Contribution of Epidemiology to the sustained development and strengthening of Tuberculosis Control

The National Tuberculosis Institute (NTI) was established in 1959 with the prime objective of developing a nationally applicable, scientifically valid and logistically viable TB (tuberculosis) control programme. This programme had to be built on a modern, broad based, economically viable, people friendly, systemic approach as India is a vast country with a widely spread population, mostly living in the villages. The epidemiology of TB disease and risk factors that enhance its transmission therefore play a fundamental role in the development of such a programme and monitoring it. For, a prudent definition, epidemiology is the study of distribution and determinants of a condition or conditions from which the community is burdened with, and factors which are powerful enough to bring about a change in its patterns over a specified period. Since the condition/conditions the NTI is concerned with is TB, the contagion of which is identified as the *Mycobacterium tuberulosis*, plans or the methods which throw light on factors that are responsible to propagate it in the community will have to be devised. While conducting investigations, statistical methods will have to be considered and many new ideas which are noteworthy will have to be discovered. They will have to be identified and listed with all explanations for others to note. Such a task is studiously thought provoking, slow to progress and still have far reaching consequences. This is very important because the NTI approach and that of the epidemiology especially, is public health oriented. All the necessary differentiations between the clinical and public health approaches will have to be considered carefully. For example, definitions will have to be evolved first on TB disease, types of TB prevalent in the community, and, how are they recognized or identified, who identifies them through specific steps or tasks in the community itself and through what process/processes and among whom. All these are daunting tasks requiring months if not years of sustained effort.

Fortunately, like the rest of the developed world, India too had vast expertise in most issues despite the fact that epidemiology was still nascent and evolving everywhere. A tuberculin survey was carried out as far back as 1921 on behalf of the government which yielded information that the number infected was quite high wherever the survey was conducted, confirming suspicions of the government that TB morbidity and mortality following it might be quite high[1]. From 1938 onwards, morbidity surveys were conducted by different investigators in different parts of the country, all confirming suspicions of high prevalence of TB[1]. However, beginning from aims, objectives, methodology to the interpretation of findings, each survey was as different and unique as its progenitor. A BCG vaccination attempt which began in 1948 as a pilot project was, by 1951, expanded and developed to cover most parts of the country. It was nurtured and sustained by the government as a mass BCG vaccination programme, and turned out to be the biggest such programme undertaken by any country. Since there was a tuberculin test as a screening tool before giving BCG, this progamme too yielded rich information on the tuberculinisation status of wider and even remote parts of the country. Thus, enough information had been generated in these endeavors assisting future workers on consolidation and standardization on various fronts. The first ever nationally applicable survey, the National Sample Survey 1955-58 (NSS), overcame many of these worrisome vital issues and yielded a goldmine of information on the size and extent of the TB problem faced by the country[2].

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The newly formed epidemiology unit of NTI (EPS) had access to all this information and well trained officers to initiate work in specific tasks oriented towards strengthening the formulation and developing a nationally applicable TB programme. It set about developing protocols and manuals for pilot runs to train newly recruited staff in different tasks and procedures: (1) ways to establish rapport with the community under investigation, (2) enumeration, (3) symptom elicitation, (4) tuberculin testing and reading, (5) mass miniature radiography (MMR) procedures, (6) sputum collection and transport of specimens, (7) data forms used in different work procedures, (8) error correction processes, (9) coverage to be achieved in the target population, etc. Task manuals for pilot runs with different objectives had to be written and work procedures clearly stated. One example to the innovative spirit of those times was sputum specimen transportation. In those early days, NTI had no bacteriology unit to process sputum specimens. Sputum specimen collected from different studies had to be transported to The Arogyavaram Centre at Madanapalle, which was, in those early days of lack of roads and inefficient transport system, almost a day's distance away. It would therefore take a minimum of two days to get the sputum specimens from field work spots to reach the laboratory for processing. Taking several factors into consideration, cool keeping to reduce contamination, easily transportable boxes capable of holding 120-150 specimen each were devised to transport the specimen collected, and a method of forwarding speedily to Madanapalle, where it would be processed on priority at the lab even on holidays.

