birthday, are now being considered and the importance of testing the duration of Mantoux conversion is also borne in mind.

Very many people have contributed to the smooth organisation and without the financial support of the Indian Tea Association and the ready co-operation of Estate Managers and Medical Officers it would not have been possible.



GOI-BCG/TB policy

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REVIEW ARTICLE

PRESENT STATUS OF IMMUNISATION AGAINST TUBERCULOSIS

G.V.J. BAILY*

The discovery of the tubercle bacillus by Robert Koch in 1882 and his classical demonstration, in 1891, of the effect of a second infection with tubercle bacilli in an already tuberculous guinea pig, which later came to be known as the 'Koch phenomenon', heralded scores of attempts to develop a specific immunising agent against tuberculosis, derived from the tubercle bacillus. The attempts were indeed inspired by the observations of Edward Jenner who about a hundred years earlier, in 1798, had also noticed the increased reactivity to vaccinia virus occurring in persons who had been previously vaccinated or who had had smallpox.

In animal experiments conducted over the years, the immunising capacity of four distinct types of 'vaccines' were studied: preparations consisting of small numbers of living tubercle bacilli; preparations containing mycobacteria that are non-pathogenic to man but pathogenic to certain animals or birds; products of tubercle bacilli or tubercle bacilli themseves, killed by a variety of physical and chemical methods and finally, preparations containing attenuated variants of originally virulent strains of tubercle bacilli pathogenic to man (Weiss 1959, a b, c).

The first was never widely tested and discarded as too hazardous. The second i.e. several mycobacteria that are non-pathogenic to man, were shown to be ineffective until the discovery of the effect of the Vole bacillus (*M. microti*) which causes naturally occurring disease among field rats (Wells, 1937) and is also pathogenic to certain other species of animals including the guinea pig. Vaccine prepared from the vole bacilli was shown to offer significant and a measurable degree of protection in man (Medical Research Council, Great Britain, 1972). The first attempts to induce immunity with killed tubercle bacilli or their products were initiated soon after the discovery of the tubercle bacillus. For instance, Daremberg in 1889 reported that several rabbits which had been inoculated with cultures of tubercle bacilli sterilised by heating for 15 minutes at 115°C or for six hours at 70°C survived longer after virulent challenge infection. Later his claim was not substantiated by others. Since then scores of animal experiments using non-living vaccines have been reported (Weiss 1959, a b, c) with conflicting results. One of the possible reasons for these conflicting results could be the fact that the test-systems used for testing the vaccines in animal models varied from experimenter to experimenter, as is seen in the varying results in the potency assay of the same BCG vaccines in different BCG laboratories (Smith, et al 1971). Thus, non-viable vaccines have never been employed though interest in these vaccines has not ceased even to-day. Although Vole vaccine has been shown to confer a significant degree of protection, vaccination with Vole vaccine causes some unpleasant reactions at the site of vaccination and as such has never been practised on any large scale. Thus, the only vaccine that has been used, and used extensively throughout the world, is the BCG (bacille Calmette Guerin) which is an attenuated variant of *M. bovis*. BCG vaccine does not cause progressive disease in man except in the extremely few recorded cases and under exceptional circumstances. It is also avirulent in experimental animals except the Syrian golden hamster.

Virtually since BCG vaccine was introduced by Calmette and Guerin in 1921, it has been a subject of controversy. It was introduced in Europe at a time when Europe was just recovering from the ravages of a war and tuberculosis was quite common, and interest in BCG, considerable. With greater 'experience' which was not uniform, interest in many countries including United States and Britain waned. Scandinavian countries however have always been very enthusiastic about BCG vaccination. In the post second world-war years, massive BCG vaccination campaigns were organised in Europe through the International Tuberculosis Campaign with Headquarters in Copenhagen. Tuberculosis at that time was still relatively common and the privations of war had aggravated the situation in many countries. Soon after, BCG was introduced in many developing countries of the world and in India, it was first tried out in 1948 and vaccination programme started on a large scale, as a mass campaign, in 1951.

