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Prior tuberculin skin testing does not boost QuantiFERON-TB results in paediatric contacts

To the Editors:

We read with interest the paper by LEYTEN *et al.* [1], which appeared in the June 2007 issue of the *European Respiratory Journal* (*ERJ*). LEYTEN *et al.* [1] showed that prior tuberculin skin tests (TST) do not induce false-positive QuantiFERON®-TB Gold in-tube (QFT-GIT) assay results when evaluated in the days immediately following TST administration. In the same issue of the *ERJ*, NASEER *et al.* [2] reported the results of a study of 10 subjects without risk for tuberculosis infection, who were tested with QFT-GIT and the T-SPOT.*TB* assay (Oxford Immunotec, Abingdon, UK) before, 48 h and 6 weeks after TST administration. NASEER *et al.* [2] confirmed the results of LEYTEN *et al.* [1] in the first days following skin testing; however, after 6 weeks, three out of nine individuals turned from negative to positive with QFT-GIT, and none of the subjects turned from negative to positive with T-SPOT.*TB*. On this basis, NASEER *et al.* [2] state that there is evidence of boosting-specific interferon (IFN)-γ responses 6 weeks after TST. According to these results, a high incidence of false-positive results with QFT-GIT should be expected when the assay is performed weeks after the skin test. This issue is potentially very relevant in clinical practice, as current guidelines indicate that contacts recently exposed should be tested for latent infection at the time of diagnosis of the index case and, if negative, after 8–12 weeks [3]. We therefore retrospectively reviewed our series of paediatric contacts to identify an effect similar to the one reported by NASEER *et al.* [2].

A total of 70 children received both TST and QuantiFERON®-TB Gold (QFT-G); 51 (72.9%) were QFT-G negative, nine (12.8%) were QFT-G positive and 10 (14.3%) were QFT-G indeterminate (low positive control). After 8–11 weeks, only one of the 51 initially QFT-G-negative contacts became QFT-G positive, and the mean values of IFN-γ units produced after stimulation with early secretory antigenic target (ESAT)-6 and culture filtrate protein (CFP)-10 did not differ before and after TST (ESAT-6 difference: 0.005 IU·mL^{-1}, p=0.745; CFP-10 difference: 0.030 IU·mL^{-1}, p=0.453). Of the 10 children with indeterminate QFT-G results, six tested indeterminate again, three became negative and one became positive. A total of 81 children were evaluated with TST and QFT-GIT. At the first visit, 63 (77.8%) contacts were QFT-GIT negative, eight (9.9%) were QFT-GIT positive and 10 (12.3%) had an undetermined QFT-GIT. Of those initially negative children, only one became QFT-GIT positive after TST. The mean IFN-γ antigen-specific production did not change 11 weeks after skin testing (ESAT-6/CFP-10/TB7.7 difference -0.030 IU·mL^{-1}, p=0.281). Of the 10 subjects who were initially indeterminate with QFT-GIT, six remained indeterminate and four tested negative (table 1). Interestingly, as already reported in other studies [4, 5], we detected imperfect agreement between TST and QFT; in particular, the presence of TST-positive, QFT-negative children is similar to data recently published in an adult population [6]. Our findings show that among children at risk of acquiring latent tuberculosis infection after contact with an infectious index case, there is minimal or no effect on QFT several weeks after initial skin testing. Only two household contacts became QFT positive and both were heavily exposed to smear-positive cases; these QFT conversions could represent true recent infections, rather than sensitisation to purified protein derivative. Conversely, such a low rate of QFT conversions might be considered unexpected, and could be explained by the fact that at the time of index case diagnosis, most children already had prolonged contact and therefore may have undergone an antigen-specific T-cell response. At initial evaluation, ~10% of contacts were QFT positive.

Our findings are consistent with those reported by LEYTEN *et al.* [1] but are in disagreement with those of NASEER *et al.* [2]; differences in size, demographic and clinical characteristics of study groups may account for this discrepancy. Our experience with IFN-γ release assays for the diagnosis of latent tuberculosis supports the concept that prior administration of TST does not induce false-positive results of the blood tests. The lack of boosting effect of repeated TST on the enzyme-linked immunospot-based blood assay has already been reported in 44 bacille Calmette–Guerin-unvaccinated TST-negative adult and paediatric contacts repeatedly tested with the skin and blood assay over a 2-yr period [7]. In that study, three conversions were observed with TST and none were observed with the blood assay.

TABLE 1 Results of QuantiFERON®-TB Gold (QFT-G), QuantiFERON®-TB Gold in-tube (QFT-GIT) and tuberculin skin tests (TST) at initial screening and at time of re-testing

	QFT-G			QFT-GIT		
	Negative	Positive	Indeterminate	Negative	Positive	Indeterminate
M/F	29/22	2/7	4/6	22/41	4/4	6/4
Age yrs	10.5±4.4	4.6±3.8	3.2±3.7	8.9±6.3	9.2±4.2	2.5±1.8
Immigrants from high prevalence countries	14	2	0	11	1	0
BCG vaccinated	15	3	1	14	1	0
Results at initial screening	51	9	10	63	8	10
Results after 8–11 weeks	53	11	6	66	9	6
TST mm at initial screening	1.7±4.3	8.0±4.3	0.3±0.9	1.1±3.9	8.5±6.4	0
TST mm after 8–11 weeks	1.7±4.3	ND	0.6±1.3	1.4±3.9	ND	0
TST ⩾5 mm at initial screening	7	8	0	5	6	0
TST ⩾5 mm after 8–11 weeks	8	ND	0	7	ND	0

Data presented as n and mean±SD. M: male; F: female; BCG: bacille Calmette–Guerin; ND: not done.

Overall, our results support the combined use of the skin and the blood assays, as indicated by recent guidelines [8]. However, it remains to be established whether this strategy is the most effective for the use of these new promising diagnostic tests.

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STATEMENT OF INTEREST

None declared.

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