

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

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Thorax 2002;57:804-809

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 tuberculous 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.

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Revised version received
11 March 2002
Accepted for publication
22 March 2002

Tuberculosis (TB) is a significant global public health challenge.¹ The accurate diagnosis of latent tuberculosis infection (LTBI) is an important component of any TB control programme and depends largely on skin testing. The appropriate interpretation of skin test results requires knowledge of the possible confounding factors such as previous Bacille Calmette Guérin (BCG) vaccination. Many countries have discontinued the use of BCG vaccination, although it is still offered in high prevalence populations and in high risk groups such as newborn Canadian Aboriginal subjects living on reserve.² Many foreign born subjects have been vaccinated at birth or at school and therefore, even in countries with no BCG vaccination programmes but a large population of foreign born individuals, interpretation of a tuberculin skin test (TST) in the context of a BCG history is important. This is especially true of immigrants who come from high prevalence countries where BCG vaccination is routinely offered. The proportion of individuals with a prior BCG vaccination who have a positive TST result has been reported to vary from 0%³ to 90%.⁴ Subsequent reactivity can vary depending on dose,⁵ manufacturer of the vaccine,⁴ age when vaccinated,^{3, 6, 7} and the interval between vaccination and testing.^{3, 6-8}

BCG vaccination provides a variable protective effect against TB. A meta-analysis suggested that it gives approximately 60% protection against the development of pulmonary TB with greater protection against tuberculous meningitis and disseminated TB.⁹ However, prior administration of the BCG vaccine has the potential to interfere with surveillance efforts,

particularly when investigating contacts of an active case of pulmonary TB. The uncertainty of the effect of BCG vaccination on TST results and interpretation affects the likelihood of treatment being offered, which is known to be effective.¹⁰ In countries with a low prevalence of TB such as Canada and the USA, treatment of LTBI has a potentially greater role than in countries with a higher prevalence where resources are concentrated on case finding and treatment of active cases.¹¹ The recent report by the Institute of Medicine on the control of TB in the US recommends that immigrants to the US should have a TST and those with a positive response should report for treatment of LTBI before receiving their green card.¹² The effect of BCG vaccination and tuberculin testing will have a significant impact on the implementation of this recommendation. A recent study in British Columbia compared 837 patients with no prior BCG vaccination and 444 who had been vaccinated with BCG; 43% of vaccinated patients were offered treatment for LTBI following a cluster outbreak of TB compared with 17% of non-vaccinated individuals.¹⁰ Several reports from Quebec suggest that BCG vaccination in infancy does not contribute to a subsequent positive PPD response, whereas BCG given in childhood or at an older age may result in a positive TST.¹¹

Uncertainty as to the effect of BCG vaccination on the TST 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 impact of BCG vaccination on skin testing. We have therefore carried out a

Table 1 Demographic characteristics of studies included in the meta-analysis

Country	Total no subjects	Definition of BCG	Skin test antigens used	Skin test results
USA ^{31 41 42}	12879	History, records	5TU PPD	Cut off 10 mm
Canada ^{18 20 23 25 32 37}	7790	History, records, scars	5TU PPD	Cut off 10 mm
Philippines ⁴⁰	2439	Scars	5TU PPD	Cut off 10 mm
Saudi Arabia ^{28 30 34}	11272	History, scars	5TU PPD	Cut off 10 mm
Soloman Island ¹⁹	3610	Records	5TU PPD	Cut off 10 mm
South America ³²	368	Scars	5TU PPD	Cut off 10 mm
Spain ³⁵	5559	History, scars	5TU PPD	Cut off 10 mm
Turkey ²⁹	3548	Scars	5TU PPD	Cut off 10 mm
Unified Arab Emirates ³⁸	785	Records	5TU PPD	Cut off 10 mm
Australia ^{21 23}	1668	History, records	5TU PPD	Discrete values
Chile ²⁶	208	Scars	2TU RT23	Cut off 10 mm
Ethiopia ³⁶	26269	Scars	2TU RT23	Cut off 10 mm
Kenya ⁴³	40365	Scars	2TU RT23	Cut off 10 mm
Pakistan ³⁹	4120	Scars	2TU RT23	Discrete values
South Algeria ²⁷	3283	Scars	2TU RT23	Discrete values
Zimbabwe ²²	2023	Scars	1TU RT23	Discrete values

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 analysed.

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 1.

