

## CORRESPONDENCE

BCG and infection with *Mycobacterium tuberculosis*

Michelsen and colleagues<sup>1</sup> usefully add to the evidence for the protective effect of BCG against active TB. However, we are puzzled by the conclusion that BCG also prevents *Mycobacterium tuberculosis* (Mtb) infection. Others have similarly used interferon gamma release assay (IGRA) responses as a surrogate for Mtb infection with similar conclusions.<sup>2,3</sup>

A positive IGRA response represents a previous interaction with Mtb that was sufficient to lead to an acquired immune response. The authors demonstrate a reduced incidence of IGRA response in individuals vaccinated with BCG despite continued risk of Mtb exposure.

The authors' hypothesis that BCG directly protects against TB infection implies it must limit interaction between Mtb and its host. Although not suggested how this could occur, in order to prevent an adaptive immune response BCG must either physically prevent airborne bacteria from reaching the alveolus or fortify elements of the innate immune system. A direct primary effect on alveolar macrophages has been suggested elsewhere,<sup>2</sup> but we are aware of no direct observational or experimental data to support this.

BCG's efficacy against active TB is well recognised, through effects on specific immunity against Mtb. It is not clear how this immunity could develop if BCG simultaneously limits interaction between the organism and the adaptive immune system.

There is an alternative explanation for the observed effect of BCG on IGRA responses. Rather than reducing the

interaction between Mtb and the adaptive immune system (i.e., the process of infection), previous BCG may alter it. Upon exposure to Mtb, immunological memory of antigens shared with BCG may diminish the response to ESAT-6 and CFP10, the protein antigens used in IGRAs but absent from BCG. A subsequent IGRA response would then be negative.<sup>4</sup> This concept of original antigenic sin has been demonstrated for sequential immune responses against other mycobacterial species. Previous exposure to Mtb leads to altered immune recognition in multibacillary leprosy and the production of high levels of antibodies against TB-specific antigens.<sup>5</sup>

A valid mechanism for BCG's implied action on limiting the interaction between Mtb and its hosts therefore needs to be proposed before we can consider the illogical conclusion that it both prevents infection and promotes an adaptive immune response. Although a positive IGRA is probably the best currently available surrogate for infection with Mtb, it does not directly correlate with the presence of bacteria and, like any surrogate marker, has limitations which if ignored can lead to overinterpretation of data.

A similar argument to that made in this letter has recently been published elsewhere by three of the same authors (Turner R, Tweed C, Bothamley G. No proof that BCG protects against infection with *Mycobacterium tuberculosis*. *BMJ* 2014;349:g5436).

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