SARS-CoV-2-Specific Immune Responses to Vaccination in Children and Adolescents with Suppressed Immune Systems: A Prospective, Observational Study

Rossa Brugha, Amanda Kirkham, Jessica Bate, G.A.Amos Burke, Ana Hughes, Sophia Magwaro, Ann M. Pope, Richard Beesley, Siân Lax, Eimear Kelly, Melanie Greenland, Angela M. Minassian, Xinxue Liu, Lucinda Billingham, Iain McInnes, Carl S. Goodyear, Pamela Kearns, Lucy R. Wedderburn, on behalf of the OCTAVE-Minor Collaborative Group^

PII: S0022-3476(25)00414-7

DOI: https://doi.org/10.1016/j.jpeds.2025.114873

Reference: YMPD 114873

To appear in: *The Journal of Pediatrics*

Received Date: 29 April 2025

Revised Date: 5 September 2025

Accepted Date: 20 October 2025

Please cite this article as: Brugha R, Kirkham A, Bate J, Burke GAA, Hughes A, Magwaro S, Pope AM, Beesley R, Lax S, Kelly E, Greenland M, Minassian AM, Liu X, Billingham L, McInnes I, Goodyear CS, Kearns P, Wedderburn LR, on behalf of the OCTAVE-Minor Collaborative Group^, SARS-CoV-2-Specific Immune Responses to Vaccination in Children and Adolescents with Suppressed Immune Systems: A Prospective, Observational Study, *The Journal of Pediatrics* (2025), doi: https://doi.org/10.1016/j.jpeds.2025.114873.

SARS-CoV-2-Specific Immune Responses to Vaccination in Children and Adolescents with Suppressed Immune Systems: A Prospective, Observational Study

Rossa Brugha[1,2*&], Amanda Kirkham[3*], Jessica Bate[4*], G. A. Amos Burke[3,5], Ana Hughes[3], Sophia Magwaro[3], Ann M Pope[3], Richard Beesley[6], Siân Lax[3], Eimear Kelly[7], Melanie Greenland[7], Angela M Minassian[7,8], Xinxue Liu[7], Lucinda Billingham[3], Iain McInnes[9], Carl S Goodyear[9], Pamela Kearns[3+&], and Lucy R Wedderburn[2,10,11+] on behalf of the OCTAVE-Minor Collaborative Group^

* Joint lead authors

+ Joint senior authors

& Joint corresponding author's contact details:

Prof. Pamela Kearns, Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham, Edgbaston, Birmingham. B15 2TT, UK. **Email:** P.R.Kearns@bham.ac.uk

Dr Rossa Brugha, Great Ormond Street Hospital NHS Foundation Trust, London. WC1N 3JH, UK. **Email:** rossa.brugha@gosh.nhs.uk

^ Additional investigators of the OCTAVE-Minor Collaborative Group are listed in Appendix Table S1.

[1] Cardiothoracic Transplantation, Great Ormond Street Hospital NHS Foundation Trust, London. WC1N 3JH, UK (R Brugha PhD, Rossa.Brugha@gosh.nhs.uk)

[2] National Institute for Health Research (NIHR) GOSH Biomedical Research Centre, London, UK (R Brugha PhD, Rossa.Brugha@gosh.nhs.uk; Prof LR Wedderburn PhD, l.wedderburn@ucl.ac.uk)

[3] Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham, Edgbaston, Birmingham. B15 2TT, UK (A Kirkham MSc, a.j.kirkham@bham.ac.uk; Prof A Burke PhD, g.a.a.burke@bham.ac.uk; A Hughes MSc, A.I.Hughes@bham.ac.uk; S Magwaro MSt, s.magwaro@bham.ac.uk; AM Pope PhD, a.m.pope@bham.ac.uk; S Lax PhD, s.lax@bham.ac.uk; Prof L Billingham PhD, l.j.billingham@bham.ac.uk; Prof P Kearns PhD, p.r.kearns@bham.ac.uk)

[4] Department of Paediatric Oncology, University Hospitals Southampton NHS Foundation Trust, Southampton. SO16 6YD, UK (J Bates PhD, Jessica.Bate@uhs.nhs.uk)

[5] Department of Paediatric Oncology and Haematology, Cambridge University Hospitals NHS Foundation Trust, Cambridge. CB2 OQQ, UK (Prof A Burke PhD, g.a.a.burke@bham.ac.uk)

[6] Patient representative for the OCTAVE study; Juvenile Arthritis Research, Tonbridge. UK (R Beesley BSc(Hons), hello@jarproject.org)

[7] Oxford Vaccine Group, NIHR Oxford Biomedical Research Centre, Department of Paediatrics, University of Oxford, Oxford. OX3 7LE, UK (E Kelly MSc, eimear.kelly@paediatrics.ox.ac.uk; M Greenland MSc, melanie.greenland@paediatrics.ox.ac.uk; A M Minassian DPhil, angela.minassian@paediatrics.ox.ac.uk; X Liu PhD, xinxue.liu@paediatrics.ox.ac.uk)

[8] Department of Biochemistry, University of Oxford. OX1 3QU, UK (A M Minassian DPhil, angela.minassian@paediatrics.ox.ac.uk)

[9] College of Medical, Veterinary & Life Sciences, University of Glasgow, Glasgow. G12 8QQ, UK (Prof IB McInnes FRCP, iain.mcinnes@glasgow.ac.uk; Prof CS Goodyear PhD, carl.goodyear@glasgow.ac.uk)

[10] Paediatric Rheumatology, Great Ormond Street Hospital NHS Foundation Trust, London, WC1N 3JH, UK (Prof LR Wedderburn PhD, l.wedderburn@ucl.ac.uk)

[11] Infection, Immunity and Inflammation Research and Teaching Department, UCL Great Ormond Street Institute of Child Health, London, WC1N 3JH, UK (Prof LR Wedderburn PhD, l.wedderburn@ucl.ac.uk)

Trial registration

ISRCTN 12821688; https://www.isrctn.com/ISRCTN12821688

Source of funding

Medical Research Council Grant Ref. MC_PC_20060) and National Institute of Health Research (NIHR) Great Ormond Street Hospital Biomedical Research Centre (GOSH BRC).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation or writing of the report; nor in the decision to submit the paper for publication.

Conflict of interest statement

AMM acts as an investigator on research studies funded +/- sponsored by vaccine manufacturers including Pfizer, GlaxoSmithKline, Janssen, Valneva SE, and Novavax. She receives no personal financial benefit for this work. AMM is a contributor to IP licensed by Oxford University Innovation to AstraZeneca. CSG declares funding from unrelated work from AstraZeneca, Bristol Myers Squibb, Eli Lilly, Galvani, GSK, Istesso, Janssen, MedAnnex,

MiroBio, Revolo, and UCB; consulting fees and/or honoraria from AstraZeneca, Bristol Myers Squibb, Galvani, MedAnnex, and UCB. IM declares institutional grants declares funding from unrelated work from BMS, Eli Lily, Astra Zeneca, and Novartis; consulting fees from Abbvie, Amgen, Absci, Causeway Therapeutics, BMS, Dextera, Cabaletta, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, Sanofi, UCB, Compugen, AstraZeneca, Moonlake, and Montai; LRW declares funding from unrelated work from Pfizer; consulting fees and/or honoraria from Pfizer and Cabaletta; PK declares Consultancy fees from Astra Zeneca for products unrelated to this trial. All other authors declare no competing interests.

Data sharing statement

Participant data and the associated supporting documentation will be available within six months after the publication of this manuscript. Details of our data request process is available on the CRCTU website: https://www.birmingham.ac.uk/research/centres-institutes/cancer-research-uk-clinical-trials-unit/data-sharing-policy. Only scientifically sound proposals from appropriately qualified research groups will be considered for data sharing. The decision to release data will be made by the CRCTU Directors' Committee, who will consider the scientific validity of the request, the qualifications and resources of the research group, the views of the Chief Investigator and the trial steering committee, consent arrangements, the practicality of anonymizing the requested data and contractual obligations. A data sharing agreement will cover the terms and conditions of the release of trial data and will include publication requirements, authorship and acknowledgements and obligations for the responsible use of data. An anonymized encrypted dataset will be transferred directly using a secure method and in accordance with the University of Birmingham's IT guidance on encryption of data sets.

Objective To investigate the concern that children and young people (CYP) receiving immune-suppressing treatments mount impaired responses to vaccines, in CYP compared with healthy controls.

Study design We prospectively enrolled CYP aged 5-17 years who are receiving we measured humoral and cellular biological response modifying (BRM) therapies for rheumatologic inflammatory conditions (RIC), or post solid organ transplant (PSOT), or cancer chemotherapy before and/or after routine vaccinations with BNT162b2 vaccine. Responses to SARS-CoV-2 vaccination were assessed by anti-SARS-CoV-2 spike antibodies (Roche Diagnostics) and T-cell responses (Oxford Immunotec). Response to wild-type and SARS-CoV-2 variants (BA.5, XBB1.5) was assessed by microneutralization assay. Control data were from ComCOV3.

