Neutralising antibody titres as predictors of protection against SARS-CoV-2 variants

We read with interest Deborah Cromer and colleagues'[1] meta-analysis of in-vitro neutralisation titres as correlates of protection against a range of current SARS-CoV-2 variants of concern.[1] Models that can accurately predict waning post-vaccine immunity and vaccine efficacy against variants of concern as they emerge have the potential to be a powerful tool in tackling this pandemic.[1]

Cromer and colleagues are candid about the limitations in compositing data from multiple studies.[1] We especially recognise difficulties in accessing demographic and clinical patient histories. However, as immunity is the synergistic result of antigen and host immune response, we believe that for any model to have a substantial effect host factors must be considered. This is particularly important in older adults, who are often poorly represented in studies that employ health-care worker sampling, where there is concern over attenuated neutralising responses,[2] as well as in the context of increasingly widespread use of immunomodulatory therapies.

Interleukin (IL)-6 inhibitors have been widely used to treat SARS-CoV-2 infection requiring hospital admission in the UK. IL-6 production appears integral to the early differentiation of antiviral follicular helper T cells and the development of potent neutralising antibodies.[3,4] Recent data suggest a significant reduction in neutralising activity in the convalescent period after IL-6 or IL-1 (upstream in the inflammatory cascade) delivery that could affect a sizeable population.[4] In August, 2021, anti-SARS-CoV-2 combination monoclonal antibodies were approved in the UK for use in the prevention and treatment of COVID-19. Any potential effect on the development of long-term immunity remains unclear.[4] If provision is extended to community-based patients, a substantial proportion of the population in countries with a high infection burden will receive immunomodulation therapy, highlighting the importance of studies across specific population subsets to help guide targeted public health policy and vaccine strategy.

Considering the effect of age, our previous work suggested older adults were capable of mounting a neutralising antibody response to both symptomatic and asymptomatic infection.[5] However, preliminary findings from our own ongoing longitudinal study (280 total participants; median age 83 years, IQR 77–89) in a long-term care facility show the presence of high-titre neutralising antibody activity in only 10 (5%) of 205 patients after natural infection, rising to 139 (72%) of 192 patients available for testing after two-dose vaccination, despite advanced age. Those with previous infection showed substantially higher neutralising activity, identifying key populations for booster programmes. Cromer and colleagues' modelling in such established longitudinal studies might help identify priority individuals for three-dose vaccine prime regimens in real-time as variants of concern emerge.

Although we support the suggestion that such models could benefit future vaccine efficacy studies, we strongly encourage study designs to provide appropriate context (including participant immunomodulation before sampling) to allow effective interpretation of results to relevant demographic groups. This strategy will be vital if such models are to be available to substantially impact the public health response to emergent variants of concern when needed.

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Scott J C Pallett, Joseph Heskin, Elisabetta Groppelli, Andrea Mazzella, Luke S P Moore
scott.pallett@nhs.net

Chelsea and Westminster Hospital NHS Foundation Trust, London SW10 9NH, UK (SJCP, JH, LSPM); Centre of Defence Pathology, Royal Centre for Defence Medicine, Birmingham, UK (SJCP); Infection Care Group, St George's University Hospitals NHS Foundation Trust, London, UK (SJCP); Clinical Academic Group in Infection and Immunity, Institute for Infection and Immunity, St George's University of London, London, UK (EG, AM); Imperial College London, NIHR Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, London, UK (LSPM); North West London Pathology, Imperial College Healthcare NHS Trust, London, UK (LSPM)

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