By 1950, even though BCG vaccination was in use for nearly 30 years and several BCG campaigns had already started, the opinion about BCG in many developed countries, especially Britain and United States could only be

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considered as lukewarm. This was best stated by D'Arcy Hart et al as "....moderate opinion on BCG in Britain and in the USA in 1949 might have been summarised as follows: (1) it gave some protection in those specifically exposed to tuberculous infection in their homes or at work; (2) it could be expected, at least in general populations with low standards of living and high tuberculosis rates, to reduce the incidence of tuberculous disease appearing within a few years of a natural first infection with tubercle bacillus....." (Hart, Pollock and Sutherland, 1957).

Opinions on the efficacy of BCG Vaccine were formed, in addition to the demonstration of its effects in animal models, in several ways: Observations based on 'experiences' with the use of BCG, early uncontrolled observations and studies on the protective effect of BCG and, the results of controlled trials. While the first two could be considered to be easily influenced by several factors, more recent observations indicate that conflicting results obtained even in well controlled trials could have been due to one or more factors as yet un-identified.

Protective Effect of BCG Vaccine

Though all BCG vaccine produced in the world in dozens of BCG laboratories to-day, comes from the original BCG culture produced by Calmette and Guerin, characteristics of the vaccines produced in different laboratories vary. This is because with repeated subculturing, the genetic characteristics of BCG (or, for that matter, several micro-organisms) undergo change. As a result of repeated sub-culturing, the changes in the BCG produced in one laboratory may not be the same as the changes obtained in another. In one instance, only the morphological characteristics of the bacilli may have changed with no changes in the protective effect. In another, while the morphological characteristics are not affected, the protective effect may have changed considerably. It is therefore, common practice to refer to BCG produced in different laboratories as 'strains' of BCG. Thus, BCG produced in Madras is referred to as 'BCG-Madras' (strain 1331) and BCG produced in Paris as 'BCG-Paris' (strain 1173) etc. In animal experiments, most strains of BCG show a higher or a lower protective effect measured as the survival time of the animals (guinea pig, mice etc) which have been vaccinated and later challenged, i.e. infected, with virulent tubercle bacilli, as compared to those that are not vaccinated but are only challenged. (Ladefoged, Bunch-Christensen and Guld, 1970),

In man, however, evidence of the protective effect of BCG vaccination can be obtained through clinical observation, or better still, through controlled trials. Literature is replete with reports on observations and controlled trials but most of these cannot be considered as statistically valid.

The first controlled trial which can be considered as statistically valid was started by Aronson and others (1958) in 1935. Prior to this study, most of the evidence in favour of a protective effect of BCG in man came from clinical observations. Some of these observations were more solid than the evidence available for several other prophylactic measures and are discussed below.

The earlier observations and studies

Heimbeck's studies :

One of the earliest observations and studies on BCG were those by Heimbeck in Norway. In 1924, Heimbeck (Heimbeck, 1948), started tuberculin testing the staff of the Oslo municipal hospital in Norway. The hospital then had about 2,000 beds and about 300 of those were occupied by patients suffering from tuberculosis. He had observed that many nurses developed tuberculosis within a few years after joining nursing. Table 1 presents the fate of the nurses joining in 1924, 1925 and 1926. Of the 109 nurses joining in 1924, 58 were tuberculin positive and 51, tuberculin negative. By the end of three years, only one of the 51 nurses who was tuberculin negative continued to be tuberculin negative and all the others had converted to the tuberculin positive state. Over the next few years whereas only 1 case of tuberculosis developed among the initially tuberculin positive, among the 51 initially tuberculin negative nurses, 18 cases developed with 7 deaths. The fate of the cohorts admitted in 1925 and 1926 was also similar except for deaths in the tuberculin negatives.