Results **125 eligible participants enrolled (RIC n=54 [43·2%], PSOT n=49 [39·2%], cancer n=22 [17·6%]); 58 (46·4%) female; mean (SD) age 12·9 (2·9) years. 79 (63·2%) participants had prior COVID-19 and 28 (22·4%) were unvaccinated prior to study; 97 (77·6%) participants received one or more vaccines; 13 (10·4%) reported COVID-19 infection during follow up.** CYP receiving chemotherapy for cancer had lower antibody responses post vaccine: anti-SARS-CoV-2 spike antibodies (median [IQR], AU/mL) = 26·7 [2·3-1088·0] compared with RIC = 6970·0 [1417·0-18163·0] and PSOT = 7899·0 [1711·0-19201·0]), both p values <0·0001. T-cell responses (median [IQR] SFC/10^6 PBMCs) were also reduced in the cancer group (8.0 [0·0-48.0]) compared with RIC (110.0 [44.0-260.0]) p=0.009 and PSOT (74.0 [32·0-160·0]), p=0·003.

Conclusions Children receiving immune-suppressing therapies for RIC and PSOT had antibody and T-cell responses after the third vaccine dose that approached levels reported in healthy controls. Children who were receiving cancer chemotherapy, however, showed substantially reduced humoral and T-cell responses.

A national program of vaccination against SARS-CoV-2 for adolescents (12-15 years) began in the UK in September 2021, following results from a randomized controlled trial demonstrating efficacy of 100% for the BNT162b2 vaccine in 12-15 year old subjects.[1] This trial, and preceding studies in older adolescents and adults,[2,3] recruited healthy control subjects. Risk prediction modelling in adults highlighted groups at increased risk from COVID-19,[4] including patients receiving chemotherapy, those receiving immune suppressive therapies, or therapy post solid organ transplant. Early studies that included paediatric patients reported impaired responses to COVID-19 vaccination in subjects post solid organ transplant,[5] building on preceding data for responses to other vaccines in patients with juvenile systemic lupus erythematosus[6] and in children receiving chemotherapy,[7] suggesting that these groups also may be at increased risk for poor vaccine response.

When the UK COVID-19 vaccine program was extended to adolescents and children, we sought to prospectively assess the magnitude of immune responses to vaccination in high-risk groups, via an extension to a multicenter adult study (OCTAVE; Observational Cohort trial T-cells, Antibodies and Vaccine Efficacy in SARS-CoV-2).[8] Initial extension covered subjects aged 12 through 17 years; as the national vaccine program was extended to children 5-11 years of age, the trial was amended to include participants in this age group. Assessments of functional humoral and cellular responses to BNT162b2 mRNA vaccine were timed around administration of vaccines provided as part of the national roll-out to children and young people (CYP) aged 5 to 17 years who were either on immune-suppressing therapy for rheumatologic inflammatory conditions (RIC) or therapies post-solid organ transplantation (POST) or receiving chemotherapy following a diagnosis of cancer. The trial took place during the delta and omicron SARS-CoV-2 variant waves of the COVID-19 pandemic in the UK. This study aimed to measure humoral and T-cell responses to SARS-CoV-2 vaccination in “at risk” children.

Methods

Study Design

OCTAVE-Minor was an extension to the OCTAVE trial, with trial methods and prior results already reported.[8] In brief, OCTAVE-Minor was a collaboration between Great Ormond Street Hospital, Southampton Children’s Hospital, Addenbrooke’s Hospital, and the OCTAVE Consortium;[8,9] sponsored by the University of Birmingham and coordinated by the Cancer Research UK Clinical Trials Unit (CRCTU) therein. The trial was approved by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the London and Chelsea Research Ethics Committee (REC Ref:21/HRA/0489) and registered at ISRCTN (12821688); Protocol version: 9.0, 15th March 2022.

The trial was overseen by the OCTAVE trial management group, including patients, and parents of patients, living with compromised immune systems.

Participants

Written informed consent was obtained from parents/carers, and age-appropriate assent obtained from participants if they chose. Eligibility was determined by; age, confirmed diagnosis to one of three disease groups (RIC, PSOT on stable immunosuppressant therapy, or for cancer patients, on or within six months of active treatment), and eligibility for SARS-CoV-2 BNT162b2 mRNA vaccine. Full criteria are listed in Appendix Table S2.

Study Procedures

Patients were recruited to the trial at any point in the UK vaccine program. Up to four vaccines were offered during the period the trial was active. Vaccine administration was as per the national program and was not offered as part of this study. Samples were collected at trial entry (prior to a vaccination) and then at 28 days (-7/+56 days) post each vaccination (referred to as post-first, post-second, post-third, or post-fourth vaccine, respectively). If vaccines fell within the trial window, participants could provide multiple samples (eg, post-first and then pre- and post-second vaccines), with a maximum of four sample timepoints per participant.

Sample Collection and Analysis of Immune Response to Vaccine

Samples were collected at routine clinical reviews where possible to avoid additional blood sampling in paediatric participants. Sample collection and analysis was as previously described in the OCTAVE trial.[8] Further information is included in Appendix 1 Extended Methods. In brief, anti-SARS-CoV-2 antibody was measured using the Roche Elecsys® AntiSARS-CoV-2 Spike (S) and Roche Elecsys® AntiSARS-CoV-2 Nucleocapsid (N) assays by the UKHSA Laboratories at Porton Down. T-cell responses were measured using the T-SPOT DISCOVERY SARS-CoV-2 assay (Oxford Immunotec).

Control Group

Data on serologic and T-cell responses from healthy adolescent controls aged 12-15 years were provided by investigators from the Com-COV3 Study Group,[10] a randomised clinical trial of fractional dose COVID-19 vaccination in adolescents. Com-COV3 used the same antibody and T-cell assays, performed at the same laboratories, during the Delta and Omicron SARS-CoV-2 variant phases of the pandemic (September-November 2021).

Outcomes

The primary outcome was magnitude of the immune response to SARS-CoV-2 vaccines in children and adolescents who are immunosuppressed; this was defined by quantity of serum antibodies (AU/ml), and number of IFNγ-secreting T-cells, for humoral and T-cell assays, respectively. Secondary outcomes were: to determine phenotype and function of SARS-CoV-2 vaccine-induced immune responses in participant groups compared with each other and healthy controls from Com-COV3; to assess serological responses to newer variants of SARS-CoV-2; and to evaluate the impact of distinct classes of immune therapeutic drugs on the development of humoral and cellular immune responses to SARS-CoV-2 following vaccination. Data on infections with SARS-CoV-2 and severity of COVID-19 disease were collected during the trial. Details of the clinical data collected are described in Appendix 1 Extended Methods.

Statistical Analysis

The number of vaccinations within the study duration determined the sample size. Trial participant demographic descriptive statistics were presented as observation number, mean, standard deviation (SD), median, and interquartile range (IQR) for continuous data, and observation number and percentages for categorical data. Data were graphically represented where applicable, and Log_{10} transformations used in graphs showing assay results to improve visualization. Comparative analyses used chi-square with Bonferroni adjustment for multiple testing for categorical data. Assay results were tested using non-parametric methods as data were found not to be normally distributed and transformations unsatisfactory. Differences in median ages between ComCOV3 control and separate disease groups were tested using Mann-Whitney with Bonferroni adjustment; Kruskal-Wallis tests with *post-hoc* Dunn's test with Bonferroni adjustments tested for differences in assay response levels between disease groups. Friedman test was used to compare multiple measurements in assays over time; Spearman's Rank Correlations were utilized to investigate relationships between different assay responses and disease groups. No data imputation techniques were applied. All analyses were conducted using available data where applicable, with complete case analysis employed where necessary. Analyses were performed using Stata version 18·0 (Stata Corps, USA).

Results

Patient Demographics

Between 11-Feb-2022 and 29-Jul-2022, OCTAVE-Minor recruited 126 participants (Figure 1), in three disease groups: RIC (n=55, 43·6%); PSOT (n=49, 38·9%); and cancer (n=22, 17·5%). One study participant from the RIC group withdrew from the trial due to non-adherence to medication (Figure 1), leaving 125 participants. Demographics of these 125 patients are shown in Table I; concomitant or recent immune suppressive drugs are included in Appendices Tables S3 and S4, respectively.

Fifty-eight of 125 (46·4%) participants were female and 39 (31·2%) reported non-white ethnicity. Mean (SD) age by disease group was 13·5 (2·6) years (RIC), 13·1 (2·4) years (PSOT), and 11·2 (4·1) years (cancer). Twenty-one of 22 (95·4%) participants in the cancer group were on active treatment (Appendix Table S4). Prior COVID-19 was reported in 79/125 (63·2%) of participants (Figure 1, Table I); 28/125 (22·4%) were unvaccinated against COVID-19 prior to enrolling in the study, 40/125 (32·0%) participants had received one SARS-CoV-2 vaccine, 39/125 (31·2%) had received two vaccines, and 17/125 (13·6%) had received three vaccines prior to recruitment.

