TUBERCULIN SURVEY: AN APPRAISAL OF ITS FUTURE ROLE IN INDIA

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There is need for establishing a National Tuberculosis Surveillance Agency that can independently take care of Tuberculosis surveillance. This agency can come out with a consort statement on National Guidelines on Tuberculin Survey in consultation with tuberculosis experts. The agency can be vested with the sole responsibility of conducting periodic tuberculin surveys and conserving the data for future use. It can undertake periodical training courses on tuberculosis surveillance and can act as a mediator for ensuring and promoting quality research. Such an undertaking is essential for warranting future credibility and comparability of tuberculin surveys within and outside India.

I. INTRODUCTION

India had made substantial contributions in the field of tuberculosis control that finally led to the development of a scientifically sound tuberculosis control program. In its concept and outline, it had found acceptance the world over. Unfortunately for India, however, the diverse geographic, social, cultural, economic and political background led to serious pitfalls in the implementation of tuberculosis control program. On the other hand, by 1970s, tuberculosis had ceased to be a major public health problem in most of the developed world, and it had gradually lost the global priority. Consequently, tuberculosis control activities in high prevalence countries got undermined among the multitudes of other health problems.

Tuberculosis is currently the leading cause of mortality and morbidity in most of the developing countries.(1) India alone contributes to 30% of global morbidity, adding 2 million cases each year and nearly half million dying of the disease. It is estimated that the economic cost of tuberculosis in India is more than US $2 billion (Rs.8,000 crore) each year.(2) In 1993 when WHO declared tuberculosis as a global emergency, India revamped the National Tuberculosis Program (NTP) and introduced DOTS under Revised National Tuberculosis Control Program (RNTCP) with important strategic reforms.

DOTS, no doubt is the best treatment currently available for tuberculosis control. Preliminary reports from India are highly encouraging with an increasing cure rate from 70.7% to 83.9% from 1993 through 1998.(3,4) Case-finding efficiency of RNTCP has considerably improved, but is still less than 50%. Until we achieve a steady and acceptable cure rate throughout the country, it is not possible for us to boost up case finding. By 1998, DOTS coverage in India was only 2% and it is expected to cover l/4th population by 2002.(5,6) On the other hand, experts have cautioned against too rapid expansion of DOTS and the need for a phased expansion to cope up with the enhanced requirements in terms of technical and diagnostic support as well as uninterrupted drug supply. With 50% case finding efficiency and 85% cure rate, the cumulative effectiveness of RNTCP can be considered to less than 50% (50% of 85%= 42.5%). Mathematical models also suggest that DOTS alone cannot reduce tuberculosis incidence in a timely fashion even when HIV is not a problem.(7) This is a clear indication for the need of close surveillance of tuberculosis control as suggested by WHO.(8)

II. TUBERCULIN SURVEY AS A SURVEILLANCE TOOL

Morbidity assessment of tuberculosis based on case finding and notification is unreliable. Even in countries where notification of tuberculosis is statutory, under-reporting is common.(9) Hence epidemiological studies usually rely on community surveys for their data source. Earlier these used to be disease surveys. Presently, the situation is studied more on the basis of annual risk of tuberculosis infection (ARTI), estimated from prevalence of tuberculosis infection among non-BCG vaccinated children. ARTI is a reflection of the incidence of sputum positive tuberculosis cases in the community. Apart from the methodological issues and high costs, direct estimation of incidence of tuberculosis infection is not rewarding, because of interference with BCG vaccination, environmental mycobacterial infections and booster reactions.

