Correspondence

BCG, tuberculin surveys & annual rate of tuberculosis infection in south India

Sir,

Gopi et al\(^1\) have shown that BCG vaccination does not interfere with tuberculin surveys for estimating annual risk/rate of tuberculosis infection (ARTI). The magnitude of the study and the clarity of results deserve appreciation. This is one of a series of similar papers in recent years, all showing the same phenomenon - many of them were cited by Gopi et al\(^1\). The accumulated evidence is that BCG vaccination, with or without scar, can be ignored in tuberculin surveys for determining point prevalence of tuberculosis (TB) infection\(^1\). This is good news for tuberculin surveys as the selection of population sample is simplified without the need for checking BCG scar or history. It is bad news for TB control programme, as the implication is that BCG does not alter the prevalence of infection - a lesson already learned from the Chingleput BCG trial\(^2\).

The more important findings in the study were the ARTI values in 3 sequential surveys in one community\(^1\). They show the alarming reality that TB is not getting under control in spite of all past and current control efforts. Very urgent additional interventions are necessary to speed up TB control in India. The emergence of human immunodeficiency virus (HIV) epidemic, multi-drug resistant TB and “extremely drug resistant TB” is like dark clouds on the horizon of national TB control. Disastrous future on TB awaits India, unless urgent additional interventions are designed and implemented to make an impact on its prevalence and incidence.

BCG was introduced in the National TB Programme (NTP) way back in 1962 and it was incorporated in the expanded programme on immunization (EPI) in 1978. Yet, the methodological question if BCG vaccinated children should be included or excluded in tuberculin surveys remained uninvestigated until recently. There has been a long period when tuberculin surveys were not conducted and point prevalence of infection was not measured. This gap was identified as a lacuna in the Revised National TB Control Programme (RNTCP) established in 1992\(^3\). An editorial published in 2000\(^3\) had demanded “a systematic approach for determining the prevalence and incidence of *Mycobacterium tuberculosis* infection among children and adults”. “This has to become the cornerstone of TB control and of assessing the change in trend of infection over time in the community, until it reaches the required less than 1 per cent level in children below 14 yr, as defined for control status”. The several reports mentioned above indicate that the above recommendation has been taken seriously and systematic tuberculin surveys have been designed and conducted in the north, east, west and south of India\(^4\). The authors provide critically important information about the prevalence of infection and ARTI in children in many regions of India, and time trend in Tiruvallur in Tamil Nadu.

The three surveys were done within a span of 6 years, during 1999-2001, 2002-2003 and 2004-2005, on large samples selected on sound epidemiologic principles. However, methods adopted to analyse and
interpret the results were not equally convincing. The distribution of reaction sizes was unimodal each time as seen in the figure. In many tuberculin surveys in the past the distribution was clearly bimodal with a visible antimode. In a bimodal pattern, the first cluster represents cross-reactions to BCG and other locally prevalent non-TB mycobacteria and the second cluster represents TB-specific reactions. Thus the antimode is essential to distinguish between the two. When the distribution is unimodal, it is not easy to demarcate between the two clusters, but at the same time it is necessary to assign a demarcation for such differentiation.

There are at least four ways to proceed further. One is what was used by Gopi et al. They took the lowest value in the middle of the curve and used it as antimode. While that is an acceptable way under the circumstances, applying the same value on two other surveys was unjustified. If one common value of antimode were to be derived from the three data sets, a second approach, more acceptable than the first (though not ideal), could have been to club all data and make one distribution curve and find the lowest value in the middle of the curve. That value could be applied to the three surveys.

A third approach (better than the two) could have been to use the appropriate antimode for each survey separately. Thus, while 12 mm was chosen for the first survey, 11 and 8 mm would have been appropriate for the second and third surveys. The antimode helps in estimating the prevalence of TB infection and calculating ARTI. If the antimode is shifted to the right, specificity would increase but sensitivity would decrease. By applying 12 mm to the subsequent surveys, the sensitivity is reduced more than in the first set, and ARTI would shrink as artifact. Therefore I argue that the declining trend of ARTI values of 1.6 in the first survey, 1.4 in the second and 1.2 in the third, qualified by the authors as “significant (P<0.001)” need not be true. Two points in favour of my argument are given below.

The three distribution curves were dissimilar in pattern. The obvious differences are the peak in third graph is 2 mm instead of 3 mm as in others; the shape of the second curve is not smooth as in the other two; the heights of the peaks in the three curves are at about 35, 25 and 50 per cent respectively; and the area under the curve with the first mode is quite obviously varied. The three graphs were drawn with different Y axis scales, obviously for uniform visual effect in the paper. Had these been drawn with uniform scale, the third curve would have shown up with the largest area under the curve. Thus, the distributions are non uniform and one value cannot fit all. The second argument is that in the short span of six years a statistically significant trend of decline in ARTI is very unlikely. If the trend were true and sustained, one would expect the continued fall of ARTI to near-zero in 6 yr, a most improbable prospect. In short, the differences in the same population but in different samples over a relatively short period were most probably inherent in the surveys themselves, due to well known variables in the test and its reading. The proportional distribution of children by year-by-year age in the three samples was not mentioned - if there was any variation in the proportions, we must expect variations of response-distribution also. The authors could easily check this out. For these reasons I believe that the surveys should have been treated as independent data sets for inter-survey comparison. If this approach was adopted, the time trend of declining ARTI may not have been statistically significant. A re-analysis is recommended.