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 2 Positive skin test results with different antigens using > 10 mm as cut off point

	BCG (+) > 10mm/total (%)	BCG (-) > 10mm/total (%)	RR	95% CI	p value
5 TU PPD ^{18-21 23-25 28-35 37 38 40-42} (n=20)	6660/26469 (25.2%)	4388/23041 (19.0%)	2.12	1.50 to 3.00	<0.0001
2 TU RT23 ^{26 27 36 39 43} (n=5)	7199/33456 (21.5%)	4208/41000 (10.3%)	2.65	1.83 to 3.85	<0.0001
1TU RT23 ²² (n=1)	46/285 (16.1%)	99/1746 (5.7%)	2.85	2.05 to 3.95	<0.0001

Table 3 Positive skin tests using different antigens and a cut off point of > 5 mm or > 15 mm

	RR	95% CI	p value
Cut off > 5 mm			
2 TU	3.02	2.77 to 3.30	0.0001
5 TU, > 6 years	4.71	1.62 to 13.71	0.0045
5TU, 2-> 6 years	4.39	1.34 to 14.39	0.0145
Cut off > 15 mm			
2 TU	3.18	0.64 to 15.61	NS
5 TU	2.73	0.64 to 11.70	NS

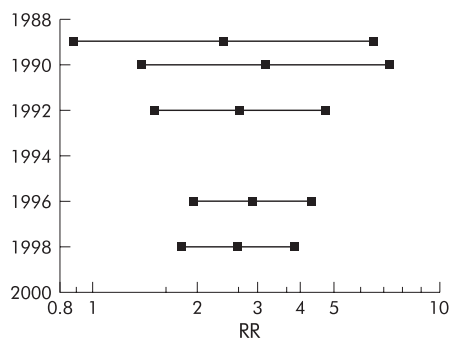


Figure 1 Cumulative RR for a positive PPD skin test using > 10 mm induration and 5 TU RT23.

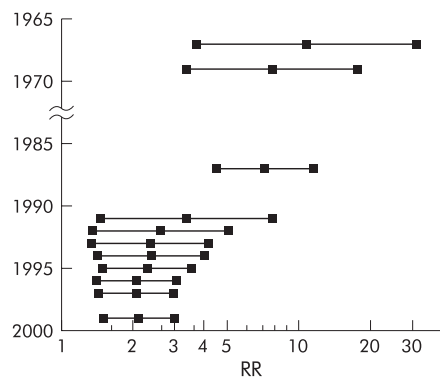


Figure 2 Cumulative RR for a positive response with 5 TU PPD using > 10 mm as a cut off point.

when 5 TU PPD was administered within 15 years of the BCG vaccination. In those tested more than 15 years after 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 (5 TU 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 5 TU 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.⁹ 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 Canada⁴⁶ and the US.⁴⁷ 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.¹² 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.²⁰ 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,²¹ the result of a TST performed within 15 years was

Table 4 Skin test results at different times of BCG immunisation and varying times between tuberculin skin testing and immunisation for different antigens

	BCG (+) > 10mm/total (%)	BCG (-) > 10mm/total (%)	RR	95% CI	p value
5TU PPD					
BCG at infancy (n=10)	2161/9712 (22.3%)	1730/9004 (19.2%)	1.16	1.09 to 1.23	<0.0001
Skin test <15 years since BCG	736/5828 (12.6%)	111/2138 (5.2%)	2.4	2.00 to 2.97	<0.0001
Skin test >15 years since BCG	1343/2843 (47.2%)	1538/3748 (41.0%)	1.2	1.09 to 1.22	<0.0001
BCG given after infancy (n=4)	1028/2890 (35.6%)	902/5192 (17.4%)	2.08	1.89 to 2.21	<0.0001
Skin test <15 years since BCG	41/141 (29.1%)	11/378 (2.9%)	10	5.29 to 18.89	<0.0001
Skin test >15 years since BCG	918/2443 (37.6%)	810/1696 (47.8%)	0.8	0.74 to 0.85	<0.0001
2TU RT23					
BCG at infancy (n=1)	807/2435 (33.1%)	74/861 (8.6%)	3.86	3.07 to 4.87	<0.0001

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

	BCG (+) > 10mm/total (%)	BCG (-) > 10mm/total (%)	RR	95% CI	p value
PPD 5TU^{23 24 33 40}					
Initial test	519/1709 (30.4%)	681/3074 (22.2%)	1.37	1.24 to 1.51	<0.0001
Second test	189/1086 (17.4%)	241/2241 (10.8%)	1.61	1.35 to 1.94	<0.0001

