Investigating Humoral Immunity to Paratyphoid Fever in a Human Challenge Model of Infection

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Background: *Salmonella* Paratyphi A (*S.* Paratyphi) is responsible for an increasing proportion of enteric fever cases, particularly in Asia. Live-attenuated and lipopolysaccharide O:2-antigen conjugate vaccines are in development, but immunological correlates of protection are not known. We aimed to study humoral-immunity to *S.* Paratyphi infection using a challenge/re-challenge model of infection.

Methods: We recruited healthy volunteers into two groups: (1)Naïve volunteers with no prior exposure to *Salmonella* Paratyphi, and (2)volunteers previously exposed to *S.* Paratyphi in earlier challenge studies. Participants were challenged/re-challenged with oral *S.* Paratyphi at a dose of 1-5x10^3 CFU. We measured antibodies to *S*. Paratyphi O:2 antigen at two time points, baseline and day 28 post-challenge, using an in-house ELISA in a subset of volunteers (Naïve=9; re-challenge=11).

Results: An interim analysis has revealed a markedly lower attack rate following *S*. Paratyphi re-challenge compared with naïve controls, corresponding to an estimated 74% protection. We were unable to demonstrate a significant difference in baseline anti-O:2 IgG between naïve and re-challenge participants: naïve 160.4 EU (95% CI 38.9-202); re-challenge 441.4 EU (99.6-783.3). Diagnosed participants showed a higher fold-rise in antibody levels across the two time points than those who were undiagnosed: naïve 21.6 fold (95% CI 8.8-34.4) vs 1.0 (95% CI 0.9-1.1); re-challenge participants 6.8 fold (95% CI –1.1-14.7) vs 1.4 (0.7-2.0). Further ELISA/ASC data will be presented on a larger cohort currently undergoing challenge, including isotype-specific responses and baseline O:2 specific B_M cell responses.

Conclusions: Understanding the role of O:2 antibodies in protection against paratyphoid fever is highly relevant to the development of a lipopolysaccharide O:2-antigen conjugate vaccine. In this study, neither baseline anti-O:2 concentration, nor fold-rise post-challenge, corresponded to protection against paratyphoid infection. Further functional antibody assays would be useful to clarify the role of anti-O:2 antibody in protection against paratyphoid fever.