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Commentary

Revaccination with Bacille Calmette-Guérin: Some issues to consider

Sir,

The article on the impact of revaccination on the incidence of tuberculosis (TB) disease published in this issue of the Indian Journal of Medical Research[1] is interesting and throws up some issues for consideration. The data presented represent a community-based controlled clinical trial on a small subgroup of individuals (2890 cases and 1546 controls) constituting 1.8 per cent of the original study population. Nevertheless, the rigour of the main study[2] applied equally to this population. Since the vaccination preceded the incidence, this makes it a prospective study. The fact that this analysis has been done long after the conclusion of the study does not make it a retrospective analysis. Hence, even though the inferences are based on small denominators, they are valid and this article has the potential to influence policy. However, policy makers should practice caution and careful consideration of a few issues in this context.

Of the 4436 individuals who formed the study population, 1713 had a reaction size of ≤12 mm. Of these, 1151 were vaccinated and 562 were in the placebo group (study Table I, *DOI: 10.4103/ijmr.ijmr_1540_22*). Among 2494 of the study participants who showed a reaction size of ≥12 mm, 1603 were in the vaccinated group and 891 were in the placebo group. The study Table II (*DOI: 10.4103/ijmr.ijmr_1540_22*) presents a composite analysis of these two groups over three-time points. The overall protective efficacy was not higher than 36 per cent. Given this, the 80 per cent protection shown in the age group of 31-40 yr could well be an artefact or just a chance finding. Taking this without careful consideration or out of context could be a decision taken in a hurry as this could be a mere reflection of differential coverages in that particular age group.

It would have also been interesting to see the protective efficacy separately for those with and without latent TB infection. Furthermore, vaccination would be a third stimulus given in the reactor group compared to the non-reactor group, in which it would be a second stimulus. It is also possible that the age distribution would be different in these groups. Hence, it will be useful for policy makers to first have these bits of information while deciding the age group for revaccination.

Investigators have used cohort as well as case–control designs to estimate the vaccine efficacy. To the best of author's knowledge, the Chingleput Bacille Calmette-Guérin (BCG) trial is the only community-based, double-blind randomized-control trial to study BCG efficacy. The protective efficacy of a vaccine in randomized-control trials is calculated conventionally using the formula:

$$VE=1-ARV/ARU$$

where, VE - vaccine efficacy; ARV - attack rate in vaccinated group; ARU - attack rate in unvaccinated group.

This is typically the ideal method to use in randomized-controlled trials. In a cohort study, where the dropouts have been minimal, the protective efficacy can be estimated from the relative risk using the formula:

$$VE=1-RR\times100$$

where, RR is the relative risk ratio[3,4].

The hazard ratio is more akin to the life table method and is used in observational studies with considerable dropouts. The hazard rate is "the probability that if the event in question has not already occurred, it will occur in the next time interval, divided by the length of that interval". The time interval is typically made short so that in effect, the hazard rate represents an instantaneous rate. The hazard ratio is an estimate of the ratio of

the hazard rate in the treated *vs.* the control groups[5]. The Cox model, a regression method for survival data, provides an estimate of the hazard ratio and its confidence interval. An assumption of proportional hazards regression is that the hazard ratio is constant over time. Thus, the hazard ratio is an estimate of the risk among the vaccinated compared to risk among the unvaccinated for developing TB over a period of time. It can be an indirect measure of protective efficacy[6,7].

The investigators[1] have used the hazard ratio extensively, and have given the protective efficacy (PE) calculated from the hazard ratio separately for each age group. It would have been good to see a similar analysis calculated from incidence. The study Table II (*DOI: 10.4103/ijmr.ijmr_1540_22*) could have been expanded to give this breakup. Calculating PE from the numbers in the study Table III (*DOI: 10.4103/ijmr.ijmr_1540_22*), it can be seen that the incidence among vaccinated was 0.22 and that among unvaccinated was 0.11. This gives a PE of 50 per cent in the 31-40 yr age group. However, it would have been better to use person-years as the denominator. From the study Table I (*DOI: 10.4103/ijmr.ijmr_1540_22*), it can be seen that the numbers in those who were 31 yr or older are small furthermore, there, were more than 800 individuals in each group with doubtful scars. BCG scars have been known to wane over time. In the Chingleput study itself, 40 per cent of the scars had waned when a sample of the population was retested after a period of four years. Thus, the numbers in the older age group could be biased estimates.

The age-wise distribution of the tuberculin reactors have been reported to level off at 15-20 yr in a given population[8]. Also there are only a few new infections beyond this age. Hence, revaccination beyond the age of 20 yr is unlikely to be useful. The force of infection in each age group is a good estimate of vulnerability to the respective infection. This has been previously calculated in another context for TB and found to be maximal in the 14-25 yr age group[9]. The protective efficacy in this age group from the study Table III (DOI: 10.4103/ijmr.ijmr_1540_22) is 39 per cent. Thus, it would be best to target this age group for revaccination.

Moving forward, it would be desirable to see a more detailed and in-depth analysis of the original trial data[2]. There is an urgent need to synthesize the results of trials addressing revaccination in a meta-analysis or at least in a systematic review. This would allow for all data to be taken into account before arriving at policy decisions. In light of the Government's intention to make India TB-free by 2025, there is no time for a randomized-control trial which would take at least 15 years to give results. However, if the age for revaccination could be fixed, it is possible to do a roll out in the community using a step wedge design for implementation. This would allow for the data to be reanalyzed multiple times each year or at least in two-year intervals, and the revaccination can be discontinued if there is no significant protection or rolled out aggressively if there is indeed a visible protection. The stepped-wedge design is a dynamic process and the respective investigators need to be on top of the data throughout. Alternatively, revaccination could be tried in vulnerable populations such as contacts, Type 1 diabetics or HIV infected individual using early breakdown as outcome. In this design, the confounder will be the time interval between the vaccinations and needs to be taken into account.

A high-level committee of experts including those who have worked with BCG to look into the role of BCG and other vaccines in the context of the epidemiology of TB and devise innovative methods for the control of TB is the urgent need of the hour.

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