Observing this striking fate among those initially tuberculin negative nurses, Heimbeck offered, from 1927 onwards, BCG vaccination to all tuberculin negative new entrants. He, however, did not compel them too much to get vaccinated with the result that of the 899 nurses (Table 2) admitted between 1927 and 1934, 436 were tuberculin positive, 95 were tuberculin negative but refused vaccination, and 368 were tuberculin negative and BCG vaccinated. Whereas 42 cases of tuberculosis developed among the 95 unvaccinated tuberculin negatives, 37 cases developed among the 368 vaccinated tuberculin negatives during the following few years after

Table 1

Heimbeck's observation among student nurses in Oslo

Year of admission	Tuberculin Positive			Tuberculin Negative		
	Total	Cases of TB	Deaths	Total	Cases of TB	Deaths
1924	58	1	0	51	18	7
1925	42	1	0	72	26	1
1926	52	1	0	62	18	0

Table 2

Heimbeck's BCG study among student nurses in oslo: 1927-1934

Tuberculin and BCG status on entry	Nos.	Cases of Tuberculosis	Percent
Tub. Positive	436	27	6.2
Tub. Negative, Not vaccinated	95	42	44.2
Tub. Negative, BCG vaccinated	368	37	10.1

vaccination—a reduction of about 76 percent among vaccinated. This early observation of Heimbeck cannot be considered as absolute proof of the protective effect of BCG mainly because the 95 'controls' were self-selected and thus the allocation was far from blind. Even so, since the study population was all uniform i.e. all women aged about 20 and all belonging to urban middle class families, of similar socio-economic status and exposed to similar risk of infection, the study can be considered as of interest and provided one of the first evidences of the protective effect of BCG in humans.

Hyge's study :

An epidemic of tuberculosis in school girls aged 12-18 years, has been described by Hyge (Guld, 1980). The epidemic occurred in a blacked out air-raid shelter where all the pupils were exposed to infection by chance. This occurred 1-3 months after routine tuberculin testing (Mantoux 100 units) and X-ray examination of all pupils and one year after BCG vaccination of the majority of tuberculin negatives.

The fate of the pupils is shown in a summarised form in Table 3. While of the 94 who were tuberculin negative and were not vaccinated, 41 cases of primary tuberculosis occurred, among the 106 tuberculin negatives vaccinated with BCG, no case of primary tuberculosis occurred. The development of progressive primary disease is also presented. Though this is a retrospective study, and again, not statistically fully valid, the complete absence of primary disease among the vaccinated is striking and can scarcely be explained as being entirely due to bias. Indeed the above two studies gave strong indications of the protective effect of BCG in man and provided an impetus for planning statistically valid studies to obtain irrefutable proof of the protective effect of BCG.

Table 3

Hyge's study: An Epidemic of Tuberculosis among school girls during the second World War

Status before epidemic	Students exposed	Cases of tuberculosis (Primary)	Progressive Pulmonary T.B. over 12 years
Tub. Negative	94	41	20
Tub. Negative, BCG vaccinated	106	0	4
Tub. Positive, Not vaccinated	105	1	14

The controlled trials

Controlled trials have come to be recognised as the most reliable methods of establishing the efficacy of therapeutic or prophylactic measures in man and confirm what has been studied in animal models as also from 'experiences' from application in humans. The trials are meant to establish not only that a curative or a prophylactic measure is effective, but the actual degree of efficacy. In these trials, after the safety of the measures is assured and ethics of the study examined, the hypotheses are clearly laid down, subjects (persons) among whom the studies will be conducted are carefully identified, the appropriate design selected and meticulous care is exercised in the follow-up of all subjects for the same period of time. Possibly, the most important characteristic of these trials is that, neither the person who administers a measure nor the subject to whom it is administered decides which measure is applied to whom. Subjects are allocated to the measures through a double-blind randomised scheme.

