Does BCG Immunization Prevent Tuberculosis?

In the article entitled "Tuberculosis in BCG Vaccinated Children", Deshpande and Deshpande have stated in the discussion, "The protective value of BCG vaccine is doubtful. Both BCG immunized and unimmunized children suffer from tuberculosis"(l).

It is well known that both natural and BCG induced tuberculin sensitivity tend to wane in the course of time. This waning could also be associated with some degree of loss of protection against superinfection(2,3). Presence of a BCG scar in later childhood may not be an indicator of presence of adequate protection against exogenous superinfection. The authors have not mentioned if there were any cases who had been given BCG booster dose (revaccination)?

The recommendation that children vaccinated at birth be revaccinated at school entry is based on the fact that post vaccination tuberculin sensitivity wanes over a period of time. Further, it has also been observed that BCG given at birth is not protective against adult type of tuberculosis. These factors suggest the need for revaccination with BCG to decrease the incidence of late childhood and adult type of tuberculosis(4-6).

The school entry age has been lowered to 3 years because of Nursery and Play Group sections in the schools which means Mantoux testing should be done in the second year of life and if required BCG be given. Similarly this first booster dose would not provide life long protection so a child should be re-evaluated after every 4-5 years for the need for BCG revaccination till the age of 18 years.

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I read with interest the article "Tuberculosis in BCG Vaccinated Children"(l). Although BCG vaccine is being given at birth as a National Health Programme, it has failed to prove it's ef-

ficacy to prevent pulmonary tuberculosis. This is evident from this and several others papers communicated from time to time. As far as the dissemination of disease is concerned, BCG seems to have rather a questionable protection. Obviously, there is a need for us to change the strategy for which more detailed information is required. As a first step I would suggest that this data(l) be re-examined in different age groups. Nearly half of the patients in the study were under the age of 5 years and l/3rd between the age 5 and 10 years, and the rest above 10 years of age. Since BCG is given at birth, the data can be reanalyzed in these three distinct categories thereby assessing the vulnerability of the different age groups. This would provide a basis for multiple BCG vaccination instead of a single dose given at birth.

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Comments

Drs. Deshpande and Deshpande have interpreted their data(l) to conclude that "BCG vaccination does not prevent infection" and also that "it offers a partial protection by preventing serious forms of tuberculosis". When they stated that BCG vaccination does not prevent infection, what they meant was that it does not prevent the disease of tuberculosis. Following on the paper, Dr. Yash Paul has suggested BCG revaccination in tuberculoin-negative children in their second year of life, and thereafter every 4-5 years till the age of 18 years. Dr. Mehta has suggested that the 300 children with tuberculosis in the study should be divided into 3 age groups, namely below 5, 5 to 10 and over 10 years of age and the case control analysis made in each age group separately.

The topics of BCG imunization and it's role in prevention of tuberculosis are very difficult to investigate. The numbers and variety of differing opinions on these topics are in inverse proportion to the availability of good data. I do not wish to re-state the many difficulties here, except to point out that they exist and are very real.

Although the data of Deshpande and Deshpande could be reanalyzed as suggested by Dr. Mehta, let me first ask if the results of the study are convincing enough for further analysis and interpretation. For the sake of argument, let us accept that all diagnoses were correct and that all 300 children really had tuberculosis. We do know that among all EPI vaccines, BCG consistently has recorded the highest coverage in many studies in India and also in many other countries as well. Suppose 85% of children are immunized with BCG in the denominator of Pune population. Now it would appear that 145 cases of tuberculosis occurred in the 85% immunized segment of catchment population and 155 cases came from the 15% unimmunized segment. If BCG had no protection, one would have expected 85% of cases among the immunized and 15% among the unimmunized. Looked at this way, one can begin to see that BCG did indeed have some degree of protective efficacy in this study-

To further this line of approach, the case control study should have been on the 300 cases and at least 300, or preferably 600 or 900 controls without tuberculosis, selected on the basis of predetermined criteria. Then the proportions of immunized children among cases and controls should be measured. We know that 145 (47.7%) cases were immunized. How many in the control would have been immunized? Perhaps 80% or 85% or even 90%. With these data the odds ratio should be calculated and that will give you an assessment of the protective vaccine efficacy of BCG.

