Plasma Cytokine Responses to *Salmonella* Typhi Vaccination and Infection in a Human Challenge Model

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Background: Cytokines are important mediators of immune cell activation, their measurement providing important insights into the dynamics of a host immune response. In multiple human typhoid vaccination/challenge models, we determined the plasma cytokine responses characteristic of vaccination and infection.

Methods: Using multiplexed cytokine technology (8-20 analytes), we quantified plasma cytokine responses to vaccination with two live attenuated oral vaccines, parenteral Vi polysaccharide or Vi-conjugate vaccine, and subsequent experimental infection with *S*. Typhi. Samples were taken at multiple time points before and after vaccination, challenge (*S*. Typhi exposure), and confirmed typhoid infection, to assess cytokine responses to each of these events. Analysis of baseline cytokine levels with respect to the development of typhoid was performed to investigate their relationship with susceptibility to infection.

Results: Statistically significant increases from baseline levels was identified in sCD40L, EGF, CX3CL1, and CXCL1 at 12 hours post-challenge, while IL17A, CXCL10, IL-8 and IL-6 were seen to decrease at this time point. These responses were independent of the subsequent development of typhoid infection, and returned to baseline levels at 24 hours after challenge. Pre-challenge levels of CX3CL1, IFNg, IL-6, IL-17A and VEGF were significantly higher in individuals who were subsequently diagnosed with typhoid infection. Analysis of cytokine responses following Vi polysaccharide and conjugate vaccinations is ongoing and may provide insights into mechanisms of protection.

Conclusions: The presence of a transient increase in plasma cytokines shortly after exposure to *S*. Typhi is a highly reproducible signature detected in our typhoid human challenge model. Although further validation is needed, these cytokines in blood may arise from inflammation at the gut mucosa. The increased level of baseline inflammatory markers in those who develop typhoid infection raises the possibility that the host's immune activation state on exposure may be an important factor in determining an individual's susceptibility to infection.