Perhaps the best tool available for tuberculosis surveillance is tuberculin testing. A great deal of information can be generated from this simple test. It is most economical, highly reliable when only the children population is tested and can be operated delinked from tuberculosis control programs.(10,11) Styblo first described estimation of ARTI from infection prevalence rate in 1960s and later Bleiker developed a simple model for estimating annual decline rate of tuberculosis from serial tuberculin surveys, the most

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important tool for surveillance of tuberculosis.(12,13) A steady decline in ARTI (not less than 5%) is indicative of a good control program. Methods have also been described to estimate the age specific prevalence and highly informative projections of age cohort effect from past to future. These indices can be further modeled to estimate the approximate year in which tuberculosis could be eradicated.(14)

Tuberculin testing carried out during the mass BCG vaccination campaign throughout the country, in the 1950s, gives an overall idea of tuberculosis infection rate throughout the country(15) Beyond this, there had been frequent surveys restricted to specific regions, mostly in and around Madras and Bangalore, where the two major tuberculosis institutes are situated. It is not appropriate to project these data to national level, owing to the peculiarities of these regions and the non-concordance of the results. There is no way to ascertain whether these variations are true reflections of the disease process itself or due to differences in methodology. This emphasizes the need for nation-wide tuberculin survey and standardizing the survey procedures.

The main objective of this article is to highlight the important challenges in the conduct and interpretation of tuberculin surveys with special reference to Indian setting. Guidelines on tuberculin surveys are many. Nevertheless, inconsistencies in methodology between and within countries seriously limit the comparability of results.(16,17,18,19,20) In countries like India, there are many practical difficulties that limit strict adherence to traditional guidelines. National guidelines for conducting tuberculin surveys should be based on the peculiarities of its setting, at the same time permitting international comparability.

III. METHODOLOGICAL ISSUES OF TUBERCULIN TESTING

Detailing the methodology is not within the perspective of this article and only a few relevant issues will be discussed. WHO had initially recommended 1 TU PPD-RT23 as the standard dose, but the current dose of tuberculin, internationally recommended, is 2TU PPD-RT23 (equivalent to 5 TU PPD-S).(16) A few countries like India continue to use 1 TU PPD-RT23, about which serious debate is going on. Recent studies indicate that the pattern of tuberculin reaction to 2 TU is not significantly different from 1 TU.(21) Further, increasing the dose would aggravate interference from non-specific reactions and limit comparability of past and future studies. Inter and intra-observer variability of measurement of tuberculin induration can be controlled by a careful standardization of procedure. It has to be considered whether existing palpation method can be substituted with the more reliable ballpoint pen technique in future.(22,23,24) Inconsistencies in using longitudinal versus transverse diameter can lead to gross disparity of results and should be avoided. Digit preference bias is a frequently reported problem of tuberculin surveys and can be minimized by use of a measuring gauge with face away from the reader.(18)

IV. BCG VACCINATION AND TUBERCULIN SURVEYS (Figure: 1, 2)

Non-specific reactions due to BCG vaccination and atypical mycobacterial infections are difficult to distinguish from true tuberculin reaction. It is argued that tuberculin surveys may not have relevance in future because of wide BCG vaccination coverage in developing countries. Identification of non-BCG vaccinated population is also a major concern. Significant degree of misclassification occurs when scar status alone is considered for identifying non-vaccinated population.(25) Despite the fact that this problem was anticipated well ahead in 1960s, no new test could substitute it till now. This goes to indicate that tuberculin surveys would remain the main stay of tuberculosis surveillance, in the years to come.

There is no controversy that the proportion of tuberculin reactors (>6mm induration) is relatively high among vaccinated population, but the distribution of BCG induced tuberculin reaction follows a pattern different from true tuberculin reaction. BCG induced reaction tends to wane off slowly and the mode gradually shifts to the left, causing less interference with true tuberculin reaction (Fig: 2).(26) In addition, neonatal BCG vaccination is associated with milder degree of tuberculin sensitivity that wanes off much earlier. Thus by recruiting older children, interference of BCG induced hypersensitivity can be minimized if neonatal vaccination is the usual practice. It is worth while to note that majority (>80%) of BCG vaccinated children show negative reaction (<6mm induration) to tuberculin testing.(27,28,29,30,31) Comparative studies indicate that the difference in distribution of tuberculin reaction between BCG vaccinated and non-vaccinated population is mainly observed in the region of 6mm to 14mm. Thereafter there is a progressive decrease in the gap and the same is almost absent beyond 20mm.(28,29,31) Most studies indicate the 'difference to be negligible and there is no significant change in the distribution pattern when BCG vaccinated population is excluded (Fig: 2). (30,31,32) This observation could partly be due to misclassification consequent to waning of BCG scar.
but in tropical countries there is every reason to believe that atypical mycobacterial infections induce more intense and sustained non-specific reaction (6mm to 14mm) than BCG vaccination. Thus in countries like India, it would be practically impossible to eliminate non-specific reaction, even when BCG vaccinated population is excluded. In the current situation, it seems most appropriate to apply better analytical techniques and target the survey on population least likely to be affected by BCG vaccination and atypical infections, ignoring vaccination status.

