Post-pandemic T-cell Responses Cross-recognize Animal Sarbecoviruses with Spillover Potential

Nguyen Thi Thu Hong[1*], Barbara Kronsteiner[2*], Tran Tan Thanh[1], Martha Zewdie[2], Mohammad Ali[3,4], Nguyen To Anh[1], Nguyen Thanh Dung[5], Le Mau Toan[5], Juthathip Mongkolsapaya[6,7,8], Chee Wah Tan[9], Nguyen Thanh Truong[10], Le Kim Thanh[1], Le Nguyen Truc Nhu[1], Cao Thu Thuy[1], Nguyen Van Vinh Chau[11], Guy Thwaites[1,2], Paul Klenerman[3,12,13], Susanna J Dunachie[2,8,13], Le Van Tan[1,2], for SEACOVARIANTS Consortium

[1]Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam; [2]Centre for Global Health Research, Nuffield Department of Medicine, University of Oxford, Oxford, UK; [3]Department of Experimental Medicine, Nuffield Department of Medicine, University of Oxford, Oxford, UK; [4]Department of Biochemistry and Molecular Biology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; [5]Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam; [6]Chinese Academy of Medical Science (CAMS) Oxford Institute (COI), University of Oxford, Oxford, UK; [7]Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK; [8]Mahidol-Oxford Tropical Medicine Research Unit, Mahidol University, Bangkok, Thailand; [9]Yong Loo Lin School of Medicine, National University of Singapore; [10]Tan Phu Hospital, Ho Chi Minh City, Vietnam; [11]Department of Health, Ho Chi Minh City, Vietnam; [12]Translational Gastroenterology & Liver Unit, Nuffield Department of Medicine, University of Oxford, Oxford, UK; [13]NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; *Contributed equally to this work.

