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Title: A blinded, randomised controlled trial to determine the minimum preventative concentration of penicillin required for secondary prophylaxis of rheumatic heart disease (The CHIPS Trial)

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Background & Aims: For the last 70 years, it has been assumed that the pharmacological correlate of protection for RHD is primarily informed by the laboratory-derived minimum inhibitory concentration (MIC) of Streptococcus pyogenes. The traditionally accepted target penicillin concentration of 20ng/mL reflects the 90th centile of individual MICs of circulating Strep A isolates. For patients receiving the majority of planned BPG injections, breakthrough infections and acute rheumatic fever are uncommon, despite not achieving this target concentration for less than 50% of the time between injections. We hypothesise that human minimum preventative concentration (hMPC) for S. pyogenes is lower than lab-derived MICs.

Methods: This assessor- and participant-blinded, placebo-controlled, randomised, human infection trial used an extensively characterised S. pyogenes with an MIC of 12 ng/mL (M75). Sixty healthy adult volunteers aged 18 to 40 years were randomised to receive continuous intravenous penicillin G infusions to maintain target steady state plasma concentrations between 0 (placebo) and 20 ng/mL via a midline catheter. Once at steady state, they received direct oropharyngeal challenge inoculum (1-5 x 105 CFU/mL) with M75. Individualised dosing to allocated target concentrations were guided by prior penicillin G pharmacokinetic assessments for each participant. Following challenge, participants were confined for up to 5 days in a healthcare facility. The primary endpoint was the development symptomatic pharyngitis according to pre-specified criteria. Secondary endpoints included systemic and mucosal immune responses during pharyngitis, bacterial colonisation dynamics, environmental contamination, and qualitative evaluation of the participant experience.

Results: To date, 45 out of 60 participants have been successfully challenged with study completion forecast in June 2023. There have been no serious adverse events reported. As an assessor- and participant blinded study, results will not be available until study completion and the primary endpoints have been locked. However, interim data suggests that an estimate of the hMPC for penicillin will be possible with some precision.

Conclusions: The CHIPS trial is the first attempt to identity the hMPC for S. pyogenes infection. We hope these data will underpin future efforts to improve long-acting penicillin preparations for the prevention of acute rheumatic fever and RHD.