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New studies of BCG: implications for tuberculosis vaccines

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BCG has been given to over 3 billion people since the early part of the 20th century. Although the vaccine is effective, its use was implemented before clinical-trial design had reached its current sophistication, and before sensitive in-vitro techniques of assessing cellular immune responses were available. Recent studies and reinterpretation of previous trials have helped to clarify the true efficacy of BCG against both infection with and disease caused by *Mycobacterium tuberculosis*, while large cohort studies have provided an accurate side-effect profile in recipients with HIV infection. A contemporary understanding of BCG is crucial to the rational development of improved vaccines against tuberculosis.

The efficacy of immunisation with BCG depends largely on whether the vaccine recipient has pre-existing mycobacterial immunity on exposure to this live vaccine. Although overall efficacy in prospective trials has been estimated at 50%,[1] striking differences exist between age groups on the basis of previous mycobacterial priming. A reanalysis of four prospective trials of BCG in mycobacteria-naive newborns (ie, no previous BCG, tuberculosis infection, or infection with non-tuberculous mycobacteria) indicated that immunisation was 73% effective against disease and 87% effective against death (in the period before availability of antibiotics).[2] Although BCG side-effects (adenitis, disseminated disease) are an important issue for newborns, especially for those with HIV or congenital immunodeficiency, development of a more effective primary vaccine for infants will be challenging.

Possible explanations for low efficacy in trials in children beyond infancy and adults include differences in vaccine strain, latitude, and method of administration; however, the most plausible answer relates to the high rate of previous infection with *M tuberculosis* or non-tuberculous mycobacteria in older children and adults. Previous infection has two consequences that reduce observed efficacy: it limits the in-vivo replication of BCG that is required for protection,[3] and both non-tuberculous mycobacteria infection and latent *M tuberculosis* infection by themselves confer partial immune protection against subsequent tuberculosis.[4,5]

BCG trials beyond the neonatal period typically relied on skin testing with tuberculin or non-tuberculous mycobacterial proteins to exclude participants with pre-existing mycobacterial reactivity. However, in-vitro studies show that people with negative skin tests may have in-vitro cellular responses to mycobacteria or antibodies to common mycobacterial antigens. In a study of adults in Tanzania, 94% of adults with HIV infection had skin-test reactivity or in-vitro reactivity to mycobacterial antigens.[6] And in countries where tuberculosis is not endemic, as many as 30–40% of adults had skin-test reactions to non-tuberculous mycobacteria,[7] and antibodies to the common mycobacterial cell-wall antigen, lipoarabinomannin, were present in 96% of people aged 15–18 years.[8] Thus, an optimum improved vaccine for mycobacteria-experienced older children and adults might require an approach that avoids the need for replication of a live mycobacterial strain.

In another example of the effect of pre-existing mycobacterial immunity, the BCG REVAC trial[9] from Brazil has shown that BCG boosters are not effective in improving protection of children with pre-existing BCG scars. In *The Lancet Infectious Diseases*, Susan M Pereira and colleagues[10] report data from a large substudy of the BCG REVAC trial of children aged 7–14 years from the same cohort who did not have a BCG scar and therefore received what was classed as first immunisation with BCG. The vaccine was 25% (95% CI 3–43) effective against subsequent tuberculosis during 9 years of follow-up in 20 622 children. Tuberculin tests were not done but reactivity rates were estimated to be about 30% in this population,[9] and one would expect detectable mycobacterial sensitivity to be even higher with in-vitro tests of cellular and humoral response.

The net effect of including such a substantial number of mycobacteria-experienced children would be to lower the apparent efficacy of BCG. Nevertheless, BCG vaccination had sufficient efficacy for the investigators to conclude that first immunisation of school-age children who had not received BCG at birth would be cost-effective. This finding has implications for other potential uses of the vaccine including first immunisation of adult health-care workers from developed countries working in health-care or refugee settings in which tuberculosis is endemic.

For inexpensive vaccines such as BCG, cost-efficacy can be influenced substantially by the severity and cost of side-effects.[11] The most serious complication is disseminated disease, which can be fatal in infants with unrecognised congenital immunodeficiency syndromes or neonatal HIV infection. These disorders would be rare in children aged 7–14 years, contributing to a low rate of serious complications and favourable cost-efficacy in Brazil.

This excellent study adds to our growing understanding of the efficacy of BCG, which is crucial to the rational design and selection of new vaccines. We now know that BCG is highly effective in mycobacteria-naive newborns, it can prevent *M tuberculosis* infection and disease,[12] its efficacy may extend into adulthood,[13] and that an inactivated whole-cell vaccine can boost BCG.[14] The present demonstration that first immunisation with BCG is cost-effective despite only modest efficacy in children from a tuberculosis-endemic country will be useful in further expansion of BCG vaccine use, but it is also a reminder that improved vaccines against tuberculosis are urgently needed for mycobacteria-experienced children and adults.

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