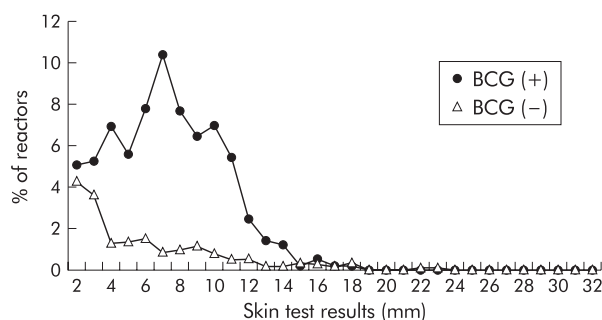


Figure 3 Percentage reactors versus skin test results in mm with 5 TU PPD (576 BCG+, 1145 BCG-).

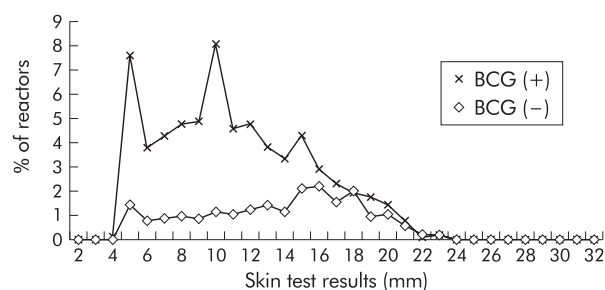


Figure 4 Percentage reactors versus skin test results in mm with 2 TU RT23 (2880 BCG+, 1425 BCG-).

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).^{22, 23}

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 (RR 3.02) and RT23 1 TU (RR 2.85) than with 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.^{48, 49} Comstock et al⁴⁹ 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.⁴⁸ There have been some concerns about equivalency in batches of PPD Tubersol and Aplisol.⁴⁹ The reasons for our observations are unclear, but infection with atypical mycobacteria and geographical latitude may have some impact.¹⁹ Other possibilities include the

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

Location	BCG (+) > 10mm/total (%)	BCG (-) > 10mm/total (%)	RR	95% CI	p value
America, Canada, Queensland, South Queensland, Spain (n=12)	3636/15962 (22.8%)	2193/10886 (20.15%)	1.13	1.07 to 1.18	<0.001
Philippines, Saudi Arabia, Solomon Island, South America, Turkey, United Arab Emirates (n=8)	3024/10507 (28.8%)	2195/8448 (26.0%)	1.11	1.06 to 1.16	<0.001

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.³⁵ 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.^{10 29}

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, the 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 tuberculous 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.⁵⁰ Our results strongly support the recommendations that emphasise the continued value of skin testing BCG vaccinated individuals in the appropriate clinical setting.^{51 52}

ACKNOWLEDGEMENTS

This study was funded in part by a grant from Medical Services Branch, Health Canada. Dr Lei Wang was funded by the World Bank. The authors thank Drs Sverre Vedal, Ruth Milner and Eduardo Hernandez for statistical advice and Edwin Mak for assistance in data management and programming.

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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REFERENCES