A fourth approach to select a cut-off value for inter-survey comparison would have been to apply the usual norm used in India, namely 8 or 10 mm. The bulk of the study sample had reactions of <8 mm in each survey. Knowing that BCG cross-reaction sizes have come down drastically over time and that true TB responses would begin with about 5 mm reaction, the use of 12 mm cut-off would have artificially reduced infection prevalence, hence
ARTI. In my opinion, the calculation of time trend has unclear outcome. A sensitivity analysis by using different methods to remove cross-reactions will help. Obviously TB experts will have to develop robust methodology to calculate ARTI in populations with high BCG coverage and also endemic non-TB mycobacterial infections. Also they have to decide how often and in which populations to conduct tuberculin surveys for assessing and monitoring the success of the TB control efforts.

While RNTCP has reached the whole country for the first time in 2006, systematic monitoring of reduction of TB prevalence in children has lagged behind. Considering the enormity of the problem of TB in India and the excellent infrastructure established to control it, the time and effort put in to establish monitoring tools and their systematic application will go a long way in encouraging the network of TB control personnel to achieve progressive successes. ARTI measurements need to be conducted periodically in every district in the country.

The ARTI in children below 10 yr in Tiruvallur and in several other parts of India remains more than 1 per cent. The prevalence of TB infection by age 14 is therefore likely to be more than 14 per cent. Way back in the 1970s TB infection prevalence was 1-2 per cent below 5 yr and 15-17 per cent by age 15 yr.5 In other words, the results of the recent tuberculin surveys seem to indicate that there has not been any discernible reduction in ARTI in children. The TB control status that RNTCP desires is 1 per cent cumulated prevalence of infection by 14 yr6,7. This translates to an ARTI of 0.07 per cent in children below 14 yr. The current rate of 1 per cent per year is disappointingly high and the TB prevalence appears to be static over 3 decades. This problem must be addressed seriously and immediately by TB experts. If the speed of control is to be faster, newer tactics will be needed. A national workshop of clinicians, epidemiologists and public health experts in addition to TB specialists and RNTCP leaders must identify elements of such new tactics.

As a paediatrician I believe that TB will not be controlled as long as we neglect childhood TB infection1. Every child with positive tuberculin reaction is a sentinel for the presence of at least one sputum-positive adult in the family, household or immediate vicinity. Similarly, every adult with sputum-positive TB would have infected some children within the family, household or immediate vicinity. Recent childhood infection deserves to be treated according to paediatric clinical recommendations. Active search for childhood infection around every adult case and screening of all adults around every child with TB infection are necessary to increase the sensitivity of case detection in communities. Without identifying increasing proportions of infectious TB in adults India cannot hope to reduce the incidence of TB infection in children. Without reducing the incidence of TB infection in children, India cannot hope to reduce the incidence of infectious TB in adults.

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References


Authors’ response

Sir,

Appropos to the major queries raised on our article entitled “Impact of BCG vaccination on tuberculin surveys to estimate the annual risk of tuberculosis infection in south India”1.

The first comment was that the methods adopted to analyze and interpret the results were not convincing. We used consistent cut-off point to define infection in all surveys and measure the trend to allow comparability. This method of analysis has already been used by us2 on the basis of similar reports published earlier3-5. This also explains as to why the three surveys were not treated as independent data sets for inter-survey comparison.

Another argument was that in a short span of six years, a statistically significant trend of decline in ARTI was very unlikely. The trend in infection was estimated from estimates of infection from the three survey done at intervals of less than 5 yr between two subsequent surveys. There was no significant difference in the prevalence of infection (0-9 yr) between two subsequent surveys. This may be an indication that this tool may not be sufficient for measuring short-term trend. However, the first and the third surveys at an interval of about 5 yr have demonstrated a 6 per cent per annum decline in infection, emphasizing the importance of this tool to measure long-term trend in high burden countries such as India. DOTS was implemented in this area in 1999, the prevalence of infection namely 7.8, 6.9 and 6.0 per cent as estimated from the three surveys carried out during 1999-20051 showed that the implementation of a DOTS-based programme for TB control was associated with a reduction in prevalence of TB infection among children aged <10 yr compared to pre-DOTS era.

The primary aim of the study was to find out whether BCG vaccinated children can be included for estimation of infection. The trend analysis and the annual decline were secondary. This has been well explained in our earlier publication2 in detail.

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References