But there were many equally important tasks requiring close attention. Ideally, all or any task must be carried out in accordance with a standard procedure with meticulous care, and different performers must replicate each one of them similarly and without any errors to the dictates of scientific rigour. As there were many singular tasks in different studies which differed with different aims of each study, all procedures were rotated systematically so that every worker got equal opportunity to gain expertise in specified tasks in order that the overall team performance attains operational efficiency. By doing this exercise repeatedly, not only work procedures got more efficient, those redundant avoided, but more importantly, drawbacks and limitations were better understood so that they could be monitored constantly and revised to keep standards higher. Further, if more than one investigative procedure were used to identify a condition, e. g, chest symptoms, MMR, bacteriology; their inter-relationships should necessarily be compared in order to arrive at parametric relationships between different procedures used, and their range of effectiveness or the extent of accuracy in identifying the condition and arrive at mutual agreement levels. In the process, definitions also got more refined and precise so that tasks through which *a state, event or a condition* is identified, better understood and replicated by all different workers at different points of time. In the process, work was generated to involve different disciplines. Therefore, many sections of NTI, e. g: transport, bacteriology, statistics, sociology, etc. came to be involved.

Concurrently, the definition of what a study group, population or a community is, sampling strategies to select representative samples to suit the particular objective of a particular study was worked out. Segmentation or stratification of any community under purview had to be estimated pragmatically to a preset degree of attainable accuracy so that statistically valid, but experimentally viable sampling methodology is evolved. Methods or investigative procedures *wherein such work as identifying sickness or other conditions of events present, and/or, proportions of some of them in that community is measured* were delineated. They were identified with great care by carrying out specified tasks on specified samples on pilot basis and evaluated so that the results would become applicable to the population under reference. In such identified communities, replicable methods to identify the condition/s for, e. g., estimation of the

TB burden by utilizing procedures e.g., tuberculin testing, symptoms, X-ray, bacteriology etc. were to be carried out.

India is a vast country and admittedly the task set before the epidemiology section was a great challenge because even after the biggest of the surveys- the NSS, certain ambiguities on the spread of the disease in towns, villages and cities persisted. This problem had to be addressed with great alacrity and shrewdness because the task set before NTI was to address the nation as a whole. The EPS therefore had to provide a statistically valid solution of selecting a sample which related to the country as a whole. Fortunately, India, had been divided into administrative districts with well demarcated boundaries, whose population and locations where they live has been well described and documented by the Census of India, which gets updated every 10th year. It was prudently thought that a sample district should be taken up to conduct detailed epidemiological as well as all other investigations and this *district model* could be extrapolated to other districts of India. Standardized investigative procedures should be used to cover majority areas so that exhaustive information would become available on TB morbidity and mortality.

This means that all the well tested, standard and replicable investigative procedures in vogue that are useful should be employed and studies/ surveys conducted which can generate valid information on the infection, morbidity and mortality of TB, and from these, proportions of yield by different procedures compared, wherever possible, suggestive links probed further to provide richer, corroborative information. Additionally, since TB morbidity is an enduring phenomenon, studies also must estimate its prevalence or morbidity at different points of time, from which *trends* could be estimated. Such work can be conducted only in a community that is clearly delineable; such as a cluster, a village, a town block, a taluk or even a district. The time interval/intervals should also be specified in ways that reflect information on the transmission of the disease. The available knowledge on all these several issues would be utilized to yield wholesome results that could be blended scientifically to the evolution of a nationally applicable control programme.

Studies undertaken in the beginnings were therefore, exploratory in nature and were aimed at strengthening all these factors cited above[3-20]. Since they were all performed with great fervour and scientific discipline, they yielded fruitful results. It was understood, thus, for example, that while using MMR, there were limitations to single picture interpretation[6]. But, no advantages were found in TB prevalence surveys, if two pictures of the same person were taken[9]. Among radiographers, inter-individual agreement for X-ray active cases was in the order of 50%; intra-individual agreement for X-ray active cases was 52% for one reader and 69% for the other reader[6]. It was discovered that even the agreement between two sputum samples collected within an interval of 1-3 days was 42% for positive results[6]. A comparison of the relative value of single and double picture techniques in TB prevalence surveys, revealed agreements between different readers or between two different readings of the same reader when two pictures of the same individual were presented. This resolved many issues concerning diagnostic abilities of MMR, and assisted in standardizing the techniques of MMR reading when different readers are reading MMR pictures. Thus, it became clear that, MMR with a single film, in spite of its inherent limitations, is the best method both for the surveys as well as for case finding programmes. This procedure had the ability to identify cases as well as potential cases in a short time. A resurvey of 15 villages of the NSS, 5 years after the first survey in the Madanapalle area yielded information that 1) there was no significant change in the prevalence rate of disease; 2) 30% cases of first survey had died during the year interval[5,6].