- 1 Raviglione MC, Snider DE, Kochi A. Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. *JAMA* 1995;273:220–6.
- 2 FitzGerald JM, Wang L, Elwood RK. Tuberculosis: 13. Control of the disease among aboriginal persons. *Can Med Assoc J* 2000;162:351–5.
- 3 Lifschitz M. The value of the tuberculin skin test as a screening test for tuberculosis among BCG-vaccinated children. *Pediatrics* 1965;36:624–7.
- 4 Horwitz O, Bunch-Christensen K. Correlation between tuberculin sensitivity after 2 months and 5 years among BCG vaccinated subjects. *Bull WHO* 1972;47:49–58.
- 5 Ashley MJ, Siebenmann CO. Tuberculin skin sensitivity following BCG vaccination with vaccines of high and low viable counts. *Can Med Assoc J* 1976;97:1335–8.
- 6 Margus JH, Khassis Y. The tuberculin sensitivity in BCG vaccinated infants and children in Israel. *Acta Tuberc Pneumonol Scand* 1965;46:113–22.
- 7 Joncas JH, Robitaille R, Gauthier T. Interpretation of the PPD skin test in BCG-vaccinated children. *Can Med Assoc J* 1975;113:127–8.
- 8 Magnus K, Edwards LB. The effect of repeated tuberculin testing on post-vaccination allergy. *Lancet* 1955;643–4.
- 9 Colditz GA, Brewer TF, Berky CS, et al. Efficacy of BCG vaccine in the prevention of tuberculosis: Meta-analysis of the published literature. *JAMA* 1994;271:698–702.
- 10 Noertjojo K, Wang L, Elwood RK, et al. The impact of BCG and PPD skin test results: results from a large number of contacts identified in cluster outbreaks. North American Regional IUATLD Meeting, Vancouver, 1998.
- 11 Menzies D, Tannebaum TN, FitzGerald JM. Tuberculosis: 10. Prevention. *Can Med Assoc J* 1999; 161:717–24.
- 12 Institute of Medicine. *Ending neglect: the elimination of tuberculosis in the United States*. Institute of Medicine Report, 2000.
- 13 Mulrow CD. Rationale for systematic reviews. *BMJ* 1994;309:597–9.
- 14 Cooper H, Hedges LV, eds. *The handbook of research synthesis*. New York: Russell Sage Foundation, 1994: 245–321.
- 15 Hedges LV, Olkin I. *Statistical methods for meta-analysis*. San Diego: Academic Press, 1985: 76–203.
- 16 Fleiss JL. *Statistical methods for rates and proportions*. 2nd ed. New York: John Wiley and Sons, 1981: 13–18.
- 17 Wilson ME, Fineberg HV, Colditz GA. Geographic latitude and the efficacy of Bacillus Calmette-Guerin vaccine. *Clin Infect Dis* 1996;20:982–91.
- 18 Menzies RI, Vissandjee B. Effect of BCG vaccination on tuberculin reactivity. *Am Rev Respir Dis* 1992;145:621–5.
- 19 Eason RJ. Tuberculin sensitivity. *Ann Trop Paediatr* 1987;7:87–90.
- 20 Jochem K, Tannenbaum TN, Menzies D. Prevalence of tuberculin skin test reactions among prison workers. *Can J Public Health* 1997;88:202–6.
- 21 Abrahams EW, Harland RD. Sensitivity to avian and human PPD in Brisbane school children. *Tubercle* 1967;48:79–94.
- 22 Borgdorff MW, Borgdorff PJ, Trommel JM. A tuberculin survey in the Buhara district. *Central Afr J Med* 1985;31:215–9.
- 23 Schwartzman K, Loo V, Paztor J, et al. Tuberculosis infection among health care workers in Montreal. *Am J Respir Crit Care Med* 1996;154:1006–12.
- 24 Abrahams EW, Harland RD. Studies with the purified protein derivative of human and avian tuberculin in South Queensland. *Tubercle* 1968;49:192–209.
- 25 Rosenberg T, Manfreda J, Hershfield ES. Two-step tuberculin testing in staff and residents of a nursing home. *Am Rev Respir Dis* 1993;148:1537–40.
- 26 Sepulveda RL, Ferrer X, Latrach C, et al. The influence of Calmette-Guerin bacillus immunization on the booster effect of tuberculin testing in healthy young adults. *Am Rev Respir Dis* 1990;142:24–8.
- 27 Liard R, Tazir M, Boulahbal F, et al. Use of two methods of analysis to estimate the annual rate of tuberculosis infection in Southern Algeria. *Tuberc Lung Dis* 1996;77:207–14.
- 28 Al-Kassimi FA, Abdullah AK, Al-Hajjaj MS, et al. Nationwide community survey of tuberculosis epidemiology in Saudi Arabia. *Tuberc Lung Dis* 1993;74:254–60.
- 29 Ildirim I, Hacimustafaoglu M, Ediz B. Correlation of tuberculin induction with the number of Bacillus Calmette-Guerin vaccines. *Pediatr Infect Dis J* 1995;14:1060–3.
- 30 Al-Kassimi FA, Abdullah AK, Al-Orainey IO, et al. The significance of positive Mantoux reactions in BCG-vaccinated children. *Tubercle* 1991;72:101–4.
- 31 Ballew KA, Becker DM. Tuberculosis screening in adults who have received Bacille Calmette-Guerin vaccine. *South Med J* 1995;88:1025–30.
- 32 Getchell WS, Davis CE, Gilman J, et al. Basic epidemiology of tuberculosis in Peru: a prevalence study of tuberculin sensitivity in a Pueblo joven. *Am J Trop Med Hyg* 1992;47:721–9.
- 33 Menzies R, Vissandjee B, Rocher I, et al. The booster effect in two-step tuberculin testing among young adults in Montreal. *Ann Intern Med* 1994;120:190–8.
- 34 El-Kassimi FA, Abdullah AK, Al-Orainey IO, et al. Tuberculin survey in the Eastern Province of Saudi Arabia. *Respir Med* 1991;85:111–6.
- 35 Miret-Cuadras, P, Pina-Guillerez JM, Juncosa S. Tuberculin reactivity in Bacille Calmette-Guerin vaccinated subjects. *Tuberc Lung Dis* 1996;77:52–8.