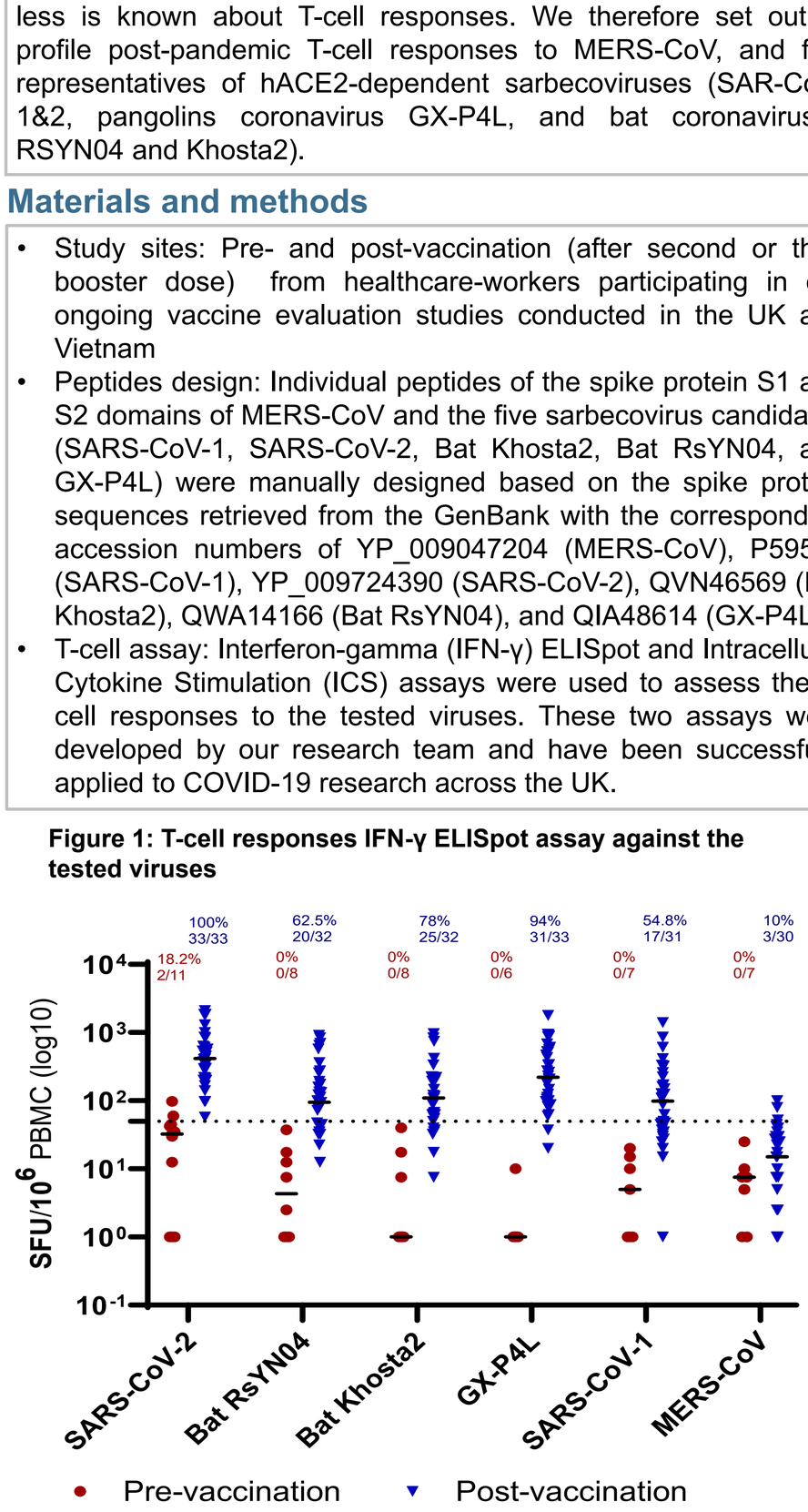
Background

Spillover events caused by animal coronaviruses spreading in humans have devastating impacts as exemplified by outbreaks caused by MERS-CoV and SARS-CoV-1&2. Worldwide diverse animal sarbecoviruses with hACE2 binding properties have been discovered with increasing frequency, raising concern about future pandemics. Antibodies cross-neutralising sarbecoviruses were generated by SARS-CoV-2 infection and COVID-19 vaccination but less is known about T-cell responses. We therefore set out to profile post-pandemic T-cell responses to MERS-CoV, and five representatives of hACE2-dependent sarbecoviruses (SAR-CoV-1&2, pangolins coronavirus GX-P4L, and bat coronaviruses RSYN04 and Khosta2).

Materials and methods

- Study sites: Pre- and post-vaccination (after second or third booster dose) from healthcare-workers participating in our ongoing vaccine evaluation studies conducted in the UK and Vietnam
- Peptides design: Individual peptides of the spike protein S1 and S2 domains of MERS-CoV and the five sarbecovirus candidates (SARS-CoV-1, SARS-CoV-2, Bat Khosta2, Bat RsYN04, and GX-P4L) were manually designed based on the spike protein sequences retrieved from the GenBank with the corresponding accession numbers of YP_009047204 (MERS-CoV), P59594 (SARS-CoV-1), YP_009724390 (SARS-CoV-2), QVN46569 (Bat Khosta2), QWA14166 (Bat RsYN04), and QIA48614 (GX-P4L).
- T-cell assay: Interferon-gamma (IFN-γ) ELISpot and Intracellular Cytokine Stimulation (ICS) assays were used to assess the T-cell responses to the tested viruses. These two assays were developed by our research team and have been successfully applied to COVID-19 research across the UK.

Figure 1: T-cell responses IFN-γ ELISpot assay against the tested viruses



Results

- Weak T-cell responses by IFN-γ ELISpot assay was documented in only two (18.2%) out of 11 pre-vaccination samples, both to SARS-CoV-2.
- The post-pandemic samples showed T-cell responses to all hACE2-dependent sarbecoviruses, with the highest responses recorded for pangolin coronavirus GX-P4L (31/33, (94%), followed by Bat Khosta2 (25/32, 78%), Bat RsYN04 (20/32, 62.5%) and SARS-CoV-1 (17/31, 54.8%), but limited reactivity was documented for MERS-CoV.
- There was a strong correlation between the level of T-cell responses and the degree of sequence homology, with responses to the S2 domain being higher than S1.
- These observed cross-reactivity profiles were comparable between the UK and Vietnam samples, despite the heterogeneity in vaccine platforms used.
- ICS assay confirmed that there is a mixture of CD4+ and CD8+ T-cells responses to the tested sarbecovirus.