Following collection of baseline data, 10 participants subsequently withdrew from the follow-up part of the trial (seven RIC, three PSOT); eight of these agreed to collection of follow-up data, with two withdrawing consent for ongoing data collection. No participants requested retrospective removal of data collected prior to study withdrawal, therefore, all information collected is included in the trial analyses. Most participants who withdrew, did so because they did not intend to seek any further doses of vaccine; data from pre-vaccine assays are included in analyses.

In comparison to OCTAVE-Minor participants, Com-COV3 participants were similar in age to the RIC group, but older than the PSOT ($p<0·001$) and cancer ($p<0·01$) groups. Recruitment into Com-COV3 showed a female preponderance (Appendix Table S5); this was significantly different compared with the PSOT ($p<0·01$) and cancer ($p<0·01$), but not the RIC group. Significant differences were also seen with respect to ethnicity, with a higher proportion of participants in OCTAVE-Minor self-reporting as being of Asian or Black ethnicity in the RIC ($p<0·001$) and PSOT ($p<0·001$) groups than in the Com-COV3 cohort (Appendix Table S5).

Humoral Immune Response to SARS-CoV-2 vaccination

One hundred and twenty-three of 125 (98·4%) participants provided samples for antibody against SARS-CoV-2 antibody Spike (anti-S) and Nucleocapsid (anti-N) assays, from whom a total of 132 samples were obtained; participants could give more than one pre- and post-vaccine sample during the trial, depending upon the number of vaccines received. Ninety-three pre- and post-sample pairs were obtained, with 34 pre-vaccine results only

(Appendix Table S6). Results were compared with data from 132 control subjects from ComCov3. Comparison of anti-S responses showed that all groups had a greater percentage of low or non-responders than healthy controls (p<0·01, Figure 2A). Comparison between disease groups showed that the proportion of low or non-responders was significantly higher in the cancer group in comparison with the RIC and PSOT groups (p<0·01, Figure 2, and Appendix Table S7). Seventy-two of 123 (58·5%) participants who provided samples had a positive anti-N result indicating natural infection with SARS-COV-2.

We then assessed post-vaccine antibody responses. Participants in the cancer group demonstrated reduced responses compared with controls (p<0·0001) and PSOT (p<0·0001) and RIC (p<0·0001) disease groups (Figure 2B).Across the three combined disease groups, median anti-S IgG increased pre- to post-vaccination (p<0·00001), with higher antibody levels seen in participants in the PSOT group who had evidence of previous wild-type SARS-CoV-2 infection (N-positive) (p<0·01). Previous wild-type SARS-CoV-2 infection did not result in higher anti-S antibodies in the RIC group (p=0·44), with the cancer group having insufficient size to analyze.

Neutralizing Assays

Blood samples from 113 participants (49 RIC [43·4%], 47 PSOT [41·6%], 17 cancer [15·0%]), who had a positive anti-S indicating the presence of antibodies against the wild-type (Victoria) SARS-CoV-2 strain, were sent subsequently for neutralization assay analysis. We examined the functional effect of antibodies formed following wild-type infections and/or vaccination detected in blood samples taken in 2022, to newer variants of SARS-CoV-2. We quantified median neutralizing dose to three separate variants; wild-type (Victoria), BA.5 Omicron, and XBB1.5 Omicron. As expected, quantity of neutralizing antibodies to BA.5 and XBB1.5 were lower than antibody to wild-type (Victoria) (Figure 3A-D). For the combined cohort, significantly increased antibody levels were seen against all three variants following a participant's third and fourth vaccines, with increased responses to Victoria and BA.5 after the second vaccine (Appendix Table S8, Figure 3A-D). Among disease groups for all vaccine doses, both the RIC and PSOT groups showed significantly increased responses to Victoria and BA.5, but not to XBB1.5; no difference in responses to any of the SARS-CoV-2 variants tested was observed in the cancer group (Figure 3E-G and Appendix Table S9).

Cellular Immune Response to SARS-CoV-2 Vaccination

Seventy-two of 125 participants (35 RIC [48·6%], 33 PSOT [45·8%], 4 cancer [5·6%]) provided samples for the T-cell assay. Results were compared with 132 samples from ComCov3. For some analyses the same sample yielded

data used to assess post-vaccine, and pre- the subsequent vaccine. Participants in the RIC and PSOT groups showed no significant differences compared with controls with respect to T-cell responses. However, there was a significantly higher proportion of non-responders in the cancer group compared with the control cohort (p=0·001, Figure 4A).

Post-vaccine, participants in the cancer group demonstrated lower responses (median [IQR]=8 [0-48]) compared with those in the ComCov3 (median [IQR]=106 [44-216]; p=0.001), PSOT (median [IQR]=74 [32-160]; p=0.003) and RIC groups (median [IQR]=110 [44-260]; p=0·009, Figure 4B). There was a reduced response in the PSOT group compared with the RIC group although this was not statistically significant. Analysis within disease groups showed no significant differences in T-cell responses with respect to the number of total vaccinations a participant had received.. Prior infection with SARS-COV-2 also was not associated with a greater subsequent cellular response to vaccination (RIC p=0·2; PSOT p=0·1; with numbers in the cancer group too small for analysis). A *post-hoc* analysis did not demonstrate any significant relationship between peripheral blood absolute lymphocyte number (Appendix Table S10) and cellular or humoral immune response.

Effect of Therapeutic Immune Modifying Drug Classes on Response to Vaccination

No differences in humoral or cellular responses were observed following vaccination for individuals in the RIC or PSOT groups who were administered specified treatments. In the RIC group, comparison of patients who were on a biologic agent at time of vaccination with those not receiving a BRM agent(irrespective of disease-modifying anti-rheumatic drug [DMARD]) showed no significant difference in serologic or T-cell responses; similarly, comparison of responses in those receiving versus not receiving a DMARD showed no significant differences (data not shown), although these analyses were limited by small numbers of individuals for comparison. Within the PSOT group, nearly all participants were on a calcineurin inhibitor (with a small proportion prescribed an mTOR inhibitor) and mycophenolate; the homogeneity of immune suppression regimes within the group made it impossible to test for an effect of drug classes on responses. Similarly, but conversely, due to small numbers and heterogenous regimens within the cancer group it was not possible to test for any effect of individual immunosuppressive medication on their response to vaccination.

Reported Adverse Events Associated with Vaccination

Adverse events were reported post vaccination by parents and patients for 56 (45·5%) participants. The majority were mild including injection site pain, headache, and myalgia (Appendix Table S11). No patient in the RIC group reported a flare of their inflammatory disease after vaccination (data not shown).

Infections and Severity

At baseline, 79 of the 125 participants recruited (62·7%) reported having had prior SARS-CoV-2 infection (Appendix Table S12). This is similar to the 72 of 123 participants (58·5%) who were anti-N positive (Appendix Table S13) and suggests that self-reporting at that point in the pandemic was accurate in these patient groups. We are not able to determine, however, what proportion of participants had either had infection and subsequent waning of their anti-N antibody levels, or had natural infection but did not generate anti-N responses. Thirteen of 123 participants who were followed up (10·6%) reported COVID-19 disease during the trial; for 11 participants this was their first infection. No participant was admitted to hospital with COVID-19 as the primary cause for their admission during the trial.

Discussion

SARS-CoV-2 is now endemic in humans and continues to circulate in the UK population at the time of publication, Omicron BA.5 and Omicron XBB appear to have waned, with the dominant variant now the XEC subvariant of Omicron JN.1. Overall morbidity and mortality in children and young people (CYP) is low,[11] but rates of hospitalization, intensive care admission, and death are greater in children with immune compromise compared with the general population.[12] Data on immune responses in this at-risk group is, therefore, an important part of the overall assessment that will inform ongoing vaccine strategies.

