A meta-analysis of the effect of Bacille Calmette Guérin vaccination on tuberculin skin test measurements

L Wang, M O Turner, R K Elwood, M Schulzer, J M FitzGerald

Background: The accurate diagnosis of latent tuberculosis infection (LTBI) is an important component of any tuberculosis control programme and depends largely on tuberculin skin testing. The appropriate interpretation of skin test results requires knowledge of the possible confounding factors such as previous BCG vaccination. Uncertainty about the effect of BCG vaccination on tuberculin skin testing and the strength with which recommendations are made to individual patients regarding treatment of LTBI have identified a need to analyse the available data on the effect of BCG on skin testing. A meta-analysis of the evidence for the effect of BCG vaccination on tuberculin skin testing in subjects without active tuberculosis was therefore performed.

Methods: Medline was searched for English language articles published from 1966 to 1999 using the key words “BCG vaccine”, “tuberculin test/PPD”, and “skin testing”. Bibliographies of relevant articles were reviewed for additional studies that may have been missed in the Medline search. Articles were considered for inclusion in the meta-analysis if they had recorded tuberculin skin test results in subjects who had received BCG vaccination more than 5 years previously and had a concurrent control group. Only prospective studies were considered. The geographical location, number of participants, type of BCG vaccine used, type of tuberculin skin test performed, and the results of the tuberculin skin test were extracted.

Results: The abstracts and titles of 980 articles were identified, 370 full text articles were reviewed, and 26 articles were included in the final analysis. Patients who had received BCG vaccination were more likely to have a positive skin test (5 TU PPD: relative risk (RR) 2.12 (95% confidence interval (CI) 1.50 to 3.00); 2 TU RT23: 26.50 (95% CI 1.83 to 3.85). The effect of BCG vaccination on PPD skin test results was less after 15 years. Positive skin tests with indurations of >15 mm are more likely to be the result of tuberculosis infection than of BCG vaccination.

Conclusions: In subjects without active tuberculosis, immunisation with BCG significantly increases the likelihood of a positive tuberculin skin test. The interpretation of the skin test therefore needs to be made in the individual clinical context and with evaluation of other risk factors for infection. The size of the induration should also be considered when making recommendations for treatment of latent infection.
structured review of the medical literature and a meta-analysis of the impact of BCG on skin test results. Meta-analysis has been recognised as a useful approach for analysing data and it provides more power to detect true differences, especially when studies are small and inconclusive.13

METHODS
A Medline search was conducted for articles published between 1966 and 1999 which measured TSTs in subjects with and without BCG vaccination using the following search terms: “BCG vaccine”, “tuberculin test/PPD”, and “skin test”. Relevant articles were identified from the title or abstract (when available) for further review. Bibliographies of the articles retrieved for review were also evaluated for other relevant references. Prospective studies that compared TST results in patients with and without BCG vaccination and those where the BCG vaccine had been given at least 5 years before inclusion in the skin test surveys were selected. The studies also needed to include a measurement of the TST result presented in a way that allowed calculation of the proportions with a positive test (>10 mm induration) or the actual measurements. All the control groups were concurrent controls. Studies that included known contacts of active cases were excluded.

Descriptive data recorded included study location, population studied, BCG type, and dose. When available, the time between BCG vaccination and the study was recorded and studies were grouped accordingly. Data on numbers in each study with and without BCG vaccine and numbers with a positive TST (defined as >10 mm) in each group were calculated using meta-analytical methods. The overall relative risk (RR) of a positive response for 5 TU and 2 TU was estimated using meta-analytical methods. The logarithmic transforms of the RRs were calculated for each study and combined using inverse variance estimates as weights.14 15 Relative risks were used in preference to odds ratios as the response rates were too high for odds ratios to provide close approximations to relative risks. Chi square tests of homogeneity were performed and, as the hypotheses of homogeneity were rejected, random effects models were used to derive the final estimates across the studies.14-15