- 36 Azbite M. Tuberculin survey in Ethiopia. *Kekkaku* 1992;67:539-44.
- 37 Young TK, Mirdad S. Determinants of tuberculin sensitivity in a child population covered by mass BCG vaccination. *Tuberc Lung Dis* 1992;73:94-100.
- 38 Bener A, Uduman S, Bin-Othman SA. Factors associated with tuberculin reactivity among children in United Arab Emirates. *Respir Med* 1996;90:89-94.
- 39 Spinaci S, De Virgilio G, Bugiani M, et al. Tuberculin survey among Afghan refugee children. Tuberculosis control programme among Afghan refugees in North West Frontier Province (NWFP) Pakistan. *Tubercle* 1989;70:83-92.
- 40 Cauthen GM, Snider DE Jr, Onorato IM. Boosting of tuberculin sensitivity among Southeast Asian refugees. *Am J Respir Crit Care Med* 1994;149:1597-600.
- 41 Nelson ME, Fingar AR. Tuberculosis screening and prevention for foreign-born students: eight years experience at Ohio University. *Am J Prevent Med* 1995;11(3 Suppl):48-54.
- 42 Scholten JN, Fujiwara PI, Frieden TR. Prevalence and factors associated with tuberculosis infection among new school entrants, New York City, 1991-1993. *Int J Tuberc Lung Dis* 1999;3:31-41.
- 43 Bosman MCJ, Swai OB, Kwamanga DO, et al. National tuberculin survey of Kenya, 1986-1990. *Int J Tuberc Lung Dis* 1998;2:272-80.
- 44 Long R, Njoo H, Hershfield E. Tuberculosis: 3. Epidemiology of the disease in Canada. *Can Med Assoc J* 1999;160:1185-90.
- 45 McCray E, Weinbaum CM, Braden CR, et al. The epidemiology of tuberculosis in the United States. *Clin Chest Med* 1997;18:99-113.
- 46 Molina-Gamboa JD, Ponce-de-Leon-Rosales S, Rivera-Morales I, et al. Evaluation of the sensitivity of RT-23 purified protein derivative for determining tuberculin reactivity in a group of health care workers. *Clin Infect Dis* 1994;19:784-6.
- 47 Comstock GW, Edwards LB, Philip RN, et al. A comparison in the United States of America of two tuberculins, PPD-S and RT23. *Bull WHO* 1964;31:161-70.
- 48 Kim SJ, Hong YP, Bai GH, et al. Tuberculin PPD RT23: has it lost some of its potency? *Int J Tuberc Lung Dis* 1998;2:857-60.
- 49 Blumberg HM, White N, Parrott P, et al. False-positive tuberculin skin test results among health care workers. *JAMA* 2000;283:2793.
- 50 Joint Tuberculosis Committee of the British Thoracic Society. Control and prevention of tuberculosis in the United Kingdom: code of practice. *Thorax* 2000;55:887-901.
- 51 American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000;49(RR-6):1-51.
- 52 Anon. Tuberculin skin test survey in a pediatric population with high BCG vaccination coverage: Botswana, 1996. *MMWR* 1997;46:846-51.

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PostScript

LETTERS TO THE EDITOR

Ultrastructural examination of bronchial specimens from children with moderate asthma

We have read the paper by Çokuğraş and colleagues on bronchial biopsies in asthmatic children with great concern.¹ 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 catheterization 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".² Other authorities state that "Non-therapeutic research is particularly difficult to defend in moral terms when undertaken on children".³

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 use of more sophisticated pathological techniques would have enhanced it; but 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 same issue.³

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References

- 1 Çokuğraş H, Akcakaya N, Seçkin İ, et al. Ultrastructural examination of bronchial biopsy specimens from children with moderate asthma. *Thorax* 2001;56:25-9.
- 2 Royal College of Paediatricians and Child Health Ethics Advisory Committee. Guidelines for the ethical conduct of medical research involving children. *Arch Dis Child* 2002;82:177-82.
- 3 Branthwaite MA. Ethical problems in respiratory care: the role of the law. *Thorax* 2001;56:78-81.

