Catch-up vaccination against tuberculosis: How effective and how expensive?

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SUMMARY
A cluster-randomized trial (BCG REVAC) to estimate the effectiveness and cost-effectiveness of BCG vaccination in school-age children (aged 7–14 years) with unknown tuberculin status who did not receive neonatal BCG vaccination was undertaken in Salvador and Manaus cities of Brazil. The study duration was between July 1997 and June 2006, in Salvador, Brazil, and between January 1999 and December 2007 in Manaus, Brazil.

Out of 763 schools which were the units of clusters, 388 schools were allocated to the BCG vaccination arm and 375 schools to the no-BCG vaccination arm. A total of 20 622 children from 385 schools were assessed for the primary outcome in the BCG vaccination arm and 18 507 children from 365 schools were assessed in the no-vaccination arm. In Salvador, schools were classified according to social variables correlated with the incidence of tuberculosis. In Manaus, schools were categorized according to the prevalence of tuberculosis and leprosy before the trial. BCG vaccination status of children was obtained from the parents (vaccination cards). Children in both groups of the trial were examined for BCG scars (masked to the information from parents) and the results validated with information collected about previous vaccination. Validity of BCG-scar reading was assessed in Manaus (sensitivity 96.6%, 95% CI 96.0–97.1, specificity 71.1%, 95% CI 55.7–83.7), and Salvador (sensitivity 90.6%, 95% CI 90.2–91.1, specificity 54.3%, 95% CI 52.2–56.4). Passive follow-up was done for 9 years by the Brazilian Tuberculosis Control programme to identify children who develop tuberculosis. Validation of cases was done on the basis of outpatient and hospital records. Case confirmation was done by two independent chest physicians (Cohen’s kappa 0.79, p<0.0001). A third physician reviewed cases with discordant results.

Cost-effectiveness was calculated only on the basis of data from Salvador. For cost-effectiveness calculation, a cost estimate of US$ 1.40 per BCG vaccination as estimated by Costa and colleagues in Salvador,4 was used. Costs were calculated by multiplying the number of children needed to prevent one case of tuberculosis by 1.4. These costs were then discounted at a rate of 5% per year and corrected for inflation with the consumer price index of US dollars to estimate their value in 1997, the year in which vaccination costs were incurred. For calculating treatment costs in Salvador, it was assumed that 20% of all new patients with tuberculosis were admitted to the hospital and that drug-resistant infection occurred in 10% of all patients. The costs of adverse effects were not included as the rates of adverse events were very low.

Intention-to-treat analysis was used. Generalized estimating equations, suitable for over dispersed Poisson data were used for the calculation of the incidence rate and correlated with observations over time. Estimation of person-years at risk was done assuming all children stayed in the study area. The estimated follow-up was 352 027 person-years, with 185 527 person-years in the BCG group and 166 500 person-years in the control group. The crude incidence in the BCG group was 54.9 (95% CI 45.3–66.7) per 100 000 person-years and 72.7 (95% CI 60.8–86.8) per 100 000 person-years in the control group (crude rate ratio 0.76, 95% CI 0.58–0.98; p=0.0332). The rate ratio calculated with generalized estimating equations was 0.75 (0.57–0.97). Vaccine effectiveness during the first 4.5 years of the trial in terms of rate ratio was 0.89 (95% CI 0.55–1.27) and in the last 4.5 years the rate ratio was 0.70 (0.50–0.99). All other parameters being equal, vaccination was as expensive as treatment at lower vaccine effectiveness of 23.4% or a tuberculosis rate of 58.8 per 100 000 person-years. The average costs of treating one patient with tuberculosis are higher than vaccinating 381 children at a cost-effectiveness ratio of 0.69.

COMMENT
The study was able to prove the vaccine effectiveness of school BCG vaccination in terms of crude incidence; 54.9% in the vaccinated group as compared to 72.7% in the non-vaccinated group. The long study duration of 9 years and the large sample size are the added strengths of the study. Though the parameters used for stratification in the two cities were different, this could help in identifying various parameters that had influenced the incidence of tuberculosis. The case detection by the Brazilian Tuberculosis Programme adds to the credits as it is the only dispensary for antituberculosis drugs in Brazil, thus not missing any cases treated by doctors in the private sector. Although the study is well designed and conducted, there are a few limitations. To start with, children who were not present on the day of the visit were excluded. This could have had an influence on the outcome. Though the authors did not include non-school-going children in the study area, this would have had negligible effect as the outcome was crude incidence of TB after vaccination. The BCG scar has high sensitivity and low specificity with a wide difference in specificity between the two study areas. This would have led to the missing of some eligible children in the vaccination group. The increase in the effectiveness of the vaccine over time is in contrast to the findings of previous studies.1 Also, it is not mentioned whether an interim analysis was done. As the study was carried out over a long period, not conducting an interim analysis might raise ethical issues. A cost-effectiveness analysis was not done for Manaus even though the vaccine effectiveness was much lower in Manaus (8% v. 34% in Salvador). This would have affected the overall cost-effectiveness ratio.