In the BCG trials, following an appropriate randomisation scheme, subjects are allocated either to 'BCG vaccination' or to 'no BCG vaccination' (controls) blindly. All the subjects are followed-up for a specified and the same duration of time, to identify the new cases of tuberculosis arising from among them. (It will be obvious that preliminary investigations are carried out to exclude from analysis of the protective effect, persons who at the time of allocation are either infected or are actually suffering from tuberculosis). The protective effect of BCG is expressed as the proportion by which the incidence of new cases is reduced among the vaccinated as compared to the controls.

A very large number of BCG trials have been reported in the literature. Most of these trials, for one reason or another do not satisfy the criteria mentioned above and are thus statistically not valid. As upto the time that the Chingleput study of the protective effect of BCG vaccination was started, the studies indicated in Table 4 can be considered as some of the studies that are statistically valid and conducted in the general population.

Table 4

Results of Six controlled trials of BCG vaccination Against Tuberculosis

Trial and age of subjects	Intake period	Duration of follow-up yrs.	Vaccination group	No. of subjects	Cases of tuberculosis	Protective effective %
North Amer.* Indians (9) 1-18 yrs.	1935–38	9–11	Control BCG	1457 1551	238 64	80
Georgia (14) 6-17 yrs.	1947	12–23	Control BCG	2341 2498	3 5	None
Puerto Rico (13)	1949–51	5½–7½	Control BCG	27338 50634	73 93	31
Georgia, Alabama (21) 5+years	1950	14	Control BCG	17854 16913	32 26	14
Great Britan (5) 14–15½ yrs.	1950–52	15	Control BCG	12699 13598	240 56	78
Madanapalle (15) All ages	1950–55	9–14	Control BCG	5808 5069	46 28	31

*Figures in brackets indicate the reference nos. of the reports on these studies.

The first of these studies was conducted among the North American Indians (Aronson, Aronson and Taylor, 1958). The study population was characterised by low socio-economic conditions and a high risk of tuberculous disease. At about the 10th year of follow-up the incidence of tuberculosis cases among the vaccinated was 80% less than the incidence among controls. At the time of the final follow-up i.e. at about the 18th year, the protective effect was still of the order of 72% since there were 42 cases of tuberculosis among the BCG vaccinated compared to 185 cases among the controls. In this study not only the emergence of new cases was evaluated but also, the deaths were carefully assessed. As at the end of follow-up, there were 13 tuberculous deaths among the BCG vaccinated compared to 68 tuberculous deaths among the controls giving a protection of 82%. Acid fast bacilli could be demonstrated among 5 deaths vaccinated and among 27 deaths that were not vaccinated again giving a protection rate of 82%. On the whole, this early but well conducted study indicated a protective effect of about 80%.

Similarly, three other studies were started in different parts of United States of America during the late forties. In the study in Puerto Rico, started in 1949, the protective effect of BCG has been assessed in 27,338 controls and 50,634 vaccinees. As at about 6 years the protective effect was 31% (Palmer, Shaw, and Comstock, 1958) while at the 18th year of follow-up it still was the same i.e. 28.7% (Comstock, Livesay and Woolpert, 1974). The effect was similar in different age groups. In another study in Georgia in a population of about 5,000 children aged 6-17 years, no protective effect was observed. In the third American study in Georgia and Alabama a very modest protective effect of about 14% was observed. (Comstock and Webster 1969).

The Medical Research Council (MRC), Great Britain carried out a study among British school leavers (all aged 14-15½ years) wherein 12,699 were unvaccinated and 13,598 were offered BCG vaccination (Medical Research Council, Great Britain, 1972) The protective effect was assessed at various intervals for 15 years and it was found that it was almost constant at about 80%. This was also true when the effect was assessed against different manifestations of tuberculosis. In the same trial, another section of the study subjects had been vaccinated with Vole vaccine and in them also the protective effect of Vole vaccine was similar to that of BCG, i.e., about 80%. In a small study in a general population of about 10,000 persons in Madanapalle in South India, the protective effect as at about 9-14 years after vaccination was assessed to be about 30% (Frimodt-Moller, Acharyulu and Parthasarathy, 1968).

