Author's response to reviews

Title: Serum indoleamine 2,3-dioxygenase activity is associated with reduced immunogenicity following vaccination with MVA85A

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Author's response to reviews: see over
Dear Dr Delogu,

Many thanks for your comments on our manuscript entitled “Serum indoleamine 2,3-dioxygenase activity is associated with reduced immunogenicity following vaccination with MVA85A” put forward for consideration for publication in BMC Infectious Diseases.

In response to your comments:

**Major comment:**
The determination of serum interferon-γ levels in the two groups of vaccinees at baseline, or of any other relevant immunological marker associated with chronic immune activation, will provide a useful information to support the author’s conclusion.

We agree this would be an interesting experiment to do and we will ensure adequate sample is collected for this analysis in future studies. However, there was not adequate sample available to address this in the current study. Blood biochemistry data from screening bloods including CRP and ESR were within the normal range for UK and South African volunteers (to permit participation in the trials), although exact values for CRP and ESR were not available for direct comparison between UK and South African volunteers.

We did however find a recent paper by Muyanja et al. (J Clin Invest. 2014;124(7):3147-3158) which provides evidence for chronic immune activation in African vs. European volunteers. Furthermore, a study of Malawian and UK adolescents showed that Malawian volunteers had greater natural exposure to various infections in the African environment.

We have now made reference to the above studies in the discussion section of our manuscript (page 16) as follows:

Line 2: In a recent study of the yellow fever vaccine YF-17D in volunteers from Uganda and Switzerland, Ugandan volunteers demonstrated higher frequencies of exhausted and activated NK cells, differentiated T and B cells, and proinflammatory monocytes at baseline, indicating immune activation [31]. Furthermore, a study of Malawian and UK adolescents showed that Malawian volunteers had a lower percentage of naïve T cells and higher percentage of...
antigen-experienced T cells and CMV seroprevalence compared with age-matched UK volunteers. The authors conclude that this difference is likely to reflect a greater natural exposure to various infections in the African environment [32]. It may be that a similar effect present in South African volunteers results in constitutively higher levels of IDO activity.

Line 20: In the yellow fever vaccine study described above, Ugandan volunteers showed an impaired vaccine response compared with Swiss volunteers, and this was associated with measures of immune activation at baseline [31].

Minor comments:
Figure 2: make the figures self-reading. Indicate the results of the statistical analysis performed on the figures and figure legend.
Figure 3: as above for figure

This has been addressed by adding indications of significance to the figures and results of the statistical analysis to the figure legends.

Please see the attached documents for the manuscript with changes marked, and corrected versions of the figures.

I look forward to hearing from you soon.

Yours sincerely,

Rachel Tanner