Reviewer's report

**Title:** T-cell-based diagnosis of tuberculosis infection in children in Lithuania: a country of high incidence despite high bacille Calmette-Guerin vaccination coverage

**Version:** 1  **Date:** 10 January 2009

**Reviewer:** Jean-Pierre Zellweger

**Reviewer's report:**

This paper compares the rate of positivity of TST and T-SPOT.TB between three groups of children (aged 10 to 17, all vaccinated with BCG) a) with active TB, b) after contacts with TB and c) without history of contacts. As expected from other studies, the rate of positivity among children with and without TB contact is much higher using TST than T-SPOT.TB, a fact that is usually interpreted as demonstrating a high rate of false positivity due to prior BCG vaccination or contact with non-tuberculous mycobacteria.

The strong points about this paper are a) the fact that the whole group of children had received BCG vaccination, b) that all children with active TB were positive with both TST and T-SPOT.TB and c) that is gives an estimate of the rate of T-SPOT.TB positivity in children living in a country with a high incidence of TB but without history of contact.

The weak points is that the authors do not address the key issue: what is the signification of a negative T-SPOT.TB in individuals with a positive TST? Claiming that only the contacts with a positive T-SPOT.TB are to be considered as latently infected and needing a preventive treatment may be right, but only if there are evidence that these individuals have a real risk of TB reactivation. Unfortunately, the authors do not discuss this fact and do not mention any of these emerging evidence. The evidence for the risk of reactivation with a positive IGRA test are to be found in Diel, AJRCCM 2008;177:1164-1170, and in Bakir, Ann Int Med 2008;149:777-86, the evidence for the absence of risk for contacts with a positive TST but negative T-SPOT is in Higushi, Respirrology 2007;12:88-92. But there are also studies demonstrating discordant results, for instance Hill, PLoS Medicine 2007;4(6), e192.

Furthermore, the authors do not mention other studies, mainly performed with the other available IGRA test (Quantiferon), which demonstrates a fairly high level of negative results even among patients (adults and children) with active TB (see for instance Connell T, PLoS One 2008,3(7):e2624. The authors should also refer to recent overviews of the sensitivity and specificity of the tests, for instance Pai, Ann Int Med 2008;149(3).

Some minor comments:

Abstract: Ref 1 is not adequate for suporting the cost-effectiveness of preventive

Abstract:

Irrational treatment of active TB may increase the risk of MDR-TB, but not preventive treatment (no evidence up to now)

Results:

the rate of T-SPOT.TB positivity is not similar in both groups of children with and without TB contacts (17.8 and 9.5%). How can the authors claim that they "do not differ"?

Repetition of TST may induce a booster effect. Should be mentioned as an hypothesis.

The reason why children with MDR-TRB still had a high degree of positivity of T-SPOT.TB may be linked with the persistence of a high bacteriological load, not with drug resistance. Please clarify.

Discussion:

Again, the presentation of the data is misleading: according to the results, 60 to 65% of children without active TB had a positive TST (not 70%) and 17.8 and 9.5% had a positive T-SPOT. TB, not 30%. Please clarify

The authors should mention studies using the other IGRA test, where the results are not similar (see Menzies, Ann Int Med 2007;146:340-6)

Children with negative TST and positive T-SPOT.TB may have false-negative TST due to intercurrent viral infection, for instance

Mentioning a number without the denominator is misleading and not informative: "3" out of the blue does not give any information, 3/52 or 6% is much better

"...in our country with high BCG coverage, where TST is currently the only tool...

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I have been invited by the producers of T.SPOT.TB to attend scientific meetings about IGRA...