Author's response: BCG and infection with *Mycobacterium tuberculosis*

Thanks to Turner *et al* for commenting on our article. Turner *et al* challenge our finding that the Bacillus Calmette-Guérin vaccine (BCG) can prevent *Mycobacterium tuberculosis* infection (MTI), and propose an alternative explanation: that the absence of a positive interferon gamma release assay (IGRA) could be due to antigenic sin and does not necessarily demonstrate absence of infection.

A positive IGRA is the best available surrogate for MTI, but we are fully aware of its limitations. With the IGRA test, MTI is defined by a T-cell-induced interferon gamma response to *M tuberculosis* antigens ESAT-6 and CFP-10; a read-out above an established test cut-off reflects MTI. Hence, a read-out below the test cut-off can reflect either no MTI or early containment of MTI, where T-cell responses remain below the cut-off, the latter resulting in measurement error (misclassification). In our study, we observed no difference in MTI vaccine effectiveness when correcting for such misclassification. Additionally, we estimated the association between BCG and MTI with a higher and lower IGRA cut-off than suggested by the manufacturer (cut-off in article 0.35 IU/mL OR 0.52 (95% CI 0.32 to 0.85), higher cut-off 0.7 IU/mL OR 0.54 (95% CI 0.33 to 0.89), lower cut-off 0.25 IU/mL OR 0.50 (95% CI 0.31 to 0.81)). Both analyses supported the association between BCG and MTI.

The concept of antigenic sin and how this would have a negative influence on a subsequent IGRA test is highly theoretical. In Greenland, the population is virtually naive to non-tuberculous mycobacteria excluding BCG, resulting in minimal cross-reactivity.[1] Furthermore, ESAT-6 and CFP-10 are highly immunodominant *M tuberculosis* antigens,[2] and no studies have reported a decreased sensitivity of IGRAs in BCG-vaccinated individuals.[3] Therefore, we find it unlikely that original antigenic sin contributes to the relation between BCG and a negative IGRA.

We fully agree that more studies on the effect of BCG are needed. Although a series of novel studies suggest that BCG can protect against MTI, there is limited knowledge on the underlying mechanism.[4] These studies have fuelled an ongoing discussion on whether or not BCG can limit or even prevent bacterial seeding upon *M tuberculosis* exposure. As an attempt to accelerate the clinical evaluation of novel TB vaccine candidates, Aeras has recently launched a prevention-of-infection trial design in which the ability of BCG to prevent infection will be measured in a randomised, controlled, prospective trial.[5] Hopefully, these studies will shed further light on the immunological mechanism, which may explain the observational evidence that BCG prevents MTI.

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