PRACTICE

UNCERTAINTIES PAGE

How does the level of BCG vaccine protection against tuberculosis fall over time?

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This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the Cochrane Library. This paper is based on a research priority identified and commissioned by the National Institute for Health Research's Health Technology Assessment programme on an important clinical uncertainty. To suggest a topic for this series, please email us at uncertainties@bmj.com

WHO estimates that in 2009, 9.4 million people developed tuberculosis and 1.7 million died of the disease worldwide.[1] In the UK, incidence has risen over the past two decades; most cases are in vulnerable groups such as migrants, people who are homeless, or those with a history of imprisonment.[2] Bacillus Calmette Guérin (BCG) vaccine offers 70-80% efficacy against severe forms of tuberculosis in childhood, particularly meningitis in infancy.[3] [4] When given later in life, efficacy against tuberculosis (which, in adults, commonly presents as pulmonary disease) varies in different regions of the world, for reasons that are not clearly understood.[3] [5] The failure of BCG to protect adults in some populations—in particular in some studies in India[6]—has sometimes been wrongly generalised to suggest that BCG never protects against pulmonary disease. However, the Medical Research Council trial established that use of BCG in school age children in the UK was highly effective against tuberculosis (80%).[7]

On the basis of criteria from the International Union Against Tuberculosis and Lung Disease,[8] universal BCG vaccination of school children with a negative tuberculin skin test (aimed at preventing the peak of tuberculosis in young adults in the UK) was discontinued in 2005. Current policy recommends vaccination in infancy of children in high risk groups to prevent severe forms of childhood tuberculosis,[9] [10] and this practice is cost effective.[4] Uncertainty remains, however, about how long the protection afforded by BCG vaccination lasts.[11] This uncertainty has implications for the cost effectiveness of vaccination at later ages and for the role of a new vaccine.

An intensive search is in progress for a new vaccine that would work under circumstances in which BCG does not, possibly used together with BCG, or as a booster after BCG, with 12 candidates currently being evaluated.[12] The process of development, testing, and delivery of a new vaccine requires a thorough understanding of the mechanism behind protection against tuberculosis, including reasons for variation in protection, duration of protection, and the magnitude of waning, and whether previous BCG vaccination might interfere with the action of a new vaccine.[13]

What is the evidence of uncertainty?

We searched Pubmed and Embase for articles and systematic reviews on the duration of protection by BCG. This analysis is limited to a selection of studies with relevance to UK policy based on a previous systematic review[11] and our knowledge of the general literature on BCG efficacy. The previous systematic review, which included nine randomised controlled trials of high quality, found no evidence of substantial protection against tuberculosis after 10 years from BCG vaccination.[13] Lack of evidence of protection, of course, is not the same as evidence of lack of protection. However, we note from recently published data the possibility of longer BCG protection: additional comprehensive follow-up of a trial in North American Indians found that protection against disease of about 50% was present 40-50 years after vaccination.[14] A cohort study in Brazil with good follow-up found efficacy of 48%, 15-20 years after neonatal BCG vaccination.[15] Other studies that were not included in the previous systematic review contained further relevant evidence. Of particular interest is a case-population study in the UK, in which information about BCG vaccination or absence of previous latent tuberculosis was available for people with tuberculosis and for the general population, allowing comparison of disease rates in a vaccinated and an unvaccinated uninfected

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cohort. This study showed 59% protection at 10-15 years after vaccination at school age.[16]

Is ongoing research likely to provide evidence?

A search of the Cochrane database and of clinical trials registers (WHO's international clinical trials registry platform, which includes several national databases, current controlled trials, and the UKCRN portfolio database) did not identify any ongoing or recently completed trials. A Cochrane systematic review entitled *Infant Bacillus Calmette-Guerin (BCG) Immunisation and Duration of Protection Against Tuberculosis* was registered in 2008, but we found no accompanying protocol or published review.

There are two ongoing projects commissioned by the National Institute for Health Research (Health Technology Assessment): a new systematic review of all trials and observational studies; and a series of case-control studies undertaken to estimate BCG protection against tuberculosis in the UK, up to 25 years after school age vaccination and up to 17 years after neonatal vaccination. Although case-control studies can be vulnerable to selection and information bias, this approach addresses the research question in the shortest possible time in countries with a low burden of tuberculosis.

What should we do in the light of uncertainty?

Clinicians should be aware of and support the current policy of infant BCG vaccination for those at higher risk.[10] The best estimate of duration of protection by BCG is currently about 10 years, with recent data suggesting that the vaccine may protect for longer, although the level of protection seems to fall with time. People vaccinated 10 years or more before coming into close contact with infectious tuberculosis might have no BCG derived protection against active disease. BCG does not protect when given to people who are already infected, and revaccination of individuals after initial vaccination does not seem to offer substantial additional protection.[17] We therefore do not recommend repeat vaccination, even in people travelling to countries with a high tuberculosis burden.

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Recommendation for further research

Populations—Adults and children at risk of tuberculosis

Interventions—BCG vaccination

Comparisons—Vaccinated and unvaccinated individuals in a randomised controlled trial, but the sample size required would be too high given the relatively low incidence of TB in the UK; there are also ethical issues. Alternatively, cases of tuberculosis and controls in a case-control design. In high burden countries, a cohort design may be feasible (although there would be ethical issues) but would require a long period of follow-up, by which time a new vaccine might be available.

Outcome—Level of BCG protection against active tuberculosis with time since vaccination