Relevance in the Indian context
India has the highest burden of tuberculosis in the world, accounting for one-fifth (21%) of the global incidence. The global annual incidence of TB is estimated to be 9.4 million cases; of these it is estimated that 2 million cases are from India and the mortality due to TB is 23 per 100 000 population.2 India is 17th among 22 high-burden countries in terms of incidence of TB.3 With such a high burden of TB, implementing catch-up vaccination would help in reducing the incidence as well as the mortality due to tuberculosis.4

As the coverage of BCG vaccination in India is 87%,5 catch-up vaccination based on scar reading without tuberculin test would be a suitable addition to the TB control programme of India. Funding for the control of TB in the 22 high-burden countries increased from $1.84 billion in 2006 to an estimated
$2.64 billion in 2010. In India, on an average each TB case incurs an economic burden of around US$ 12 235 and a health burden of around 4.1 disability-adjusted life-years (DALYs). This economic burden could possibly be reduced by the implementation of childhood vaccination. Though the coverage of DPT booster dose in children aged 18–23 months in the year 2009 was only 41.4 %, the same might be expected to occur in case school-age children are targeted for catch-up BCG vaccination. This should not be a deterrent for scaling up such a programme and community awareness and mobilization could be a pragmatic solution. Implementation of catch-up BCG vaccination in schoolchildren in India is feasible as the percentage of primary school participation with net enrolment ratio in primary schools in 2007–10 for boys and girls was 97 % and 94 %, respectively. In India, tuberculosis is treated mainly by private practitioners, many of whom are unqualified. This leads to inadequate management and rate of infusion and end-points for resuscitation are still hotly debated notwithstanding a number of studies that have attempted to answer these questions.

REFERENCES

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SELECTED SUMMARIES

Resuscitation in the intensive care unit: Choosing the right fluid

Myburgh JA, Finer S, Bellomo R, Billot L, Cass A, Gattas D, Glass P, Lipman J, Liu B, McArthur C, McGuinness S, Rajbhandari D, Taylor CB, Webb SA; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. (George Institute for Global Health, University of New South Wales, St George Hospital, University of Sydney, Royal North Shore Hospital, and Royal Prince Alfred Hospital, Sydney; University of Melbourne and Austin Hospital, Melbourne, Victoria, University of Queensland and Royal Brisbane and Women’s Hospital, Brisbane, Queensland, and University of Western Australia and Royal Perth Hospital, Perth, Western Australia, Australia; and Auckland City Hospital, Auckland, New Zealand.) Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012;367:1901–11. Epub 2012 Oct 17.

SUMMARY
The Crystalloid versus Hydroxyethyl Starch Trial (CHEST) aimed to determine whether normal saline or 6% hydroxyethyl starch (HES, 130/0.4) is the preferred solution to resuscitate patients admitted to intensive care units (ICUs). It was a multicentre, prospective, blinded, randomized, controlled trial that enrolled 7 000 patients from 32 centres across Australia and New Zealand.

Patients were recruited on admission to the ICU if they were above 18 years of age and were considered to require bolus intravenous fluids beyond maintenance or replacement requirements by their treating physician. They were followed till death, discharge or 90 days from randomization. The rate and volume of resuscitation was determined by their physicians, who were blinded to the fluid that was administered; however, no patient was administered greater than the maximum acceptable dose of 50 ml/kg/day for HES. Patients were excluded from the trial if they were found to have established or impending dialysis-dependent renal failure, intracranial haemorrhage or if they had already received more than 1 litre of HES before admission to the ICU.

There was no difference in the 90-day mortality (HES 18 % v. saline 17 %; relative risk [RR] in the HES group 1.06; 95 % CI 0.96–1.18, p=0.26), which was the primary end-point of the trial. Results were similar when analysed in six pre-defined subgroups to counter the effect of potential confounders such as pre-existing risk of renal injury, presence of sepsis, trauma or brain injury, APACHE score >25 and receipt of HES before randomization. Renal replacement therapy (RRT) was required more often in the HES group (7 % v. 5.8 %; RR 1.26; 95 % CI 1.0–1.4, p=0.04). Renal injury as well as renal failure were more frequent in the HES group—38 % v. 34.6 % and 10.4 % v. 9.2 %, respectively (p=0.005 and p=0.12, respectively). HES was also associated with significantly more adverse effects (5.3 % v. 2.8 %, p<0.001).

COMMENT
The ideal fluid resuscitation protocol for ICUs remains elusive despite extensive ongoing research in this field. The nature of the fluid (colloid or crystalloid), triggers for resuscitation, the quantity and rate of infusion and end-points for resuscitation are still hotly debated notwithstanding a number of studies that have attempted to answer these questions.