It will thus be observed that while animal models almost always showed a measurable degree of protection by BCG, experience in humans varied considerably. In the words of Ian Sutherland, who was always associated with the MRC trial in Britain, "....the instinctive reaction of any scientific worker, when he finds that his results differ from those of another scientific worker, is to mistrust the other man's results, and so it was not surprising that there was a good deal of coming and going across the Atlantic between the MRC workers and the U.S. Public Health Service Workers, each group prepared to be very critical about the other's investigations. The results of this exercise have, however, been entirely beneficial in that our mistrust has been dispelled...." (Sutherland, 1971). After considerable deliberations, they agreed that, of the many reasons that can be associated for the lack of protective effect in American studies, two reasons might be the most relevant; firstly, the vaccine used in some of the American studies could have been prepared from poor strains of BCG and secondly, that infection with atypical mycobacteria prevalent in the United States may have itself offered some degree of protection which masked the protection offered by BCG. When the Chingleput study was planned and started in 1968, this was the state of knowledge regarding the protective effect of BCG vaccination.

The Chingleput BCG trial

In 1963, the Government of India took up the question of conducting a BCG trial in India. There was still some controversy in the country about the use of BCG and it was felt that the problem had to be settled by a controlled field study under Indian conditions. The study (Tuberculosis Prevention Trial, Madras, 1980) was planned in collaboration with the World Health Organisation and the Centre for Disease Control, United States Public Health Service and conducted by the Indian Council of Medical Research as a separate project.

The study was undertaken in Trivellore taluk of Chingleput district in Tamil Nadu. The intake (i.e. admission of population to the study) was started in July, 1968 and completed in March, 1971. During this period, a total population of about 3,60,000 persons in 209 contiguous villages and one town were registered on individual cards. All persons aged one month and above were offered one of two doses of BCG vaccination (0.01 mg or 0.1 mg) or a placebo on a random basis. Two strains of

BCG, the Copenhagen and the Paris strains were used. At the same time, all persons aged 1 year and above were tested with Tuberculin (PPD-S) and an antigen prepared from an atypical mycobacteria (PPD-B), the former, to elicit the status of infection with *M. tuberculosis* and the latter to elicit infection with atypical mycobacteria. All persons aged 10 years and above were also X-rayed and for those in whom X-rays showed any abnormality sputum examination by direct smear and culture was done.

The study population was systematically and intensively followed up by X-ray and sputum examinations in an effort to diagnose all new cases of pulmonary tuberculosis occurring in the community. In addition, representative samples of population were tuberculin tested using PPD-S in order to elicit the status of tuberculin sensitivity after BCG vaccination.

The population was characterised by high prevalence and incidence of tuberculous infection as well as high prevalence of non-specific sensitivity. The overall prevalence of tuberculous disease (pulmonary) was also high being very much higher in males than in females.

Table 5 presents, in brief, the main results regarding the protective effect of BCG vaccination in the prevention of pulmonary tuberculosis as observed in the study.

Table 5

The Chingleput BCG trial: Results (7½ Years)*

Tuberculin reaction at intake	Given Standard Does BCG (0.1 mg.)	Given Stand-dard Dose BCG (0.01 mg.)	Placebo
0-7 mm	37	37	28
8-11 mm	14	17	17

(i) Distribution of definite bacillary cases of pulmonary tuberculosis only.

(ii) Results similar for less definite bacillary cases (culture negative on one specimen only) and cases positive on X-ray only.

(iii) Nos. vaccinated are similar in all three groups.