V. SURVEY POPULATION, SAMPLE SIZE AND SAMPLING

Many methods are employed for estimating the risk of tuberculosis infection, but the most widely applied is the indirect estimation by tuberculin testing of subjects of same age or age group at 5 to 10 years intervals. (33) Annual decline rate of tuberculosis infection estimated from such surveys has proved to be as reliable as that estimated from annual surveys among different age groups. School surveys are much more economic and manageable than community surveys provided school non-attendance and drop out rates of the region are insignificant. The design of sampling strategy and sample size estimation has been extensively covered by various authors. (17,34) The general recommendation is for a multistage sampling, with sampling proportional to size in selecting districts, schools being sampled by simple random sampling and to include all eligible children in the selected schools.

VI. ESTIMATING PREVALENCE OF TUBERCULOSIS INFECTION

Cutting point method

Prevalence of tuberculosis infection is usually estimated by cutting point technique, but is confronted by many complex issues. No cutoff point is both 100% sensitive and specific and gauging the error precisely may not be feasible at all. Although sensitivity can be measured with reasonable accuracy, assessment of specificity is practically impossible in high prevalence countries, further it is reported to be variable over time and place. (29,35,36) Hence an unequivocal separation of infected from not infected is not possible and the ultimate aim is to derive the near accurate estimate of the proportion infected. Choosing a cut off point is very crucial and should be based on the knowledge of the diverse influencing factors. Fortunately for tuberculosis low-prevalence countries, interference with BCG vaccination and atypical mycobacterial infection is minimal. Hence traditional cutoff points in the region of antimode (usually within 6mm to 14mm) give reasonably reliable estimate of infection prevalence. In tropical countries where tuberculosis is common, the distribution of tuberculin reaction attributable to atypical mycobacterial infections completely obscures the antimode of true tuberculin reaction. This implies that estimates derived from the traditional cutoff points would over-estimate the prevalence of infection. Unfortunately most investigators have ignored this aspect during analysis. (37,28,31,38) At these points, mathematical correction should be based on the level of specificity, which is very difficult to gauge. Some investigators have used cutoff points beyond 18mm, without any adjustment for low sensitivity. (39) This is not justifiable, as nearly half of truly infected subjects would be distributed to the left of this point as the mode of true tuberculin reaction is located between 16mm to 20mm. (40,41,42) Often discrimination analysis has been adopted for deciding on best cutoff point, but is complex and involves procedures for assessing sensitivity and specificity. (43) Lower limit of 95% confidence interval of distribution of true tuberculin reaction more or less corresponds to the antimode and is again confronted with low specificity for reasons specified above. Critically going through all the issues, it seems most appropriate to choose higher cut off points adjusting for low sensitivity assuming non-specific reactions are rare beyond 14mm. (41,44,45) Assuming 100% specificity, mathematical correction can be done by dividing the estimated prevalence by the sensitivity of the given point. Sensitivity at different cut off points can be estimated from distribution of tuberculin induration among sputum positive tuberculosis patients. This, however, is only possible provided the tuberculin test result profile of the confirmed TB cases are concurrently available for the same area. For example, if the sensitivity and estimated prevalence rate at 14mm is 82% and 10% respectively, the corrected prevalence rate would be 12.2% (10% divided by 0.82).