Analogous methods were applied to the estimation of the relative risks at cut off points of >5 mm and >15 mm wheal diameters, respectively. Response rates at specific diameters were compared between subjects who had and had not received BCG vaccination. Since the estimated proportions were low, rate differences rather than RRs were used in these comparisons and high precision estimates of the corresponding variances were employed.16 Rate differences were again combined using random effects models with inverse variance estimates as the weights. We used several a priori hypotheses to address differences between studies in an attempt to explain heterogeneity. Studies using different types of tuberculin (5 TU PPD and RT23) were analysed separately. The age at which BCG was administered may affect the TST measurement, as can vaccinations. Studies using two step testing were compared with studies using a single TST. As geographical location may affect the efficacy of BCG vaccination,17 studies were grouped according to latitude.

The articles were independently reviewed by two investigators (MOT, RKE) to decide on eligibility for inclusion in the meta-analysis. The reviewed articles were not blinded to author or setting of each study.

RESULTS
A total of 980 potential articles were identified from the Medline search and bibliography review, 370 of which were retrieved. Fifty six studies met the inclusion criteria. Studies were excluded if they were found to be not prospective or if they did not have concurrent controls. There was combined agreement between the two reviewers to include 24 studies. A further two were included after consensus review, giving a total of 26 studies in the meta-analysis.18-43 The demographic characteristics of the selected studies are summarised in table I.

The meta-analysis showed that subjects who had received BCG vaccination were more likely to have a positive skin test reaction to both 5 TU PPD and RT23. The RR for 5 TU PPD, 2 TU RT23, and 1 TU RT23 was 2.12 (95% CI 1.50 to 3.00), 2.65 (95% CI 1.83 to 3.85), and 2.85 (95% CI 2.05 to 3.95), respectively (table 2). Table 3 shows the RR when cut off points of >5 mm and >15 mm induration were used. Figures 1 and 2 show the cumulative RR of a positive TB skin test using 5 TU PPD and RT23, respectively.

Temporal association of BCG vaccination
The timing of the BCG vaccination was also important. Immunisation given after infancy was almost twice as likely to result in a positive skin test as vaccination at birth when using 5 TU PPD. When 2 TU RT23 was used as the antigen, BCG vaccination was significantly associated with a positive reaction even when given at infancy. There was a higher RR of a positive skin test

<table>
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<th>Table 1 Demographic characteristics of studies included in the meta-analysis</th>
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When 5TU PPD was administered within 15 years of the BCG vaccination, there was a significant but attenuated effect. Subjects immunised after infancy and tested less than 15 years later had a high RR of a positive skin test but, even when given after infancy, skin testing more than 15 years after vaccination did not result in a significant reaction (table 4).

Booster effect and geographical location
Four studies addressed the boosting phenomenon with two step testing being performed. Those with a prior history of BCG were more likely to boost their reaction, adding 17.4% to the positive group, but 10% were also added to the group without BCG vaccination (table 5).

The effect of geographical location was evaluated by grouping studies according to latitude (5TU PPD only). No difference in RR of a positive test based on geographical location was observed (table 6).

Size of tuberculin skin test and BCG status
Four studies had discrete data for each measurement of the TST response (figs 3 and 4). There was no difference between the proportions of BCG positive and negative subjects at 14 mm with 5TU PPD (p=0.31) or at 16 mm with RT23 (p=0.17).

DISCUSSION
This meta-analysis has extended our understanding of the effect of BCG on the likelihood of having a positive PPD skin test in patients without a known TB contact. An argument frequently used against the use of BCG vaccination in TB control programmes (apart from questions of efficacy) is the subsequent effect on the TST as it might interfere with the identification of infected individuals, especially contacts of active cases of TB. This is not a problem for most people born in North America because BCG vaccination is not commonly administered. However, the proportion of TB cases occurring among foreign born individuals is increasing both in Canada and the US. Many of the contacts of these active cases will also be foreign born and are likely to have been vaccinated with BCG. Our results should therefore simplify interpretation of a positive TST in foreign born individuals and facilitate recommendations for the treatment of LTBI. This clarification is particularly important as the recent Institute of Medicine report has recommended that immigrants to the US should have a TB skin test performed in their country of origin. If positive, they would need to complete a course of treatment for LTBI before obtaining their final immigration status. Our data suggest that, if the BCG vaccination was given more than 15 years previously, it should be ignored as a cause of a current positive TST result, especially if the induration is > 15 mm. In addition, our data show that use of RT23, a common tuberculin used outside North America, is much more likely to be associated with a positive TST response than PPD.