The table shows the distribution of new cases of pulmonary tuberculosis that were positive on culture of at least two specimens of sputum i.e. in all probability, these were definite cases of tuberculosis. The protective effect is studied among those who were initially tuberculin negative i.e. reacting with 0-11 mm to PPD-S. These are again divided into two groups, one reacting with 0-7 mm i.e. definitely not infected at intake and the other reacting with an induration of 8-11 mm. Some of the latter could be considered to have been infected with *M. tuberculosis*. Because of the large size of the study population the denominators can be taken as similar. The difference observed between the three groups do not attain statistical significance. Thus, BCG gave no protection against the development of bacillary pulmonary tuberculosis in this study. The results were similar when analysis was done for less definite bacillary cases as well as X-ray positive but abacillary cases.

Current Status of Immunisation Against Tuberculosis in India Based on the Results of Well-Conducted BCG Trials

The Chingleput study was conducted on the hypothesis that BCG offers protection against tuberculosis and one of the objectives was to measure the exact degree of protection offered by BCG. With the present result in hand it is scientifically appropriate to examine the possible reasons for this result.

The study was meticulously conducted and the procedures followed were constantly monitored in order to obtain accurate results. Even so, a committee of experts was appointed to scrutinise the methodology and it, concluded that no errors could have been introduced. In further discussing the possible reasons for this result in the Trial in India, one major assumption is made. That all trials listed in Table 4 and the persent one are scientifically valid. Only those hypotheses that are *amenable to testing* are presented.

One of the reasons put forward by the American workers was that the low protective effects observed in the trials conducted in the U.S. were due to the masking of the protective effect of BCG by the protection afforded by previous infection with atypical mycobacteria. Examining the problem in animal studies, Palmer and Long (1966) found that atypical mycobacteria do give some protection against tuberculosis in animals. While BCG confers about 80% protection, photochromogens confer 68%, Scotochromogens and non-chromogens 50% and rapid growers 15%. Further, if animals which have been previously infected with photochromogens, are injected with BCG the protection is not additive but goes up to 80% as in the case of BCG. Thus—in an animal study, if animals are first infected with photochromogens and

then vaccinated with BCG the protection that will be attributable to BCG would be only 12%=(80%-68%). If what is observed in animals is true of man, then in areas with high prevalence of non-specific mycobacteria in the environment, only the *residual* protection would be observed in the BCG trials. As has been said earlier, the prevalence of nonspecific sensitivity was very high in the study area indicating a high prevalence of environmental atypical mycobacteria.

A rough estimate of the type (photochromogens, scotochromogens, etc) of environmental mycobacteria prevalent in the area of the study can be obtained from cultures of sputa collected from study subjects, usually in a survey such as this, at their homes. From the sputum samples collected under field conditions, such environmental mycobacteria would be grown as contaminants. In the over 2,00,000 sputum samples collected and cultured during the study, in nearly 6% such contaminants were grown indicating the very high prevalence of environmental atypical mycobacteria. However, it was observed that most of the mycobacteria were those that gave only a low degree of protection. In effect, only 1% of all the atypical mycobacteria isolated were typed as photochromogens which were shown by Palmer and Long to confer a protection close to that of BCG. If BCG were to confer a high degree of protection of the order of 80%, one should have observed some residual protection in the study population since most infections with atypical mycobacteria would probably be caused by organisms that confer low degree of protection. Thus infections with atypical mycobacteria may not, at least fully, explain the zero protection observed in the study.

Disease occurring as a direct extension of the first infection (primary) itself is most common in children and the forms of disease can be termed as childhood forms of tuberculosis. These include, besides the primary complex, complications such as miliary, meningitis, bone and joint tuberculosis etc. In contrast, adult forms of tuberculosis represented mainly by cavitating bacillary pulmonary tuberculosis is considered to be mainly a result of later endogenous reactivation of a healed primary complex, and not as a result of another exogenous reinfection with tubercle bacilli. Since Koch demonstrated that a second infection with tubercle bacilli in a guinea pig is far more difficult than the first, it has occurred to most workers that much of adult forms of tuberculosis occurs as a result of endogenous reactivation. The role of BCG was based on this hypothesis as it will be obvious that if exogenous reinfection is the main cause of adult type of tuberculosis, BCG obviously cannot help.