In this trial we show that CYP who are on, or have recently received, cancer chemotherapy, mount serologic and cellular responses to SARS-CoV-2 vaccination (with and without prior infection) that are significantly below those of healthy controls. In contrast, CYP receiving immune suppressing treatments for rheumatologic inflammatory conditions, or following solid organ transplantation, mount and maintain immune responses that are similar to healthy control subjects. These findings between different disease groups appear robust across multiple assays assessing immune responses. Similar to previous reports,[13,14] we demonstrate an additional impact of vaccination for individuals PSOT who have had a wild-type infection, although this effect was not observed in the RIC or cancer groups. We also demonstrate that effective levels (equivalent to those seen in healthy controls) of anti-S-antibody and T-cell responses appear to be established over a short time frame. Most CYP in the RIC

and PSOT groups had “high responder” antibody levels and T-cell responses to their third vaccine, similar to healthy controls, and antibody levels in these groups typically plateaued after two doses. However, this was not observed in the cancer chemotherapy group. In addition, we show that CYP in the RIC or PSOT groups are able to produce functional neutralizing antibody to later variants of SARS-CoV-2, which continue to circulate, whereas CYP in the cancer group, the majority of whom were on active treatment, show significantly reduced responses. Similar to conclusions in the adult OCTAVE DUO study,[9] it is reasonable to infer from these data that children with RIC, and those on standard immune suppression regimes following solid organ transplantation, may have a level of protection from COVID-19 that equates to their healthy peers following three doses of mRNA vaccine. Our data in the RIC group align well with those observed in a single center study with a mixed sample of children with rheumatologic diseases both receiving and not receiving BRM therapies[15] and with pediatric cohorts PSOT.[14,16] The plateau observed in antibody levels after two doses raises the possibility that additional doses may result in little additional benefit, with the caveat that we do not know how quickly this level of putative protection wanes. It is more challenging to infer what strategies should be pursued in the cancer chemotherapy group, as our data demonstrate persistently reduced responses (serologic, neutralizing, and cellular) to SARS-CoV-2 that do not appear to improve despite repeated administration of vaccines. It is reported that children with cancer generally have better outcomes with COVID-19 than adults with cancer, however, some studies suggest risk of hospitalization, admission to an intensive care unit and mortality are greatly increased compared with the general pediatric population.[17,18] We cannot infer from our data whether additional vaccination may result in increased responses at a later time point, or whether pursuit of alternative strategies, such as targeted secondary prevention in confirmed infections, is indicated.

We found that the anti-S responses were significantly lower in the cancer group compared with healthy controls and with the RIC and PSOT groups. Other studies in children with cancer evaluating vaccine response to BNT162b2 mRNA vaccine report a higher proportion of responses than in our study. Parker et al report that spike reactive antibodies (S-IgG) and/or T cells (SRT) were detected in 16 of 20 (80%) vaccinated paediatric adolescent and young adult patients with acute lymphoblastic leukemia.[19] Lehrnbecher et al report seroconversion of anti-S antibodies in 19/21 (90%) paediatric patients after three mRNA vaccine doses.[20] However, it is important to note the use of different cut off values for an adequate antibody response of >300 binding antibody units/ml, compared with $\geqslant$380·0 AU/mL in OCTAVE-Minor. Other studies have reported

mixed responses in paediatric cancer cohorts depending on time. This trial recruited a heterogenous group of diagnoses in the cancer group with a spectrum of immunosuppressant drugs received and variable treatment intensity timepoints. Due to small numbers, it has not been possible to ascertain any effects of these variables on vaccine response. Other published studies suggest reduced vaccine responses following intensive chemotherapy and for those patients with underlying hematologic malignancy.[19,20] We were not able to record any delays to cancer-directed therapy during this trial. National UK guidance recommends re-vaccination with childhood vaccines from three months after completion of standard dose chemotherapy and from six months after hematopoietic stem cell transplant.[21] However, children with cancer are recommended to receive seasonal inactivated influenza vaccine and SARS-CoV-2 vaccines seasonally during active treatment. Although children are less likely to achieve an optimal immune response to vaccination while on treatment, some protection may reduce prolonged infections, hospital admissions, and potential delays to cancer therapy. Optimizing vaccination coverage in family members and healthcare workers also can contribute to reduced transmission to susceptible patients.

In this large prospective multicenter cohort of children with immune compromise, we confirm findings from multiple single center studies that demonstrate reduced antibody and cellular responses in some groups of children with immune compromise,[13,22-26] although not all groups are similarly affected.[16,27] We can infer that a unified approach to vaccination in this population is likely an oversimplification.

Of note, within the trial timeframe 28 of the 125 patients (22·4%) opted to have no further vaccine as they did not perceive additional benefit from further vaccines, or cited concerns in other studies in this age group.[28] Given the low rates of severe COVID-19 seen in the majority of subgroups of immunocompromised children,[12] it seems reasonable to suggest that offers of additional vaccine doses should follow a disease-specific, or measured-antibody-levels approach in future. Data from the neutralizing assays suggest that CYP in the RIC and PSOT groups are able to mount responses that react to the newer SARS-CoV-2 variants of Omicron, and this suggests that they should benefit from booster doses with newer iterations of vaccines.

OCTAVE-Minor was set up at pace as vaccines became available for CYP in the UK in September 2021. We did not feel it was ethical to counsel our patients to wait for trial enrolment prior to vaccination during the rapid initial period of public health driven vaccine uptake. Therefore, our trial limitations include a heterogenous sample both in terms of underlying disease type and number of vaccines received prior to enrolment, and

cohorts were not exactly matched by demographics to the sample in the contemporaneous control data available. The group was further heterogeneous by presence or absence of prior wild-type infection. As we sought to sample blood for research only at the same time as children had blood samples for clinical indications, we did not tightly control timing of follow-up sampling post-vaccine. By focusing on a limited number of disease groups where significant concerns regarding risk existed at the onset of the pandemic, we were able to quickly recruit a large cohort of children with rare diseases, with results that could be considered to reflect a real-world setting.

Ongoing exposure to SARS-CoV-2 variants in the community is associated with quality and quantity of antibody responses[29] and it is likely that our patient cohort will continue to be exposed, potentially receiving natural boosts to their immunity. Future studies in this cohort should assess the duration and efficacy of these responses, to determine if vaccination should continue to be offered to high-risk children.

Contrary to initial concerns, it appears that many of this cohort can generate near-normal responses to wild-type infection and vaccination. This trial provides information on how these groups are likely to respond to newer variants of concern and highlights the fact that children who have received cancer chemotherapy appear to remain at risk. Alternative approaches to protect this last group from COVID-19 should be considered.

Contributors

Conceptualization: RBr, AK, JB, LRW, PK, CSG, IM, RBe. Data curation: AK. Formal analysis: RBr, AK, JB, LRW, PK, CSG, LB. Funding acquisition: PK, LRW. Investigation: GAAB, JB, RBr, LRW, EK, MG, AMM, XL, MS. Methodology: PK, RBr, JB, LRW, CSG. Project administration: AH, SM, AMP. Resources: RBr, LRW, JB, GAAB, AH, SM, AMP. Supervision: PK, IM, LRW. Writing – original draft: RBr, AK, JB, LRW, PK. Writing – review & editing: RBr, AK, JB, GAAB, AH, SM, AMP, SL, RBe, EK, MG, AMM, XL, LB, IM, CSG, PK, LRW. AK and LB accessed and verified the underlying data. RBr, LRW, and PK were responsible for the decision to submit the manuscript.

Acknowledgements

This work was supported by the Medical Research Council (Grant Ref. MC_PC_20060). Additional funding was received from the National Institute of Health Research (NIHR) Great Ormond Street Hospital Biomedical Research Centre (GOSH BRC). Staff at the CRCTU are supported by a core funding grant from Cancer Research UK (CTUQQR-Dec22/100006).

Abbreviations

CYP, children and young people; IQR, interquartile range; POST, post-solid organ transplantation; RIC, rheumatological inflammatory conditions.

References

1 Frenck RW, Jr., Klein NP, Kitchin N, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. *N Engl J Med* 2021; **385**: 239-50. DOI: 10.1056/NEJMoa2107456

2 Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; **383**: 2603-15. DOI: 10.1056/NEJMoa2034577

3 Ali K, Berman G, Zhou H, et al. Evaluation of mRNA-1273 SARS-CoV-2 vaccine in adolescents. *N Engl J Med* 2021; **385**: 2241-51. DOI: 10.1056/NEJMoa2109522

4 Hippisley-Cox J, Coupland CA, Mehta N, et al. Risk prediction of covid-19 related death and hospital admission in adults after covid-19 vaccination: national prospective cohort study. *BMJ* 2021; **374**: n2244. DOI: 10.1136/bmj.n2244

5 Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA* 2021; **325**: 2204-06. DOI: 10.1001/jama.2021.7489

6 Maritsi DN, Eleftheriou I, Vartzelis G, Spyridis N, Tsolia MN. Risk factors associated with accelerated rubella IgG antibody loss in previously vaccinated, treatment-naive patients with juvenile systemic lupus erythematosus: A prospective study. *Arthritis Rheumatol* 2019; **71**: 1022-23. DOI: 10.1002/art.40831

7 Goossen GM, Kremer LC, van de Wetering MD. Influenza vaccination in children being treated with chemotherapy for cancer. *Cochrane Database Syst Rev* 2013; **2013**: CD006484. DOI: 10.1002/14651858.CD006484.pub3

8 Barnes E, Goodyear CS, Willicombe M, et al. SARS-CoV-2-specific immune responses and clinical outcomes after COVID-19 vaccination in patients with immune-suppressive disease. *Nat Med* 2023; **29**: 1760-74. DOI: 10.1038/s41591-023-02414-4

9 Goodyear CS, Patel A, Barnes E, et al. Immunogenicity of third dose COVID-19 vaccine strategies in patients who are immunocompromised with suboptimal immunity following two doses (OCTAVE-DUO): an open-label, multicentre, randomised, controlled, phase 3 trial. *Lancet Rheumatol* 2024; **6**: e339-e51. DOI: 10.1016/S2665-9913(24)00065-1

