Reviewer's report

Title: Negative effect of smoking on the performance of the QuantiFERON -TB Gold In Tube test

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Reviewer: Alamelu Raja

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General comments:
Cigarette smoking is known to increase the risk of tuberculosis (TB) and to impair Interferon-gamma (IFN-γ) responses to antigenic challenge, but the impact of smoking on IGRA performance is not known. The aim of this study is to evaluate the effect of smoking on IGRA performance in TB patients in a low and high TB prevalence setting respectively. Median IFN-γ level in smokers and non smokers were compared and smoking was analysed as a risk factor for false negative and indeterminate QFT. Smokers from both DK and TZ had lower IFN-γ antigen responses, less positive and more false negative QFT results. In Tanzanian patients, showed an association of smoking with false negative and indeterminate QFT results. Thus, cigarette smoking was associated with false negative and indeterminate IGRA results in both a high and a low TB endemic setting independent of HIV status.

Is IGRA useful for TB diagnosis? HOW DOES THE ASSOCIATION AFFECT THE DIAGNOSIS?

Specific comments:
Several publications have previously shown that IFN-γ and other T-cell functions are impaired in smokers. This manuscript assesses the IGRA in smokers.
What do the authors want to say? IGRA assays have been recommended by the regulatory authorities only for identification of LTBI and not for the clinical disease. The present observation shows that there is a negative impact of smoking on the diagnostic utility of IGRA in smokers. What is the use of this observation for clinical TB diagnosis? It is not clear and there is no discussion on this aspect.

There is no clinical or basic scientific value in this observation.

Do the authors hint that even for LTBI diagnosis also smoking will be an interfering factor? If so there is no clear discussion about this fact. Except the clinical Tb group, no LTBI group have been included.

Level of interest: An article of limited interest

Quality of written English: Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
There is no competing interest of any nature for the reviewer.