The specificity of interferon-γ-based blood tests in the identification of latent tuberculosis infection

To the Editors:

I have read with interest several papers describing the use of cellular interferon (IFN)-γ-based blood tests, including the editorial by DAVIES and DROBNIEWSKI [1]. Whilst reviewing the study by LEE *et al.* [2], DAVIES and DROBNIEWSKI [1] indicate that the T-SPOT.*TB* assay has higher sensitivity than QuantiFERON-TB Gold, but that the QuantiFERON-TB Gold may have better specificity.

I do not agree with this tentative conclusion as the study by LEE *et al.* [2] does not report the true specificity of the two tests, as the control group of 15- and 16-yr-old students used to examine the specificity of the assays, although healthy, had a defined risk of existing tuberculosis (TB) infection. This was acknowledged by LEE *et al.* [2] in the discussion section of their study as follows.

''The present study has several limitations. First, some of the low-risk subjects may actually have been infected with MTB [*Mycobacterium tuberculosis*] and this might lead to an underestimation of the specificity of the IFN-γ assays. According to a South Korean national survey conducted in 1995, the MTB infection rate was ~15% in 15 yr olds, but rose dramatically to about 52–60% in 18–33 yr olds. Accordingly, 15–16-yr-old students were selected as a low-risk group because they have a lower chance of being infected with MTB.''

T-SPOT.*TB* reported a 15.3% infection rate in this healthy control group *versus* 8.4% for QuantiFERON-TB Gold. In the absence of a true gold standard for latent TB infection (LTBI), it is impossible to definitely resolve whether the discrepancy between the T-SPOT.*TB* and QuantiFERON-TB Gold results in this group was due to the higher specificity of QuantiFERON-TB Gold or the higher sensitivity of T-SPOT.*TB*. Nonetheless, the available data suggest that it is more likely that the discrepancy is due to the higher sensitivity of the T-SPOT.*TB* test rather than the higher specificity of QuantiFERON-TB Gold, for the following reasons.

First, LEE *et al.* [2] demonstrated that T-SPOT.*TB* has higher sensitivity than QuantiFERON-TB Gold in the diagnosis of culture-confirmed active TB disease, and this finding has also been reported by GOLETTI *et al.* [3]. Whilst active TB disease is clearly not the same as LTBI, it might be hypothesised that this difference in sensitivity is also true in LTBI. In the study by FERRARA *et al.* [4], this hypothesis was suggested by head-to-head evidence of the higher sensitivity of T-SPOT.*TB* over QuantiFERON-TB Gold in LTBI.

Secondly, both QuantiFERON-TB Gold and T-SPOT.*TB* use the same antigens (ESAT-6 and CFP-10). Therefore, it is hard to argue that T-SPOT.*TB* is any less specific for MTB infection than QuantiFERON-TB Gold, as both examine the cellular immune response to identical antigens. Furthermore, to my knowledge, there are no published data showing higher specificity for the QuantiFERON-TB Gold assay over the T-SPOT.*TB* assay. Additionally, four previous studies [5–8] investigating the specificity of the T-SPOT.*TB* test (using pre-approval versions of the test) have demonstrated a specificity of 100%, where truly low-risk controls in a low-endemicity country (UK) were studied.

Finally, Lee *et al.* [2] predicted the prevalence of tuberculosis infection in the healthy control cohort to be 15%. The fact that T-SPOT.*TB* reported a rate of infection of 15.3% provides further evidence that T-SPOT.*TB* was detecting true latent tuberculosis infection. It is felt that, on the basis of the above arguments, the lower rate of detection by QuantiFERON-TB Gold is more likely to be attributed to the lower sensitivity of this assay, rather than its higher specificity.

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STATEMENT OF INTEREST

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