10 Kelly E, Greenland M, de Whalley PCS, et al. Reactogenicity, immunogenicity and breakthrough infections following heterologous or fractional second dose COVID-19 vaccination in adolescents (Com-COV3): A randomised controlled trial. *J Infect* 2023; **87**: 230-41. DOI: 10.1016/j.jinf.2023.06.007

11 Gotzinger F, Santiago-Garcia B, Noguera-Julian A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. *Lancet Child Adolesc Health* 2020; **4**: 653-61. DOI: 10.1016/S2352-4642(20)30177-2

12 Greenan-Barrett J, Aston S, Deakin CT, Ciurtin C. The impact of immunocompromise on outcomes of COVID-19 in children and young people-a systematic review and meta-analysis. *Front Immunol* 2023; **14**: 1159269. DOI: 10.3389/fimmu.2023.1159269

13 Di Chiara C, Cantarutti A, Raffaella Petrara M, et al. Stronger and durable SARS-CoV-2 immune response to mRNA vaccines in 5-11 years old children with prior COVID-19. *Vaccine* 2024; **42**: 263-70. DOI: 10.1016/j.vaccine.2023.12.006

14 Adler AL, Waghmare A, Smith J, et al. SARS-CoV-2-Specific Antibodies in Pediatric Solid Organ Transplant Recipients: Benefits of Additional Vaccine Doses. *Pediatr Transplant* 2025; **29**: e70050. DOI: 10.1111/petr.70050

15 Hamad Saied M, van Straalen JW, de Roock S, et al. Humoral and cellular immunogenicity, effectiveness and safety of COVID-19 mRNA vaccination in patients with pediatric rheumatic diseases: A prospective cohort study. *Vaccine* 2024; **42**: 1145-53. DOI: 10.1016/j.vaccine.2024.01.047

16 Roznik K, Xue J, Stavrakis G, et al. COVID-19 vaccination induces distinct T-cell responses in pediatric solid organ transplant recipients and immunocompetent children. *NPJ Vaccines* 2024; **9**: 73. DOI: 10.1038/s41541-024-00866-4

17 Millen GC, Arnold R, Cazier JB, et al. Severity of COVID-19 in children with cancer: Report from the United Kingdom Paediatric Coronavirus Cancer Monitoring Project. *Br J Cancer* 2021; **124**: 754-59. DOI: 10.1038/s41416-020-01181-0

18 Kahn AR, Schwalm CM, Wolfson JA, Levine JM, Johnston EE. COVID-19 in Children with Cancer. *Curr Oncol Rep* 2022; **24**: 295-302. DOI: 10.1007/s11912-022-01207-1

19 Parker RS, Le J, Villa M, et al. COVID-19 vaccinated children, adolescents, and young adults with acute lymphoblastic leukemia show spike reactive antibodies and multifunctional T-cells. *Int J Cancer* 2024; **155**: 2190-200. DOI: 10.1002/ijc.35096

20 Lehrnbecher T, Sack U, Speckmann C, et al. Longitudinal Immune Response to 3 Doses of Messenger RNA Vaccine Against Coronavirus Disease 2019 (COVID-19) in Pediatric Patients Receiving Chemotherapy for Cancer. *Clin Infect Dis* 2023; **76**: e510-e13. DOI: 10.1093/cid/ciac570

21 Dr Soonie R.Patel PRSaPPTH. Vaccinations For Paediatric Patients Treated With Standard-Dose Chemotherapy And Haemopoietic Stem Cell Transplantation (HSCT) Recipients. Children's Cancer and Leukaemia Group; 2023.

22 Gualtieri R, Yerly S, Garcia-Tarodo S, et al. Rituximab-to-vaccine interval on SARS-CoV-2 immunogenicity in children: The potential role of prior natural infection. *Pediatr Allergy Immunol* 2024; **35**: e14161. DOI: 10.1111/pai.14161

23 Funaki T, Yamada M, Miyake K, et al. Safety and antibody response of the BNT162b2 SARS-CoV-2 vaccine in children aged 5-11 years with underlying diseases: A prospective observational study. *J Infect Chemother* 2024; **30**: 773-79. DOI: 10.1016/j.jiac.2024.02.020

24 Vanetti C, Stracuzzi M, Crivellaro E, et al. Humoral and cell-mediated immune responses in HIV-vertically infected young patients after three doses of the BNT162b2 mRNA SARS-CoV-2 vaccine. *Front Immunol* 2023; **14**: 1301766. DOI: 10.3389/fimmu.2023.1301766

25 Matkowska-Kocjan A, Owoc-Lempach J, Ludwikowska K, et al. COVID-19 mRNA Vaccine Tolerance and Immunogenicity in Hematopoietic Stem Cell Transplantation Recipients Aged 5-11 Years Old-Non-Randomized Clinical Trial. *Vaccines (Basel)* 2023; **11**. DOI: 10.3390/vaccines11010195

26 Morgans HA, Bradley T, Flebbe-Rehwaldt L, et al. Humoral and cellular response to the COVID-19 vaccine in immunocompromised children. *Pediatr Res* 2023; **94**: 200-05. DOI: 10.1038/s41390-022-02374-4

27 Ziv N, Gimelraikh Y, Ashkenazi-Hoffnung L, et al. Serologic response to COVID-19 infection or vaccination in pediatric kidney transplant recipients compared to healthy children. *Transpl Immunol* 2023; **78**: 101839. DOI: 10.1016/j.trim.2023.101839

28 Siebald B, Groll AH, Salou S, et al. Pediatric cancer patients vaccinated against SARS-CoV-2-a clinical and laboratory follow-up. *Support Care Cancer* 2024; **32**: 221. DOI: 10.1007/s00520-024-08422-5

29 Cheetham NJ, Kibble M, Wong A, et al. Antibody levels following vaccination against SARS-CoV-2: associations with post-vaccination infection and risk factors in two UK longitudinal studies. *Elife* 2023; **12**. DOI: 10.7554/eLife.80428

Figure legends

***Figure 1*: Overview of the OCTAVE-Minor study cohort**

The number of patients included within the OCTAVE-Minor study are shown. The main reasons for withdrawal were due to patient-decision to not want any further doses of vaccine. Prior COVID-19 infection was confirmed by PCR or antibody testing.

PSOT, post solid organ transplant (kidney, lung, heart-lung, heart); RIC, rheumatological inflammatory conditions.

***Figure 2*: Serological anti-SARS-CoV-2 spike antibody responses to vaccination**

(A) Stacked bar chart showing percentages of pre- and post-vaccine immune response quantified by the Roche anti-SARS-CoV-2 spike receptor binding domain assay for the ComCOV3 control cohort, and the RIC, PSOT, and cancer OCTAVE-Minor disease groups. Proportions of each response level in each group divided into non-response <0·8 AU/ml (red bars), low response ⩾0·8 to <380·0 AU/ml (pale blue bars), and high response ⩾ 380·0 AU/ml (blue bars) as shown. Chi-square test comparison of proportions of pairwise comparisons of control and disease groups using Bonferroni correction (adjusted alpha = 0·0083) performed, * indicates statistically significant by Bonferroni-adjusted alpha. Lines denote pairwise tests; RIC and PSOT compared with cancer group were both statistically significant with Bonferroni-adjusted alpha.

(B) Box plot with corresponding data points showing on-trial post-vaccination response quantified by the Roche anti-SARS-CoV-2 spike receptor binding domain assay for the ComCOV3 control cohort, RIC, PSOT and cancer disease groups. Kruskal-Wallis testing found a statistically significant difference between groups (p=0·0001, *post-hoc* Dunn's Test with Bonferroni correction) and found statistically significant differences by Bonferroni-adjusted alpha (adjusted alpha = 0.0083) between each disease group when compared with the cancer disease group.

(C) Log_{10} transformed pre- and post-vaccine Roche anti-SARS-CoV-2 spike receptor binding domain assay results for disease cohorts: RIC group (upper panel); PSOT group (middle panel); and cancer group (lower panel). Each group is presented by number of vaccinations received, with indicator of natural SARS-CoV-2 infection as detected by the Roche anti-N assay as shown (Roche N assay Negative, Roche N Assay Positive). Median anti-S IgG is increased pre- to post-vaccination (p<0·00001, Friedman test). Within specific patient groups and broken down by vaccine number, after correction for multiple testing the following remained significant : in the PSOT group, pre- to post- second vaccination (p=0.0362, paired Wilcoxon rank), pre-second vs. post-fourth vaccination

(p=0.0014, Mann Whitney) and pre second vs. combined group of post-second, post-third and post-fourth vaccination (0.0031 Mann Whitney test). Other disease and vaccine number comparisons did not reach statistical significance. Plots include data from participants who elected not to receive vaccination while enrolled in the trial and have pre-vaccine results only.

PSOT, post solid organ transplant (kidney, lung, heart-lung, heart); RIC, rheumatological inflammatory conditions.

