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# Evaluation of the non-specific effects of Bacille Calmette-Guerin (BCG) vaccination in healthy UK adults

Morven Wilkie*[1], Rachel Tanner[1], Danny Wright[1], Michael Riste[2], Raquel Lopez Ramon[1], Oliver Griffiths[3], Stephanie Harris[1], Iman Satti[1], Samantha Vermaak[1], Paul Moss[4], David Wyllie[5], Helen Mcshane[1]

[1]*Jenner Institute, Nuffield Department of Medicine; University of Oxford*

[2]*Heartlands Hospital; Dept of Infectious Disease*

[3]*University of Oxford; Jenner Institute*

[4]*University of Birmingham*

[5]*Public Health England; John Radcliffe Hospital*

**Background:** The potential non-specific effects (NSE) of vaccination are widely recognised with Bacille Calmette-Guérin (BCG) vaccination key to the debate. Randomised and observational studies in low income countries, with high childhood mortality rates, have suggested that BCG-vaccinated neonates have lower all-cause mortality within the first 6-12 months of life. The most consistent effects are reduction in sepsis, respiratory infection and fever; however, the biologically plausible mechanisms underpinning this phenomenon remain poorly understood. Demonstrating an effect of recent BCG-vaccination on an individual's ability to control growth of common bacterial pathogens, using an *in-vitro* human model, would provide supporting evidence for large scale clinical studies of infants in TB high burden countries.

**Material/methods:** Healthy, BCG-naïve, HIV-negative, adult volunteers were randomised to receive BCG SSI (2-8x$10^5$cfu) or remain unvaccinated controls in two phases. Blood samples were obtained pre-randomisation (Day0) and at D2, D4, D7, D10, D14, D21, D28 and D84 post-vaccination. Blood was used in a whole blood *in-vitro* growth inhibition assay (GIA) with four pathogens: blood from volunteers in phase 1 was inoculated with *Staphylococcus aureus* and *Escherichia coli* and those in

phase 2 with group B streptococci and *Klebsiella pneumoniae*. Peripheral blood mononuclear cells were isolated and stimulated with purified protein derivative (PPD) from *Mycobacterium tuberculosis* in an *ex-vivo* IFN-γ ELISpot assay. Serum was also stored and used to detect BCG-specific IgG and IgG against the four pathogens in a whole bacteria ELISA. Full blood count analysis was performed and faecal and nasal swab samples obtained for bacterial colonisation status.

**Results:** 35 volunteers were enrolled (phase 1: 15 vaccinated, 5 controls, phase 2: 12 vaccinated, 3 controls). All volunteers were T-Spot negative to ESAT-6 and CFP-10. 55% of volunteers were negative for *S. aureus* on nasal swab and 45% positive. There was no correlation between nasal swab status and inhibition of *S. aureus* growth in the GIA. Vaccinated volunteers demonstrated a significant rise in PPD responses between D0 and D14 ($p=0.0005$ Wilcoxon matched-pairs) and BCG specific IgG responses between D0 and D28 ($p=0.0002$ Wilcoxon). There was a significant reduction in growth in the *S. aureus* GIA between D0 and D10 in the vaccinated group, which was also seen in the control group. A significant increase in bacterial growth was seen in the *K. pneumoniae* GIA. No other GIA demonstrated a significant difference at any time-point post BCG-vaccination.

**Conclusions:** There was no clear effect of recent BCG-vaccination on whole blood control of growth of any of the four pathogens tested using the *in-vitro* GIA. Possible reasons for this include lack of assay sensitivity, wrong study population (NSE best seen in infants) and/or impact of confounding variables such as background colonisation status. Further work is required to investigate these potential reasons.