Menzies et al have previously shown in patients studied in Quebec that BCG vaccination given in infancy was unlikely to cause a subsequent positive TST result. Our data refine their conclusions by demonstrating a temporal effect between BCG vaccination and TST. The RR of a positive TST result was 3.56 (95% CI 3.05 to 4.15) when the skin test was performed within 15 years of BCG vaccination but only 1.46 (95% CI 1.40 to 1.53) after 15 years. When BCG vaccination was given after infancy, the result of a TST performed within 15 years was
strongly associated with a positive test (RR 9.99, 95% CI 5.29 to 18.89). In the two studies in which the TST was performed more than 15 years after BCG vaccination given after infancy there was no association with a positive TST (RR 0.80, 95% CI 0.74 to 0.85).

The type of tuberculin used for testing had a significant effect on heterogeneity. The extent of the differences in the magnitude of effect was unexpected. Non-vaccinated patients were three times as likely to have a positive TST when tested with RT23 (2 TU RT23 v 0.96 for 5 TU PPD). Subjects who had received BCG vaccination in infancy were even more likely to have a positive test when RT23 was used (RR 3.86 for 2 TU RT23 v 0.96 for 5 TU PPD). Several studies have compared RT23 PPD with 5 TU PPD-S and Tubersol. Comstock et al compared 5 TU PPD-S with doses of RT23 in Inuit children, TB patients, and US navy recruits and found equivalence in the Inuits but more positive reactions with RT23 in the navy recruits. This result was attributed to non-specific sensitivity and raised a caution about interpretations in areas with a decreasing prevalence of TB. A recent Korean study suggested decreased potency of RT23, but this remains controversial.

There have been some concerns about equivalency in batches of PPD Tubersol and Aplisol. The reasons for our observations are unclear, but infection with atypical mycobacteria and geographical latitude may have some impact.

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<th>Location</th>
<th>BCG (+)</th>
<th>BCG (–)</th>
<th>RR</th>
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<td>America, Canada, Queensland, Spain (n=12)</td>
<td>3636/15962 (22.8%)</td>
<td>2193/10886 (20.15%)</td>
<td>1.13</td>
<td>1.07 to 1.18</td>
<td>&lt;0.0001</td>
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<tr>
<td>Philippines, Saudi Arabia, Solomon Island, Turkey, United Arab Emirates (n=8)</td>
<td>3024/10507 (28.8%)</td>
<td>2195/8448 (26.0%)</td>
<td>1.11</td>
<td>1.06 to 1.16</td>
<td>&lt;0.0001</td>
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Table 4 Skin test results at different times of BCG immunisation and varying times between tuberculin skin testing and immunisation for different antigens

Table 5 Skin test results in two step tuberculin testing by different antigens

Table 6 Geographical location and skin test results with 5 TU PPD

Figure 3 Percentage reactors versus skin test results in mm with 5 TU PPD (576 BCG+, 1145 BCG–).

Figure 4 Percentage reactors versus skin test results in mm with 2 TU RT23 (2880 BCG+, 1425 BCG–).
type of vaccine used, a true difference in potency of the tuberculin, or other unknown nutritional or genetic factors.

A positive TST of > 15 mm is less likely to be due to BCG vaccination, regardless of the type of tuberculin used for testing (figs 3 and 4). It seems that a strongly positive reaction (>15 mm) is more likely to be caused by tuberculosis infection than the effect of previous BCG vaccination. These data are particularly important if the timing or status of BCG vaccination is unknown.