Figure 3: **Neutralizing antibody titers to SARS-CoV-2 variants**

(A-D) Log_{10} transformed pre- and post-vaccine responses to variants of SARS-CoV-2 on micro-neutralization assay, stratified by number of vaccines received. (A) Pre- and post-first vaccine; (B) pre- and post-second vaccine; (C) pre- and post-third vaccine; and (D) pre- and post-fourth vaccine. Colored lines in A- D: RIC = black, PSOT = orange, cancer = blue.

(E-G) Log_{10} transformed pre- and post-vaccine responses to variants of SARS-CoV-2 on micro-neutralization assay, stratified by disease group. (E) Rheumatological inflammatory conditions (RIC); (F) post-solid organ transplant (PSOT); and (G) cancer disease group. Line color in E-G indicates number of vaccines, 0-4 as shown. Plots include participants who had received one, multiple, or no vaccines during the study.

Wilcoxon rank sum test comparison of pre- and post-vaccination neutralization assay measurements was performed, *indicates statistically significant at 5% significance level.

Figure 4: **T-cell responses to vaccination**

(A) Stacked bar chart showing percentages of post-vaccine immune response quantified by the ELISpot T-cell assay for the ComCOV3 control cohort, RIC, PSOT and cancer disease groups. Proportions of each response level, divided into non-responders $\leqslant$4 interferon-γ-secreting T-cells (SFC)/10^6 peripheral blood monocytes (PBMC) (red bars), and responders >4 SFC/10^6 PBMC (blue bars). $\chi 2$ test comparison of proportions of pairwise comparisons of control and disease groups using Bonferroni correction (adjusted alpha = 0·0083) performed, * indicates statistically significant by Bonferroni-adjusted alpha. Control versus cancer group (p=0·001) was statistically different after applying the Bonferroni-adjusted alpha.

(B) Box plot with corresponding data points shows on-trial post-vaccination vaccine response quantified by the ELISpot T-cell assay for the ComCOV3 control data, RIC, PSOT, and cancer disease groups. Kruskal-Wallis test found a statistically significant difference between groups (p=0.04), * indicates statistically significant by

Bonferroni-adjusted alpha. Kruskal-Wallis test with *post-hoc* Dunn's test found no statistically significant differences between individual disease groups after applying the Bonferroni-adjusted alpha.

(C) Log_{10} transformed pre- and post-vaccine ELISpot assay results for disease cohorts: RIC group (upper panel); PSOT group (middle panel); and cancer group (lower panel). Each group is presented by number of vaccinations received, with indicator of natural SARS-CoV-2 infection as detected by the Roche N assay as shown (Roche N assay Negative, Roche N Assay Positive). Within specific patient groups and broken down by vaccine number, after correction for multiple comparisons, no specific pre- to post- vaccine comparison reached statistical significance. Plots include data from participants who elected not to receive vaccination while enrolled in the trial and have pre-vaccine results only.

PSOT, post solid organ transplant (kidney, lung, heart-lung, heart); RIC, rheumatological inflammatory conditions.

Table 1: Demographics, baseline characteristics and vaccines received

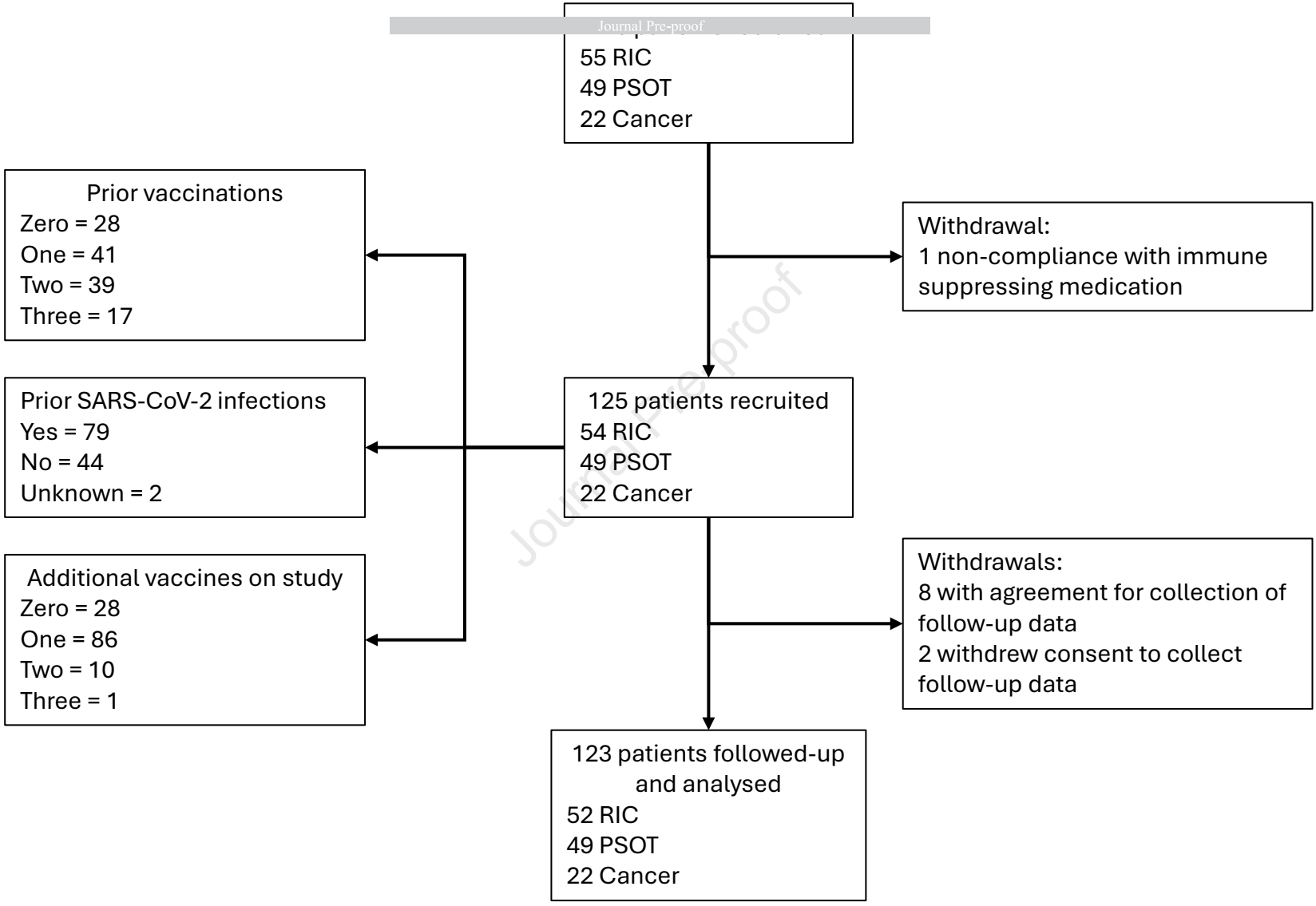
	Disease Group			
	RIC	**PSOT**	**Cancer**	**Total**
N	54 (43·2%)	49 (39·2%)	22 (17·6%)	125 (100%)
Subgroup diagnoses	JIA with uveitis: 9 (16·7%) JIA without uveitis: 31 (57·4%) Juvenile SLE: 14 (25·9%)	Heart: 20 (40·8%) Lung or Heart-Lung: 2 (4·1%) Kidney: 27 (55·1%)	ALL: 14 (63·6%) Lymphoma: 3 (13·6%) CNS tumour: 1 (4·6%) Non-CNS tumour: 2 (9·1%) Other: 2 (9·1%)	N/A
Sex				
Female	34 (63·0%)	18 (36·7%)	6 (27·3%)	58 (46·4%)
Male	20 (37·0%)	31 (63·3%)	16 (72·7%)	67 (53·6%)
Age (years)				
Median (IQR)	14·2 (12·0, 15·2)	13·3 (12·2, 14·3)	13·1 (6·7, 14·9)	13·7 (11·8, 14·9)
Ethnicity				
White	31 (57·4%)	36 (73·5%)	17 (77·3%)	84 (67·2%)
Black	4 (7·4%)	0 (0%)	0 (0%)	4 (3·2%)
Asian	16 (29·6%)	9 (18·4%)	1 (4·5%)	26 (20·8%)
Mixed/Other	1 (1·8%)	4 (8·1%)	4 (18·2%)	9 (7·2%)
Unknown	2 (3·8%)	0 (0%)	0 (0%)	2 (1·6%)
Vaccines prior to study				
Zero	14 (25·9%)	3 (6·1%)	11 (22·0%)	28 (22·4%)
One	15 (27·8%)	22 (44·9%)	3 (13·6%)	40 (32·0%)
Two	19 (35·2%)	12 (24·5%)	8 (36·4%)	39 (31·2%)
Three	5 (9·3%)	12 (24·5%)	0 (0%)	17 (13·6%)
Unknown	1 (1·8%)	0 (0%)	0 (0%)	1 (0·8%)
Vaccines during study				
Zero	12 (22·2%)	8 (16·3%)	8 (36·4%)	28 (22·4%)
One	40 (74·1%)	40 (81·6%)	6 (27·3%)	86 (68·8%)
Two	2 (3·7%)	1 (2·0%)	7 (31·8%)	10 (8·0%)
Three	0 (0%)	0 (0%)	1 (4·5%)	1 (0·8%)
Prior COVID-19				
Yes	34 (63·0%)	33 (67·4%)	12 (54·5%)	79 (63·2%)
No	19 (35·2%)	15 (30·6%)	10 (45·5%)	44 (35·2%)