The next question was identifying appropriate sampling technique to select the study sample, and methodology/ investigative procedures (namely, house to house survey, registration of all persons of all ages, pulmonary symptoms elicitation and X-ray and bacteriology) that would be adopted. The best minds set to work and all available resources were utilized to conduct pilot studies in nearby areas resolving several issues, culminating in taking up the work of a landmark survey, *Some aspects of a TB prevalence Survey in a South Indian District*, Tumkur district, in Karnataka state[8]. Besides being near to Bangalore taking care of several logistics issues, Tumkur had all the characteristics of an average Indian district; the majority of population (88%) lived in about 2400 villages of the district, and there were 10 towns besides the district headquarters. The main objectives were to estimate the prevalence of infection, radiologically active pulmonary TB and bacteriologically confirmed disease. The results were, respectively: 38.3%; 1.86% and 0.41%. Both the infection and disease increased with age; of the total diseased, more than half were in the age group 40+ years and morbidity was higher among males[8-12].

Just as difficulties were faced with MMR reading, not only at the interpretation level, but even at the agreement levels between *intra* (readings made by the same reader of the same tested individuals at two points of time) and *inter* (readings of different readers done simultaneously of the same individuals), consistencies of tuberculin test readings posed problems[10-12]. Besides, other issues which directly influence the allergy inducing capacity: previous BCG vaccination, infections with mycobacterium other than *M. tuberculosis*, enhancing of tuberculin allergy if tests were repeated in the same individual after a lapse of time etc, to name a few, also clouded clarity in interpreting the test results. Studies were planned to better understand all these vexing issues resulting in a spate of papers which helped in better understanding and quantifying them. Pooled information indicated that 1) over 80% of the total number of infected occurred in households without cases[12]; 2) cases of TB occurred mostly singly in households[12], and the chance of finding an additional case in the same household is extremely small[19] 3) in households with bacteriologically confirmed cases, only 12% of children in 0-4 age group showed evidence of infection, belying the common belief that prevalence of infection is a good index of disease in households[12]. This resulted in developing a hypothesis that in spite of possible exposures, primary complex does not develop and children may show resistance to acquiring infection[12].

These were major inputs to developing a nationally applicable programme. By this time, a protocol had been developed with the objectives to study various vexing correlatory issues in disease determinants/ screening tools incorporating an additional factor, namely time: the same population would be followed up, say, 4 times at regular/ specified time intervals. Termed the *longitudinal study,* a population of 62000 belonging to 119 villages in Bangalore district was followed up during the years 1961-1968[21]. The study began yielding rich dividends on not only about prevalence of infection and morbidity of TB but also about fate of cases. During the period of surveys, sustainable tuberculosis program had not been implemented and developmental activities in the community were at very slow pace. This gave an opportunity to study the fate of cases and study the contributory forces that possibly determine the natural history of TB. Analysis of the basic data that the study generated extended to years, and papers after paper were published. One example is *Problems in defining a "case" of pulmonary tuberculosis in prevalence surveys*[15]. Published in 1974, the main findings of the study were: prevalence rate of tuberculous infection in the population was about 30% (among females 25% and males 35%). The overall prevalence rates of infection were fairly constants at all the four surveys, but a steady decrease in the prevalence of infection was observed in age group 0-24 years. Annual incidence rate of infection on the average was about 1%. During the study period, the incidence of infection showed a decline from 1.63% to 0.8% for all ages combined. Prevalence rate of disease ranged from 337 to 406 per 100,000 populations during the study period, the highest being at the time of first survey and lowest at the time of third survey. For the younger age group of 5-34 years, the rates showed continuous decrease during the study period. Annual incidence rate of disease ranged from 79 to 132 per 100,000 population, highest being between first and second surveys and lowest between second and third surveys. The incidence rates in younger age groups below 35 years showed a decline during the study period. Those with tuberculin test induration of 20mm or more (longitudinal diameter) had highest annual incidence rate of disease. The annual incidence rate of bacteriologically confirmed disease in the three radiological groups of population was (i) 185 per 100,000 with normal-rays, (ii) 958 per 100,000 with abnormal shadows judged as inactive tuberculous or non-tuberculous and (iii) 4530 per 100,000 with abnormal shadows judged as active or probably active tuberculous but bacteriologically not confirmed. The third group constituted 1% of the total population and contributed 34% of the total incidence cases. In each of the above three radiological groups, the incidence of disease was highest among those with tuberculin test induration of 20 mm or more to 1 TU RT 23 with Tween 80. Incidence rate for males was nearly double that of females. More than half of the new male cases were 35 years of age. Out of 126 cases followed up at three subsequent surveys over a period of 5 years, 49.2% died, 32.5% got cured and 18.3% continued to remain sputum positive. Both death and cure rates were highest during the first one and a half year period[15, 22-26].