One important lesson emerging from the study of Deshpande and Deshpande is that childhood tuberculosis continues to be an important public health problem in India, in spite of extensive BCG immunization. Childhood tuberculosis is the consequence of open pulmonary adult tuberculosis, which will not be prevented by BCG. BCG does not control tuberculosis in adults; hence its role is limited in the public health-sense of tuberculosis control. This is one, and not the only, reason why I believe that additional doses of BCG has not much merit as a national policy.

Before considering repeated BCG doses, we must answer two questions. One, how many times can a child get primarily infected with *M. tuberculosis,* wild or attenuated? The answer is only once. Second, does tuberculin sensitivity indicate protection from tuberculosis? The answer is, no. I am illustrating here the formidable difficulties in arguing for multiple doses of BCG on theoretical basis. So, we need data, but if it is difficult enough to measure the protective efficacy of one dose of BCG how can we investigate the benefits of 2 doses?

Yet another problem highlighted by the study is the difficulty in diagnosis of tuberculosis in children. According to the authors, only 50 (32%) among the 155 unimmunized children with tuberculosis were tuberculin test positive. On the other hand all 145 immunized children with tuberculosis were tuberculin positive, presumably as a result of BCG inoculation. Was tuberculosis over diagnosed in both groups?

The authors stated that children immunized with BCG had less severe forms of tuberculosis and that most unimmunized children were seriously ill and required prolonged hospital stay. I wish that they had attempted to quantify these findings and analyzed if the differences were statistically significant. Without this, the conclusion that BCG offers partial protection appears to be a subjective opinion rather than a conclusion from the analysis of the data. The opinion may indeed be correct, but it has not been proven to be so.

The answer for the control of tuberculosis lies elsewhere, not in BCG. One dose of BCG will do for infants, since what we can achieve with BCG is to reduce the risk of progressive primary tuberculosis with dissemination (miliary, meningeal and bone tuberculosis). BCG cannot be expected to prevent tuberculosis altogether.

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Typhoid Vaccine

The recent Immunization Dialogue on typhoid vaccine(l) was extremely useful and cleared the confusion arising after introduction of newer commercial products. A further clarification on dosing may prove beneficial. The standard textbooks mention the dose of TA vaccine as 0.5 ml if the child is beyond 10 years of age, 0.25 ml for subjects younger than 10 years and 0.1 ml if given intradermally. Does Professor Jacob John recommend the same? What are the possible local changes after intradermal injection of TA vaccine?

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Comments

The whole cell killed Salmonella typhi vaccine contains 1000 millions of organisms per ml. If it is TA vaccine, it would also contain 500 or 750 million S. paratyphi A. The adult dose is generally recommended as 0.5 ml, for primary immunization (2 doses 4 weeks apart) and for booster immnization, when given subcutaneously.

For children, no uniform recommendation has been evolved since there have not been any efficacy studies among them. There are generally two types of recommendations. One is to grade doses for 3 age groups, namely one-year-olds (0.2 ml 4 weeks apart), 2-10 year-olds (0.3 ml 4 weeks apart) and those above 10 years (0.5 ml 4 weeks apart). The other is to give half adult dose for all ages between 1 and 10 years of age. Except for ourselves, no one else has suggested that TA vaccine could be given to infants(l). Indeed we gave 0.5 ml doses and not lesser volume(l). Our rationale is that we are in typhoid-endemic region; hence we need good immune responses, and also that the reactions to primary doses are quite tolerable in infants and children. I am not 'recommending' but stating that we used the full doses in infants and children. The official recommendation from the manufacturer *(e.g.,* King Institute, Guindy, Madras) is the graded dose regime mentioned earlier.

Intradermal inoculation is usually 0.1 ml irrespective of age, both in children and adults. Again, intradermal route is more commonly accepted only for booster doses; we used it even for primary immunization quite successfully in infants and young children(l). The local reactions following intradermal inoculation is typical of delayed type hypersensitivity with erythema and induration. In hyperimmune persons, vesicle formation and ulceratioin may occur. But that happens only after several booster inoculations; hence only in adults.

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