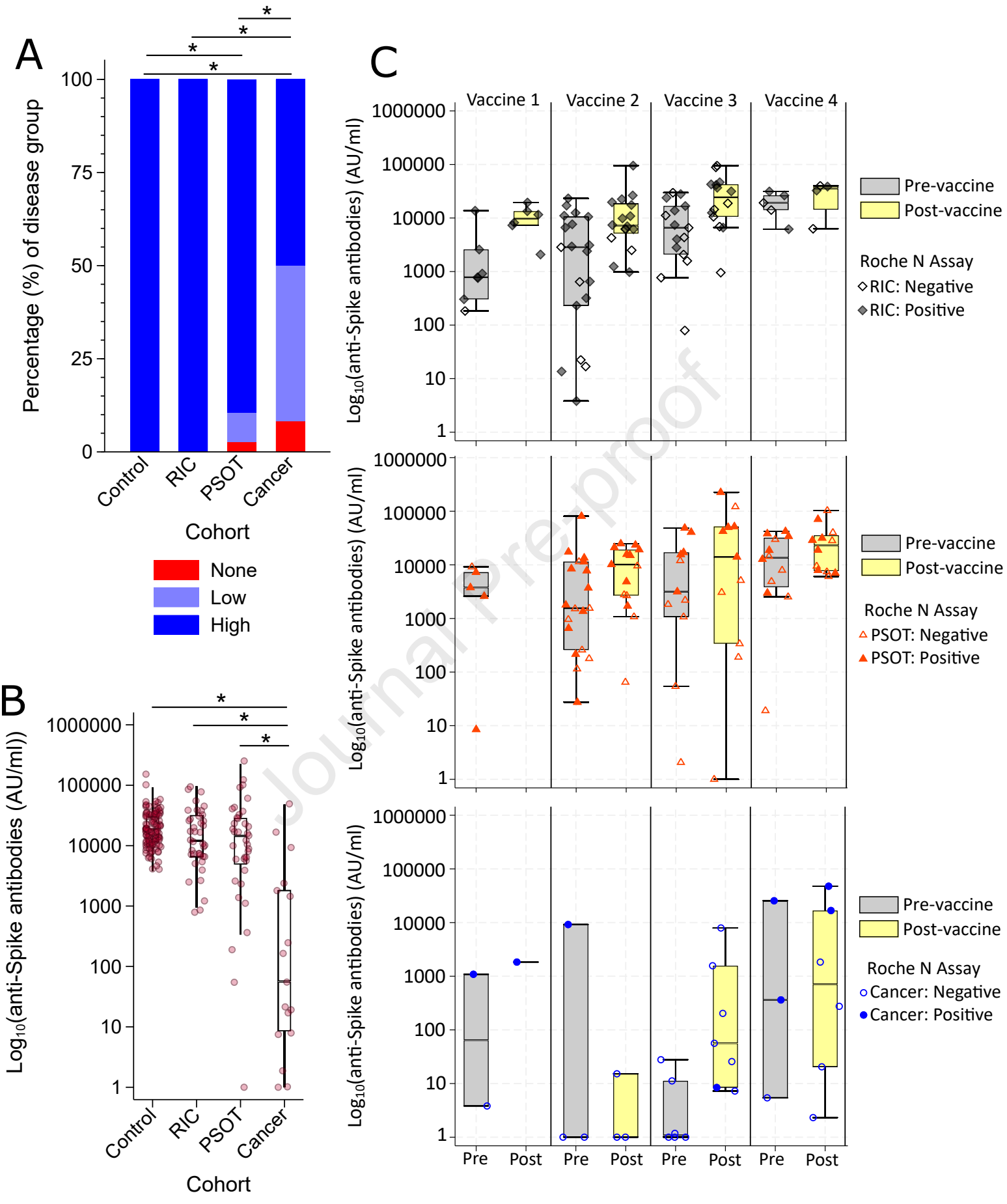
	Disease Group			
	RIC	**PSOT**	**Cancer**	**Total**
Unknown COVID-19 during study	1 (1·8%)	1 (2·0%)	0 (0%)	2 (1·6%)
Yes	4 (7·4%)	6 (12·2%)	3 (13·6%)	13 (10·4%)
No	35 (64·8%)	33 (67·3%)	8 (36·4%)	76 (60·8%)
Unknown	15 (27·8%)	10 (20·4%)	11 (50·0%)	36 (28·8%)

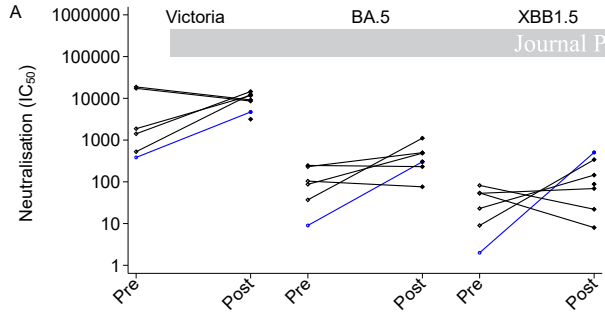
ALL, acute lymphoblastic leukaemia; CNS, central nervous system; IQR, interquartile range; JIA, juvenile idiopathic arthritis; PSOT, post solid organ transplant (kidney, lung, heart-lung, heart); RIC, rheumatological inflammatory condition; SLE, systemic lupus erythematosus.

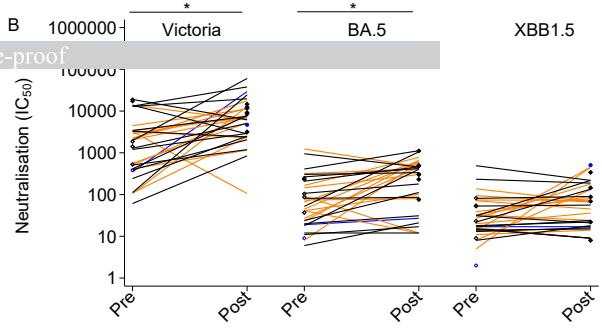
Note: Cancer diagnoses included Non-Hodgkin Lymphoma, Precursor B Lymphoblastic Lymphoma, Rosai-Dorfman Disease, Langerhans Cell Histiocytosis, CNS tumour, Sarcoma and T-Lymphoblastic Lymphoma. No patients were recorded as having undergone haematopoietic stem cell transfer (HSCT) or CAR-T therapy

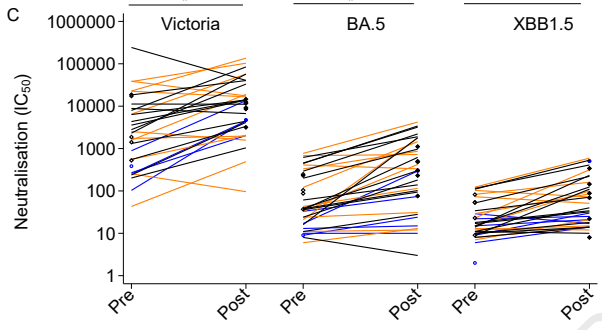
Note: Variables are presented as N (%) unless otherwise specified.

