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Title: Humoral immune responses to Streptococcus pyogenes within a household cohort study in The Gambia.

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Background & Aims: A safe, effective and affordable vaccine against Streptococcus pyogenes (Strep A) is needed to reduce the substantial Strep A disease burden including Rheumatic heart disease (RHD). Understanding naturally protective immunity in settings with a high RHD burden is a WHO-recognised priority. Little is known regarding mechanisms of protective immunity induced by colonisation, pharyngitis and skin infections. Furthermore, a practical correlate of protection is required for future vaccine studies. This study, nested within the SpyCATS longitudinal household cohort study in The Gambia, used a recently-developed Luminex 5-plex assay to gain insights into serological responses to Strep A events.

Methods: A cohort of 442 participants from 44 households in Sukuta, The Gambia, was followed longitudinally between July 2021 and September 2022. Active disease surveillance and Strep A carriage identification at monthly visits was performed with microbiological culture from oropharyngeal and skin swabs. Disease events were defined as presence of signs or symptoms of pharyngitis or pyoderma plus a positive culture for Strep A. Colonisation events were defined as detection of Strep A from throat or skin swabs without symptoms. Serum was collected from participants over the age of 2 at entry into the study. Dried blood spots (DBS) were collected monthly and at any symptomatic presentation from participants of all ages and eluted. IgG titres to key StrepA vaccine antigen candidates SLO, SpyCEP, SpyAD, GAC, as well as DNAseB, were quantified in a Luminex multiplex assay. Log10 transformed mean titres were compared between groups using t tests. a

Results: IgG titres were measured from 355 serum samples at study baseline, from 356 DBS samples taken before, during and after 142 Strep A events (cases). Titres were also measured in 1662 DBS samples from 293 uninfected household contacts (controls) who were present in households at the time of an index event, with a DBS sample taken between 0-28 days before the index event. For all antigens, first timepoint DBS IgG titres were significantly lower in participants below 2 than in any other age category and were higher in 6-12 year olds that adults for all antigens except GAC. (fig 1A). IgG titres rose rapidly in the first five years of life (fig 1B). 142 participants had at least one Strep A event during the study, with 98 participants experiencing a single event only, and 44 participant experiencing multiple events. Only first events were included in this analysis. Following any Strep A event antibody titres were higher to DNAseB, GAC, SLO and SpyCEP, but not SpyAD (fig 1C) compared to household controls. No significant difference in pre- and post-event IgG titre fold-change was observed between disease and colonisation events, nor between throat and skin events, however age adjustment was not performed. Detailed analysis of age-dependant antibody responses to events at different sites and according to disease status is underway and will be presented, as well as the impact of baseline IgG titre on disease and carriage incidence accounting for age, sex and household size.

Conclusions: IgG titres to five streptococcal antigens were significantly lower in participants under 2 and rose rapidly each year in the first years of life, likely reflecting high streptococcal exposure in early years. By the age of two, many participants had antibody titres comparable with teenagers and adults in the study. In settings with high RHD disease burden early life exposure may be significant in generation of protective and pathological immunity. IgG titres in DBS were generally higher after events in cases compared to controls. Further exploration of this dataset will yield insights into generation of natural immunity to Strep A.