The contribution of BCG vaccination to the booster response was only addressed by four studies. BCG vaccinated subjects were more likely to have a positive TST on first testing (28.7% v 22.3% (RR 1.28, 95% CI 1.15 to 1.43)). BCG had a greater effect on boosting with a positive second test in 17.3% compared with 11.8% in a non-vaccinated group (RR 1.47, 95% CI 1.22 to 1.76). These data are consistent with a study from Montreal that associated previous BCG vaccination (p < 0.001), interval from BCG vaccination to testing (p = 0.01), and older age when vaccinated (p = 0.02) with a greater likelihood of having a booster response.29 The impact of BCG vaccination on boosting the TST is particularly relevant in evaluating groups at risk of exposure to TB such as healthcare workers, in which subgroups of foreign born workers are likely to have received one or more BCG vaccinations.30 31

This meta-analysis has several methodological limitations. We limited our search strategy to the English language literature and Medline. We did not hand search any journals and therefore may have missed some published studies. However, this study did include pooled data from 117 507 subjects and therefore the conclusions should be robust. We sought data regarding the type of BCG used from primary authors of the included studies (25 letters, 12 replies) and also group data to interpret graphically presented data, but otherwise made no attempt to identify unpublished data.

In summary, this meta-analysis addresses important clinical and epidemiological questions about interpreting the TST in patients with previous BCG vaccination. The finding of a temporal association between a positive TST result and BCG vaccination should help TB workers and consultants to educate patients and their primary care physicians when offering treatment for LTBI in a setting of previous BCG vaccination, a positive skin test, and no known TB contact. In our experience there is a strong tendency for primary care physicians to attribute any positive skin test in a vaccinated foreign born patient to BCG. Large or strongly positive skin tests are most probably due to tuberculosis infection rather than BCG. This observation is supported by a recent study from Botswana in children aged 3-60 months with >90% BCG vaccination rates which found positive TST results to be most strongly associated with close TB contact in mothers and aunts.32 33 Our results strongly support the recommendations that emphasise the continued value of skin testing BCG vaccinated individuals in the appropriate clinical setting.34 35

ACKNOWLEDGEMENTS
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Dr FitzGerald is a recipient of a Vancouver General Hospital Scientist Award and also a Canadian Institute of Health Research/BC Lung Association Investigator Award.

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LETTERS TO THE EDITOR

Ultrasound examination of bronchial specimens from children with moderate asthma

We have read the paper by Çokugraş and colleagues on bronchial biopsies in asthmatic children with great concern. These authors performed a study in asthmatic children in which prophylactic medication was discontinued for 1 month before a bronchoscopic examination which was performed solely as a research procedure. The Royal College of Paediatricians and Child Health states that “High risk procedures such as lung or liver biopsy, arterial puncture, and cardiac catheterisation are not justified for research purposes alone. They should be carried out only when research is combined with diagnosis or treatment intended to benefit the child concerned”. Other authorities state that “Non-therapeutic research is particularly difficult to defend in moral terms when undertaken on children”. The risks of rigid bronchoscopy are surely no less than an arterial puncture, and discontinuing presumably necessary medication could only increase those risks. How can such a study possibly be justified by the authors or their ethics committee, and how can the Editors of a reputable journal possibly justify the publication of such a study? That the science is valuable is unquestionable, even though the scientific value by no means justifies the disregard of ethical principles. A journal such as Thorax should know better, particularly in the light of the scholarly and ethical review in the very same issue.

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An Associate Editor’s view

The article published by Çokugraş et al reported the results of bronchial biopsies performed in 10 children with moderate asthma. The study showed thickening and “hyalinisation” of the basement membrane in nine of the patients as well as the presence of “overactive fibroblasts, degranulating mast cells, and lymphocyte infiltration in the submucosa”. The authors concluded that these changes were similar to the bronchial inflammation seen in adults with asthma. Importantly, however, eosinophils were seen in only one biopsy specimen. Data such as these are not commonly available from children with asthma, partly because of the practice of performing bronchoscopies in children under general anaesthetics.

This article has prompted Dr Bush and colleagues to write berating Thorax for daring to publish such data which they contend were collected without regard for proper ethical standards. They quote from the guidelines for the ethical conduct of medical research involving children. Arch Dis Child 2002; 87:177-82.