Figure 2: Association between the spike sequence homology of the tested viruses and SARS-CoV-2 and the proportion of individuals with positive T-cell responses above cut-off

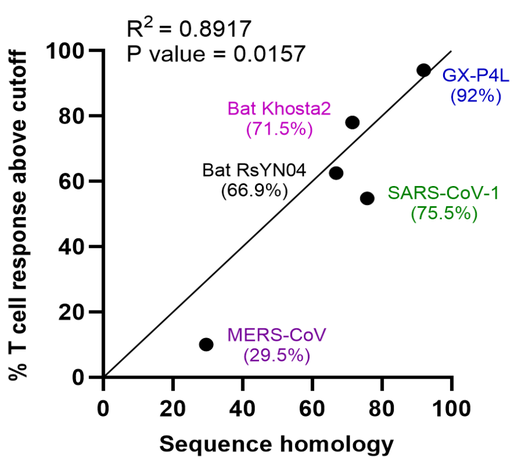


Figure 3: T-cell responses by IFN-γ ELISpot assay to spike protein subunit S1 and S2

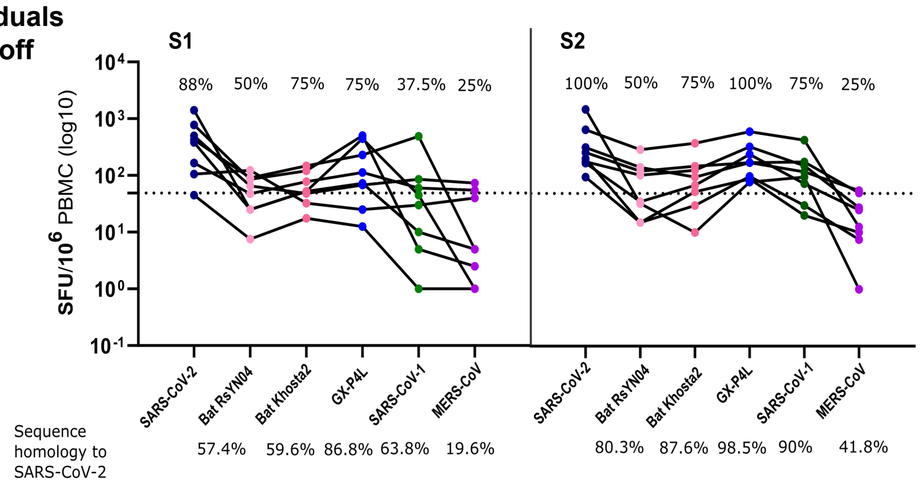


Figure 4: Comparison between the levels of T-cell responses in samples collected post vaccination of the UK and Vietnam cohorts