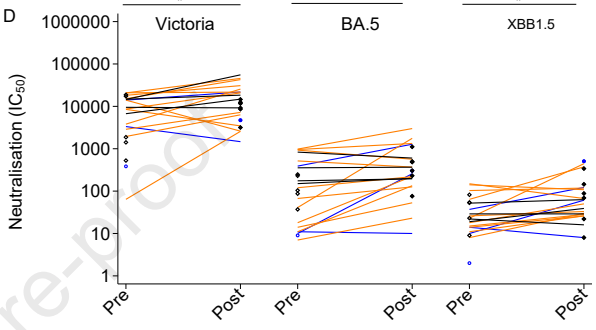




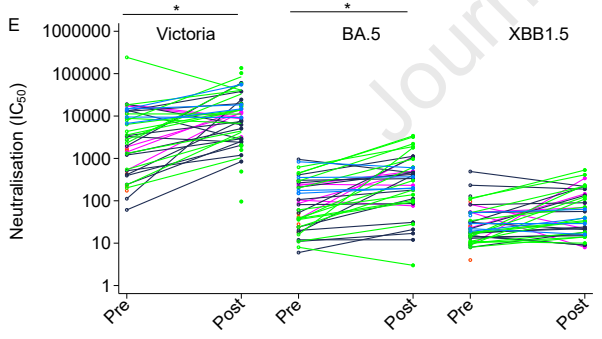


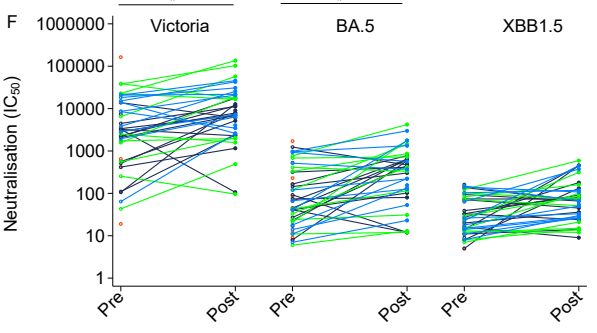


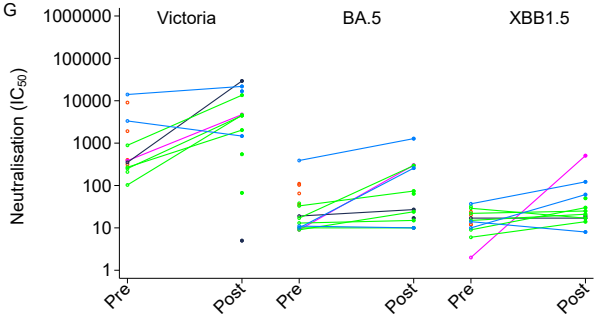




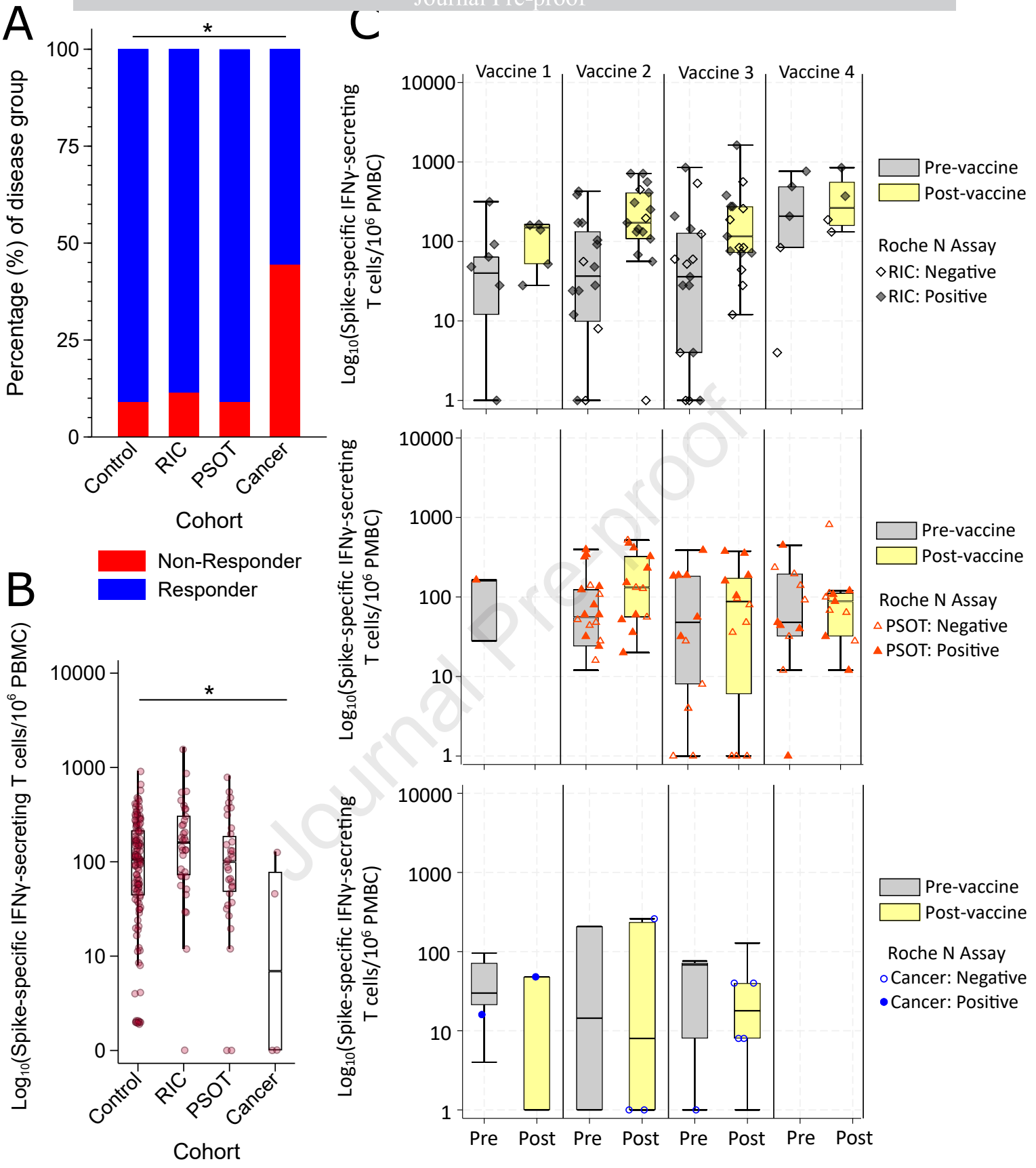
KEY: RIC Group PSOT Group Cancer Group







KEY:
0 Vaccines
1 Vaccine
2 Vaccines
3 Vaccines
4 Vaccines



Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Pamela Kearns reports financial support was provided by Medical Research Council. Lucy R Wedderburn reports financial support was provided by NIHR Great Ormond Street Hospital Biomedical Research Centre. Angela M Minassian reports a relationship with Pfizer that includes: funding grants. Angela M Minassian reports a relationship with GlaxoSmithKline Inc that includes: funding grants. Angela M Minassian reports a relationship with Janssen Pharmaceuticals Inc that includes: funding grants. Angela M Minassian reports a relationship with Valneva SE that includes: funding grants. Angela M Minassian reports a relationship with Novavax Inc that includes: funding grants. Carl S Goodyear reports a relationship with AstraZeneca PLC that includes: consulting or advisory and funding grants. Carl S Goodyear reports a relationship with Bristol Myers Squibb Co that includes: consulting or advisory and funding grants. Carl S Goodyear reports a relationship with Eli Lilly and Company that includes: funding grants. Carl S Goodyear reports a relationship with Galvani Bioelectronics Ltd that includes: consulting or advisory and funding grants. Carl S Goodyear reports a relationship with GlaxoSmithKline Inc that includes: funding grants. Carl S Goodyear reports a relationship with Istesso Limited that includes: funding grants. Carl S Goodyear reports a relationship with Janssen Pharmaceuticals Inc that includes: funding grants. Carl S Goodyear reports a relationship with Medannex Limited that includes: consulting or advisory and funding grants. Carl S Goodyear reports a relationship with MiroBio Ltd that includes: funding grants. Carl S Goodyear reports a relationship with Revolo Biotherapeutics that includes: funding grants. Carl S Goodyear reports a relationship with UCB Pharma SA that includes: consulting or advisory and funding grants. Iain McInnes reports a relationship with Bristol Myers Squibb Co that includes: consulting or advisory and funding grants. Iain McInnes reports a relationship with Eli Lilly and Company that includes: consulting or advisory and funding grants. Iain McInnes reports a relationship with AstraZeneca UK Limited that includes: consulting or advisory and funding grants. Iain McInnes reports a relationship with Novartis that includes: consulting or advisory and funding grants. Iain McInnes reports a relationship with AbbVie Inc that includes: consulting or advisory. Iain McInnes reports a relationship with Amgen Inc that includes: consulting or advisory. Iain McInnes reports a relationship with Absci Corp that includes: consulting or advisory. Iain McInnes reports a relationship with Causeway Therapeutics that includes: consulting or advisory. Iain McInnes reports a relationship with Dextera Biosciences Inc that includes: consulting or advisory. Iain McInnes reports a relationship with Cabaletta Bio Inc that includes: consulting or advisory. Iain McInnes reports a relationship with Gilead Sciences Inc that includes: consulting or advisory. Iain McInnes reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory. Iain McInnes reports a relationship with Pfizer Inc that includes: consulting or advisory. Iain McInnes reports a relationship with Sanofi that includes: consulting or advisory. Iain McInnes reports a relationship with UCB Pharma SA that includes: consulting or advisory. Iain McInnes reports a relationship with Compugen that includes: consulting or advisory. Iain McInnes reports a relationship with MoonLake Immunotherapeutics Ltd that includes: consulting or advisory. Iain McInnes reports a relationship with Montai Therapeutics that includes: consulting or advisory. Lucy R Wedderburn reports a relationship with Pfizer Inc that includes: consulting or

advisory and funding grants. Lucy R Wedderburn reports a relationship with Cabaletta Bio Inc that includes: consulting or advisory. Pamela Kearns reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory. Angela M Minassian has patent licensed to Astrazeneca. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.