Author's reply

In our study all the parents were informed and gave their consent. At the time of the

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The editors will decide as before whether to also publish it in a future paper issue.

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 diagnosis and for treatment.

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An Associate Editor's view

The article published by Çokuğraş *et al*¹ 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 anaesthesia.

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 published by the Royal College of Paediatrics and Child Health (UK), stating that high risk procedures are not justified for research purposes alone. The authors have responded, saying that they believe they had taken appropriate precautions, informed the parents fully, and obtained appropriate

consent. They went to some lengths to point out in their original paper the precautions they undertook to ensure the safety of the children.

That research, like all human behaviour, must follow appropriate ethical guidelines is a fundamental principle under which we all work. However, the development of modern codes of ethics is a relatively recent phenomenon, accelerated by the unethical research practices carried out during the Second World War. The Belmont Report,² published in 1978, established three basic ethical principles. The first was *respect for persons*—that is, that individuals should be treated as autonomous agents and that persons with diminished autonomy (such as children) are entitled to protection. The second, *beneficence*, describes the obligation to maximise possible benefits and minimise possible harms; and the third, *justice*, expounds the principle that the burden of research should be spread widely to ensure that the benefits are also widespread. This principle is likely to be behind the current push by regulatory and granting agencies to ensure that all groups in society are represented equally in research studies unless valid scientific reasons dictate otherwise. In addition to these three principles, the integrity of researchers is of extreme importance. This integrity includes the commitment to research questions that are designed to advance knowledge; the fundamental commitment to the pursuit, protection and propagation of truth; and a commitment to use appropriate methods to conduct scientifically valid research.

While the basic principles recognised by the authors of the Belmont report reflect the high value that the dominant Western tradition places on individual autonomy, it is important to realise, as stated in the National Statement on Ethical Conduct in Research Involving Humans published by the National Health and Medical Research Council of Australia,³ that this is not the only way in which human interaction and responsibilities are conceptualised. In various non-Western societies, and in some communities within Western societies, individual rights are viewed differently or constrained by community values. Thus, it is not always a straightforward exercise to impose the ethical standards of one community onto another. Even within a relatively homogenous community such as Australia, a single ethics committee is not considered to be acceptable. Each local community has its own standards to which it expects its researchers to conform.

As mentioned above, research involving children imposes additional responsibilities on the community. Children are not legally able to consent to their own participation in research and this consent is given on their behalf by parents or legal guardians. In the Australian National Research Ethics Guidelines³ specific conditions are imposed on research involving children and young people. These guidelines state that such research should only be conducted where:

- (a) the research question posed is important to the health and well being of children or young people;
- (b) the participation of children or young people is indispensable because information

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 Çokuğraş *et al*¹ 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.⁴ 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.⁵ In addition, recent reports from the Childhood Asthma Management Program (CAMP) study⁶ 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, Çokuğraş *et al*¹ 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 Çokuğraş *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 Çokuğraş *et al*¹ are required to place the use of corticosteroids in children with asthma on a firm scientific basis.

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References

- 1 Çokuğraş H, Akçakaya N, Seçkin İ, *et al*. Ultrastructural examination of bronchial biopsy specimens from children with moderate asthma. *Thorax* 2001;**56**:25–9.
- 2 National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, Department of Health, Education, and Welfare. *The Belmont report: ethical principles and guidelines for the protection of human subjects of research*. Publication No (OS)78-0012. Washington: US Government Printing Office, 1978.
- 3 National Health & Medical Research Council (NHMRC). *National statement on ethical conduct in research involving humans*. Canberra: NHMRC, 1999.
- 4 Jeffery PK, Laitinen A, Venge P. Biopsy markers of airway inflammation and remodelling. *Respir Med* 2000; **94**(Suppl F):S9–15.

5 Martinez FD, Wright AL, Taussig LM. Asthma and wheezing in the first six years of life. The Group Health Medical Associates (see comments). *N Engl J Med* 1995;**332**:133–8.

6 Anon. Long term effects of budesonide or nedocromil in children. The Childhood Asthma Management Program Research Group (see comments). *N Engl J Med* 2000;**343**:1054–63.

NOTICE

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CORRECTION

In the paper entitled “A meta-analysis of the effect of Bacille 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 (RR) 2.12 (95% confidence interval (CI) 1.50 to 3.00); 2 TU RT23: **2.65** (95% CI 1.83 to 3.85))”.