About 30% of newly detected cases came from population who were uninfected at an earlier survey. Both infection and disease showed a decline in the younger age group. There was no evidence of an increase in drug resistance among newly diagnosed cases. The status of cases found at the initial and subsequent surveys showed changes with time, and such changes showed considerable differences for the various types of cases. These findings indicated that tuberculosis cases were not a uniform entity but embraced cases of several types, differing considerably in their tuberculin sensitivity, results of X-ray and sputum examination. It was felt that a single straight-forward definition of a case was not appropriate to suit all situations. One had to use more than one definition because there were serious diagnostic issues. For example, although theoretically, finding a single bacillus in sputum should be adequate proof of pulmonary tuberculosis, it was shown that finding of a few bacilli (3 or less) was very often due to artifacts and should not be the basis for a diagnosis. It was also found that positive radiological findings, in the absence of bacteriological confirmation, indicated only a high risk of the disease and not necessarily pulmonary tuberculosis. However, direct microscopy appeared to be a consistent index of disease; but in community surveys, it had the limitation of missing a substantial proportion of cases and of adding some false ones. All this pointed out that there could be different gradations from the point of view of diagnosis and ability to benefit from treatment. The differences between male and female patients with regard to death and cure rates supported this view. The study not only assisted in estimating parametric relationships between major determinants influencing the course of the disease, but also threw light on developing an epidemetric model that could depict the course of the disease in time, i.e., the natural history of disease, from which trends could be estimated. Results also tended to indicate that TB was declining in certain sectors of the population[26-28].

That tuberculin allergy in humans could be utilized to estimate TB morbidity was in the minds of researches for a long time. The first ever tuberculin survey conducted in India was in 1920s[1]. Even though the survey design was poor, it still pointed out to the government that tuberculosis infection was high wherever the survey was conducted and therefore it could be surmised the TB morbidity would also naturally be high. Tuberculin skin test was also extensively used during the mass BCG vaccination programs from 1948 onwards, which also indicated the same findings[1]. Unlike, MMR, tuberculin skin test was not an expensive tool and its predictive abilities could be exploited rationally and utilized in disease measurement surveys. After having carried out several major studies of lasting importance by using different tools and methodologies, EPS set out to thinking about ways of utilizing this tool. Towards this end, several tuberculin allergy related studies were conducted during the next decade: effect of BCG engineered sensitivity following vaccination, infection with Mycobacteria other than *M.tuberculosis* (M.TB), effect of malnutrition, techniques of interpretation and utilizing tuberculin sensitivity as a measure for estimating disease burden leading to the surveillance of TB. Intensive work in all these fields, yielded rich dividends culminating in developing the basic factors and inputs that are required to develop protocol for estimating risk of tuberculous infection on the model developed by K. Styblo in the 90's. Entitled the annual risk of tuberculous infection, ARTI is defined as the probability of acquiring new infection with M TB during the course of one year. Tuberculin surveys seemed also to hold the key for evaluating epidemiological trends of the disease in the community. Indeed, 23 years after the intake phase of the longitudinal study, an estimate of the annual decline in the risk of infection for the area was calculated at 3.2%. Further, the efficiency of the programme was estimated to be an average 33% during the nearly 3 decades of its existence which had resulted in an annual declining trend of the following extent: 1.4% in case rate, 2.0% in smear positive rate, and 3.2% in ARTI [29-36].

As India is vast country with poor resources, it was thought that the infrastructure already existed in the general health services system in different states could be utilized to conduct tuberculin surveys with time frames on models developed at the NTI. The NTI would receive raw data, analyze and calculate area specific estimates on the risk of tuberculous infection. When pooled, these estimates would ultimately provide basic information on the size of TB as well as throw light on the trend it would take. Indeed, the NTI invested a lot of energy in implementing this model initially in three different states (Tamil Nadu, Maharashtra, and Andhra Pradesh). Experience gained in this activity gave several necessary inputs and logistic insights in conducting such surveys in different parts of our vast country. Shortly afterwards, the first survey was conducted in the remote deserts of Rajasthan. Following it, a number of tuberculin surveys were conducted both in urban and rural set up with objectives of gaining valuable information on the conduct of tuberculin surveys in different epidemiological settings[34-40].

