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Use of T Cell-based Diagnosis of Tuberculosis Infection to Optimize Interpretation of Tuberculin Skin Testing for Child Tuberculosis Contacts.

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BACKGROUND: The clinical consequences of not treating infected children aged <2 years are more severe than those of treating uninfected children, because of the high risk of progression to tuberculosis and its attendant high morbidity and mortality. However, diagnosis is hindered by the inaccuracy of the tuberculin skin test (TST). The lower relative sensitivity of the TST for children aged <2 years suggests that the delayed‐type hypersensitivity response to *M. tuberculosis* infection in infants is weaker than that in older children. However, ELISPOT can detect very low levels of T cell responses to *M. tuberculosis* infection. This explains its high diagnostic sensitivity, relative to the TST, for infants and young children, who have immature cellular immune systems, and for HIV‐infected individuals. Prior bacille Calmette‐Guérin (BCG) vaccination may affect the specificity of the TST, and some countries adjust TST cutoff points for vaccinated children. However, there is no consensus as to whether or how much the TST cutoff point should be increased. More-accurate T cell-based tests of infection could enhance diagnosis by optimizing interpretation of the TST results.

METHODS: A total of 979 child tuberculosis contacts in Istanbul underwent the TST and enzyme-linked immunospot assay. Using enzyme-linked immunospot test results as a reference standard, we assessed the effect of age and bacille Calmette-Guérin (BCG) vaccination on the sensitivity and specificity of the TST, and we computed the optimal TST cutoff points, using receiver operating characteristic curves.

RESULTS: With a TST cutoff point of >or=10 mm, the sensitivity of the TST was 66% for children aged <2 years, which was lower than that for older children (P= .006). Specificity was 75% for BCG-vaccinated children, compared with 92% for unvaccinated children (P= .001). Optimal cutoff points improved TST specificity for children with 1 BCG scar, with little loss of sensitivity. Despite the use of optimal cutoff points, TST sensitivity remained <70% for children aged <2 years, specificity remained <87% for BCG-vaccinated children aged >or=2 years, and overall accuracy was low for children with >1 BCG scar.

CONCLUSIONS: Given the relatively poor sensitivity, negative results of the TST cannot exclude tuberculosis infection for child tuberculosis contacts aged <2 years, which supports the use of preventive therapy regardless of the TST results for this age group. In children aged >or=2 years, the accuracy of the TST can be improved by adjustment of cutoff points for BCG-vaccinated children but remains poor for children with >1 BCG scar.

Specificity of the TST varies across different populations and regions of the world and depends, in part, on the level of environmental mycobacterial exposure, as well as BCG vaccination status. Thus, although our optimal cutpoints have direct relevance to clinical practice in Turkey, they cannot be extrapolated to other populations. Our approach to derivation of optimal cutpoints, however, is generalizable. Where deployment of T cell-based IFN-gamma tests is not yet possible, testing of sentinel populations by the TST and T cell-based IFN-gamma tests would enable tuberculosis control programs to set more ‑ accurate TST cutoff points tailored to the whole target population.This methodology can define optimal TST cutoff points for diagnosis of tuberculosis infection tailored to target populations.

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