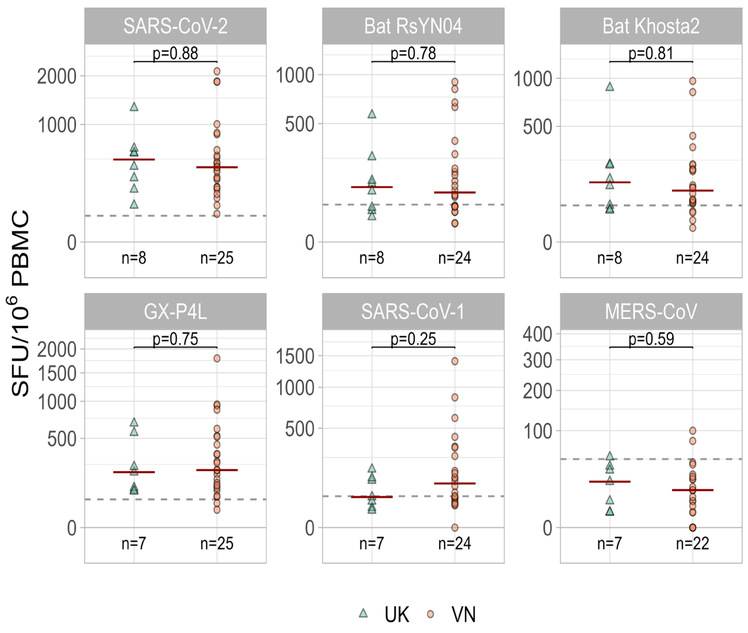


Figure 5: CD4+ and CD8+ T-cells responses by ICS assay

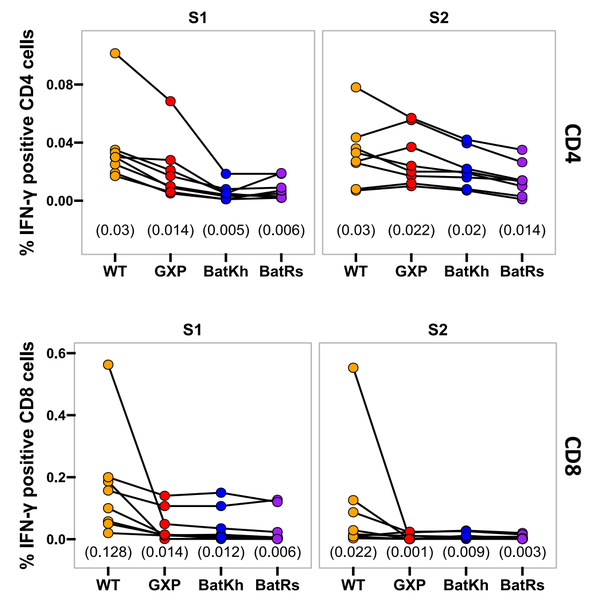
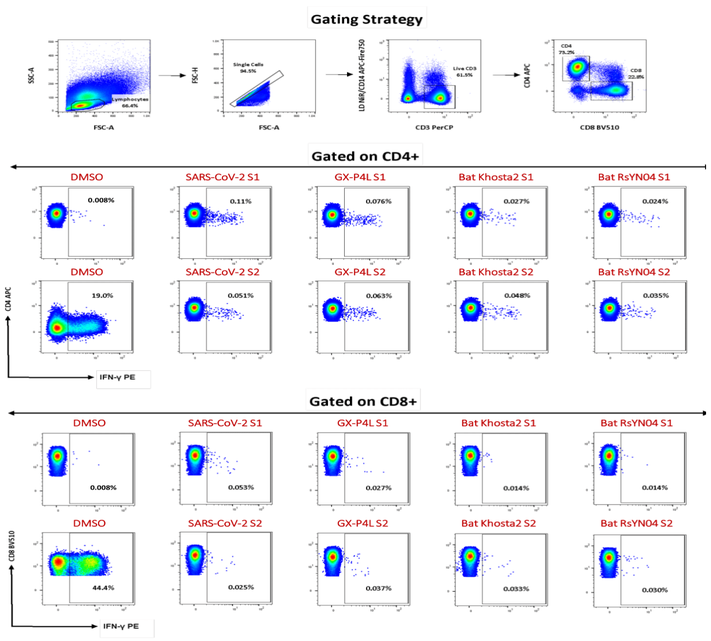


Figure 6: Gating strategy for ICS assays



Conclusions

- We report for the first time that COVID-19 vaccination and SARS-CoV-2 infection induced cross-reactive T-cell responses against a wide range of sarbecoviruses with hACE2 binding properties.
- The correlation seen between sequence homology and cross-reactivity may allow for predictions regarding cellular immunity against future threats.
- Our data should be used to inform research on countermeasures against sarbecoviruses.