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References


Author’s reply

In our study all the parents were informed and gave their consent. At the time of the examination all children were clinically stable. We stopped inhaled steroid and sodium cromoglycate treatment 4 weeks before bronchoscopy and followed each patient very closely. The parents were informed about the probable complications of stopping treatment and we agreed to give bronchodilators such as salbutamol in cases of exacerbation; however, no exacerbations occurred. If it occurred we could exclude the patient before bronchoscopy; the life and the comfort of all our patients is very precious to us.

I believe this study is very important for childhood asthma as it shows that bronchial inflammation of children with moderate asthma is very similar to that observed in adults, which is important for treatment.

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available from research on other individuals cannot answer the question posed in relation to children or young people; (c) the study method is appropriate for children and young people; and (d) the circumstances in which the research is conducted provide for the physical, emotional and psychological safety of the child or young person.

Let us now examine the study by Çokugraş et al. in the light of the above discussion. They received appropriate permission to conduct the study and adequately informed the parents about the risks involved. There is no doubt that the question that the authors were addressing was one of fundamental importance to the health and well being of children with asthma in general and, arguably, to the individual participants in their study. Most knowledge of the pathogenesis of chronic asthma, especially the current focus on chronic airway inflammation and remodelling, has come from studies in adults with asthma.1 Studies such as these have been partly responsible for the current practice of treating adult asthma with corticosteroids in order to prevent and/or reverse airway fibrosis and remodelling. This practice has been translated to children with inhaled corticosteroids considered to be first line treatment in many parts of the world. This treatment approach may be reasonable if the pathogenesis of asthma in children is essentially the same as that in adults. However, considerable doubt exists as to whether all asthma in children does have a similar basis to chronic asthma in adults. For a start, different wheezing syndromes are recognisable in children and many children with asthma lose their symptoms later in childhood.1 In addition, recent reports from the Childhood Asthma Management Program (CAMP) study2 do not support the contention that all children with asthma require treatment with inhaled corticosteroids.

Furthermore, many parents would prefer not to treat their children with corticosteroids, especially if they are not warranted. Steroid therapy is not without risk. While the risks are small if inhaled steroids are used according to current guidelines, even small risks are unacceptable if the treatment is not warranted. Thus, the question of the need to treat asthmatic children with corticosteroids is important to the health and well being of children and can only be answered in asthmatic children. Furthermore, Çokugraş et al. made sure that the methods used were appropriate for children and the physical safety of the children was safeguarded.

So are Bush and colleagues wrong to complain about Thorax publishing the original paper by Çokugraş et al. I believe that they were well within their rights, both as well respected members of the paediatric respiratory community and as advocates for the rights and well being of children. The ethics of research, as well as of medical practice, are not straightforward and should be the subject of continued and vigorous debate. Asthma management is also fluid. Studies such as the one by Çokugraş et al. are required to place the use of corticosteroids in children with asthma on a firm scientific basis.

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3 National Health & Medical Research Council (NHMRC). National statement on ethical conduct in research involving humans. Canberra: NHMRC, 1999.

NOTICE

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A 5-day residential course on “The lungs: function, diagnosis and treatment” will be held at St Edmund Hall, Oxford University, on 6–11 July 2003. The course will be given at a postgraduate level by internationally acclaimed speakers/world experts in their fields and will be of benefit to scientists, clinical staff, postgraduate students and others wishing to have a better understanding of the function of the lungs.

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CORRECTION

In the paper entitled “A meta-analysis of the effect of bicalcium Calmette Guérin vaccination on tuberculin skin test measurements” by L Wang et al which appeared in Thorax 2002; 57:804–9, an error occurred in the Results section of the abstract. The second sentence should have read “Patients who had received BCG vaccination were more likely to have a positive skin test (5 TU PPD: relative risk, 2.12 (95% confidence interval (CI) 1.50 to 3.00); 2 TU RT23: 2.65 (95% CI 1.83 to 3.85)).”