Experience gained from this body of work led to the natural conclusion that the tuberculin skin test indeed could be utilized in measuring annual risk of tuberculous infection. It was a historic moment when the NTI was given the responsibility of conducting *zonal level tuberculin surveys 2000-03,* that covered the nation as a whole. For the purpose of the survey the country was divided into 4 geographical zones: north, east, south and west-each having about a fourth of the country's population. An elaborate, district based, random stratified design to take care of both urban and rural populations as extant during the period and to estimate the average ARTI facilitating inter-zonal comparison. The survey in each zone was conducted following a uniform methodology. Using appropriate statistical techniques, 26 districts from the 4 zones were selected for the survey – 6 each from the north, south and west zones and eight from east zone. The survey was conducted in rural and urban clusters of the selected districts. From each cluster, 85 children, 1-9 years of age were registered for tuberculin testing with 1 TU PPD RT23 with Tween 80 and the maximum transverse diameter of the reactions were read about 72 hours later. The data analyzed among children without BCG Scar, pertained to 85,218 children – 25,816 from north zone 17,811 from south zone, 22,259 from west zone and 19,332 from east zone. The prevalence of infection was calculated both by the cut-off point method (Method I) and mirror image technique (Method II). The modes of tuberculin reactions attributable to tuberculous infection were observed at 20 mm in north, west and east zones and 19mm in south zone. The anti-modes varied from 14 to 16 mm in rural areas and 12 to 16 mm in urban areas of the four zones[34].

The ARTI computed from the estimated prevalence was found to be lowest in south zone (Method I- 1.1%, Method II – 1.0%). It was higher in east (1.3% by both methods) and west zones (Method I-1.8%, Method II-1.6%) and highest in north zone (1.9% by both methods). The proportion of infected children was found to be significantly higher in urban compared to rural areas in all the zones. The prevalence of infection estimated by Method I was also standardized by age, considering the study population in south zone as the standard population. The inter-zonal differences observed were almost similar to the non- standardized rates. The average ARTI from the country was computed as 1.5% after pooling the data for the four zones. Therefore the ARTI in India was at least 15 times higher than the estimates of less than 0.1% in many developed countries. Applying Karel Styblo's parametric relationship between the ARTI and incidence of smear positive cases, it was expected that there would be 95, 55, 90 and 65 smear positive TB cases per 100,000 population for the north, south, west and east zones respectively. The high ARTI is largely due to the unsatisfactory performance of the erstwhile NTP. However, the introduction of the RNTCP in the country has raised hopes of controlling TB[33, 34]. Further to this, an important step was taken to analyze data of these surveys which included children with BCG scar as well. The results were found to be similar. Therefore for such surveys when undertaken, scar status would be of little significance.

Following this rich experience, 3 state level ARTI surveys were undertaken: Orissa (2003-04), Andhra Pradesh (2005-06) and Kerala. District level surveys were undertaken in Khammam tribal district (2000-02); another was carried out among orphanages. In a resurvey carried out among randomly selected schools of Bangalore, the average annual decline in ARTI of about 4% was observed between the two surveys. But it cannot be stated with certainty whether this trend was achieved by the RNTCP program or changes in the population pattern or effects of overall socio-economic improvements that is occurring in that area. However, rich experiences gained from the above studies were utilized effectively in drafting of the protocol and work procedures of repeat zonal ARTI surveys (2009-2011). In-order to bring about changes and sharing of experience with different institutions of repute, the NTI became the *nodal centre* and the study has just been completed in collaboration with 5 institutions. Results from this ambitious study are expected to bring out a lot of information on morbidity of TB as well as its trend[38-40].

A protocol with objectives to find out point prevalence of pulmonary tuberculosis among adults in 7 different locations of India was prepared in 2006 facilitating 7 selected institutions to carry out the surveys in their respective areas. On its part, the NTI selected Nelamangala Taluk, Bangalore district. The just completed survey in this area revealed a substantial decline when compared to the previous survey in the same area in 1975 (unpublished data). Besides regular work the section has also extended technical support to epidemiology studies in Indonesia, Bhutan and DPR Korea. It has also been providing support to research fellows, PG students, workshops, training activities and South East Asia Regional Organization of the World Health Oganization as and when warranted.

The section is now gearing to take a lead in the measurement of impact of TB control programmes, using newer methods.

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