In Chingleput area, infection with tuberculosis is very high and the virulence of *M. tuberculosis* isolated in the area is probably low. If the high incidence of tuberculous infection results in exogenous reinfection being the prime cause of adult forms of tuberculosis, BCG may not be expected to protect against such disease. This hypothesis appears promising in explaining the *complete lack* of protective effect in Chingleput study. Attempts are being made to investigate this hypothesis. This is relevant not only for the explanation of the failure of BCG to protect in this study but also for the Tuberculosis Programme in general.

Several other hypotheses can be put forward. Two of these are: the differences in immunological responses in different population groups; the effect of nutrition on immunological responses in the body. While the former could be investigated, the latter appears to be not relevant because one cannot classify the entire population of the study area as undernourished or malnourished. Further, tuberculin sensitivity, which is an immunological response to antigens derived from the tubercle bacilli, is not influenced by the state of nutrition in the population. In a study by Ganapati and Chakraborty (1981) where the state of under-nutrition was classified into 4 grades depending on the severity of under-nutrition, tuberculin sensitivity status was similar in children in all the four grades of undernutrition as also in children classified as normal.

The present status of BCG vaccination stems from the knowledge as it stands to-day. BCG offered no protection against pulmonary tuberculosis. At the same time, one cannot assume that BCG may not protect against childhood forms of tuberculosis which were not investigated in the trial. It is however quite likely that BCG would protect against such disease for the following reasons: disease forms in animal studies, where BCG almost always conferred a measurable degree of protection, resemble more closely childhood forms of tuberculosis rather than adult forms. Secondly, several controlled trials wherein protection against other forms of tuberculosis has been investigated (Medical Research Council, 1972; Rosenthal et al 1961) have shown that BCG offers protection against childhood forms of tuberculosis. It is thus appropriate that BCG vaccination, at present in India, is limited to the prevention of tuberculosis in childhood.

In all studies, except the small study in Madanapalle, where BCG was shown to be protective, it was demonstrated that the protection was durable i.e. it lasted as long as the follow-up of the population was continued. This is true irrespective of the degree of protection as evidenced in the British trial where the protection was high, and Puerto Rico where the protection was low. On this basis, if a good vaccination is offered at an young age, revaccination may not be indicated as, in those studies, protection lasted from 15 to 20 years. Primary infection is most frequent in the younger ages and so is primary disease. Thus if BCG vaccination has to be given to prevent primary disease, it should be given before primary infection occurs i.e. in India well before the age of 5 years. After 20 years of age, primary infection is less frequent in India and risk of primary disease even less frequent. Revaccination is indicated only when the first vaccination has not been satisfactory—i.e. given either with a poor vaccine with a poor technique. It may however be remembered that post vaccination allergy tends to wane with time (Tuberculosis Prevention Trial, 1980) and deciding on revaccination on the basis of waned post-vaccination allergy may not be quite appropriate. In animal experiments it has been shown that BCG induced allergy wanes very fast but can be restored by repeated tuberculin testing. With the waning of allergy, the acquired resistance does not wane nor, at the same time, with restoration of allergy by repeat 'tuberculin test' is the acquired resistance enhanced (Magnus, 1957). In a study in children it was shown that BCG induced allergy wanes with time but can be restored by repeated tuberculin testing (Guld et al. 1968). Thus, revaccination may be practised only if a group of children vaccinated very early in life show poor post-vaccination allergy shortly after vaccination—say between 2 to 6 months. For all practical purposes, revaccination is not indicated if the first vaccination has been good.

Discussed above is the status of immunisation against tuberculosis in India to-day. In developed countries, with the sharp decline of tuberculosis, interest in immunisation has also declined. However, developing countries like India, which have missed those winds of change, may have to continue their interest in immunisation. The story of immunisation against tuberculosis is not yet over.

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