Mirror image method or curve reconstruction method (33, 41,44)

This method is advisable for situations where tuberculin distribution has lost its bimodal pattern due to high level of non-specific reaction. The model assumes a normal distribution for true tuberculin reaction, with a mode located in the region between 16mm to 20mm. This mode is observed to be reasonably stable over time and space. It is also assumed that beyond this point there is no overlap by non-specific reactions, i.e. the number beyond the mode represents approximately half the number of true reactors. Assuming a normal distribution for true tuberculin reaction, the total number of subjects with true
reaction can be calculated by adding the number of subjects showing reaction size equal to the mode to double the number with reaction sizes larger than the mode. For example, if the mode is identified at 18mm and if the number of reactors at 18mm and beyond 18mm is 50 and 400 respectively, then the total number infected is 850 i.e. 50 + (2 x 400). The major disadvantage with this method is that even 1mm difference in mode can lead to major differences in prevalence estimates and often the mode cannot be identified at all. A concurrent study of distribution of tuberculin reactions among tuberculosis patients would settle this issue.

Mixture analysis

Mixture model analysis is a new method and is supposed to overcome the shortcomings of the cutting point technique. This model is usually applied when the population studied is heterogeneous, like in a tuberculin survey. The individuals fall into any of the 3 groups i.e. individuals with Omm induration, those reacting to M. tuberculosis and those reacting to environmental mycobacteria. Information on distribution pattern of tuberculin reaction of M. tuberculosis infection and other atypical organisms can be included in the model. The main advantage of mixture model is that cutoff point is not needed. By using cutting point method, a lot of information is lost, since all in durations above the cutoff point is considered same, although the significance of each degree of reaction is different. The main disadvantage of mixture model is its complexity, requiring high level statistical expertise. This cannot be considered a major issue, as mixture model has recently been applied in many other situations as well.(46) The most recent example of its application is that of Korea, where retrospective data from seven tuberculin surveys from 1965 to 1995 was re-analyzed using mixture model.(36) The prevalence of environmental mycobacteria in Korea, is very high and BCG vaccination coverage had increased from 26% to 92% over the three decades, leading to a total absence of bimodal pattern. The results of this analysis are highly inspiring and it can be hoped that this new method would be able to take care of the inherent problems of cutting point method. However, it requires a wider application and comparison with ongoing techniques before universal acceptance.

VII. CONCLUSION

It is almost a decade since RNTCP was launched in India. Success stories of RNTCP are highly inspiring. It is essential to sustain the vigil and enthusiasm for it might take a few more decades to bring down tuberculosis problem, significantly enough. Considering the relative simplicity of the survey procedure and a high potential for future predictions, tuberculin survey remains the best epidemiological tool available for tuberculosis surveillance. The need of tuberculin surveys has not been recognized to its full extent in developing countries, where it is really indicated. There are still many unanswered methodological issues in the conduct and interpretation of tuberculin surveys that had contributed to a gradual waning of its credibility. Most challenging is the need for recruiting non-vaccinated children and it is variously proposed that all children irrespective of vaccination be included with relevant adjustment during analysis.

An attempt has been made to describe the possible ways in which interaction with non-specific reactions could be controlled. Ensuring uniformity in survey methodology and maintaining the quality is of utmost importance. This highlights the need for establishing a National Tuberculosis Surveillance Agency that can independently take care of Tuberculosis surveillance. This agency can come out with a consort statement on National Guidelines on Tuberculin Survey in consultation with tuberculosis experts. The agency can be vested with the sole responsibility of conducting periodic tuberculin surveys and conserving the data for future use. It can undertake periodical training courses on tuberculosis surveillance and can act as a mediator for ensuring and promoting quality research. Such an undertaking is essential for warranting future credibility and comparability of tuberculin surveys within and outside India.

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Fig 1: Tuberculin Reaction at 2 1/2 months & 4 years after BCG vaccination

![Graph showing tuberculin reaction at 2 1/2 months and 4 years after BCG vaccination.]

Figure 2 Model of composite distribution of (a) non-reactors, (b) non-specific reaction and (c) true tuberculin reaction. The distribution curves for BCG vaccinated (―) and non-vaccinated (−−) follow the same pattern. The proportion having reactions from 6mm to 14mm is slightly higher among vaccinated, but the difference become imperceptible beyond 20mm. Even in non-vaccinated population, the antimode is completely obscured by non-specific reaction.