Examining the immunological effects of COVID-19 vaccination in patients with conditions potentially leading to diminished immune response capacity – the OCTAVE Trial

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Abstract

SARS-COV-2 vaccines have been shown to be efficacious primarily in healthy volunteer populations and population level studies. Immune responses following SARS-CoV-2 vaccination are less well characterised in potentially immune vulnerable patient groups, including those with immune-mediated inflammatory and chronic diseases (inflammatory arthritis [IA] incorporating rheumatoid arthritis [RA] and psoriatic arthritis [PsA]; ANCA-Associated Vasculitis [AAV]; inflammatory bowel disease [IBD]); hepatic disease (HepD), end stage kidney disease requiring haemodialysis (HD) without or with immunosuppression (HD-IS); solid cancers (SC) and haematological malignancies (HM), and those that have undergone haemopoietic stem cell transplant (HSCT). The OCTAVE trial is a multi-centre, multi-disease, prospective cohort that will comprehensively assess SARS-CoV-2 vaccine responses within and between the above-mentioned disease cohorts using common analytical platforms in patients recruited across the United Kingdom (UK). The majority of subjects received either COVID-19 mRNA Vaccine BNT162b2 (Pfizer/BioNTech) or ChAdOx1 Vaccine (AstraZeneca formerly AZD1222) as part of the UK National COVID19 vaccination programme. As of 13th August 2021; 2,583 patients have been recruited. We report herein the humoral and T cell immune response results from the first 600 participants recruited where serology data are available at baseline, pre-second vaccine dose (boost) and/or 4 weeks post second dose. We also include in the analysis, data obtained from 231 healthy individuals from the PITCH (Protective Immunity from T cells in Healthcare workers) study. Overall, in comparison to PITCH where 100% of tested individuals (n=93) generated anti-Spike antibodies after vaccine doses, 89% of patients within OCTAVE seroconverted 4 weeks after second vaccine dose**.** By corollary, approximately 11% of patients across all disease cohorts fail to generate antibodies that react to SARS-CoV-2 spike 4 weeks after two vaccines. Failure to generate spike reactive antibodies was found at a higher proportion in some specific patient subgroups, particularly AAV (72.4%), HD-IS (16.7%) and HepD (16.7%). Importantly, all recruited AAV patients had received Rituximab; a targeted B cell depletion therapy. Furthermore, even in those who seroconverted, 40% of patients across disease cohorts generate lower levels of SARS-CoV-2 antibody reactivity compared to healthy subjects after two SARS-CoV-2 vaccines; the functional significance of these findings in providing protection from subsequent SARS-CoV-2 exposure is not currently known. In contrast to the observed serological response, evaluation of the Spike-specific T cell response revealed that across all patient sub-groups (including AAV) a response similar to healthy individuals was generated. Our data argue strongly for further vaccination strategies to optimise humoral immune responses against SARS-CoV-2 in patients with chronic diseases and/or patients on immune suppressive therapies.

Introduction

The rapid development and subsequent authorisation of vaccines against SARS-CoV-2 has been a major step forward in the management of the COVID-19 pandemic (1, 2). In the UK, four COVID-19 vaccines are already approved by the Medicines and Healthcare products and Regulatory Agency (MHRA): mRNA Vaccines BNT162b2 (Pfizer/BioNTech) and Spikevax (Moderna); adenovirus-based vaccines ChAdOx1 (AstraZeneca; formerly AZD1222) and Ad26.COV2-S (Janssen). It is likely that further vaccines will be approved in the coming months. National vaccination programmes have been initiated and population level datasets now demonstrate considerable protection in the general population against severe COVID-19 infection (2). The populations evaluated in the trials of these vaccines were generally healthy volunteers without known chronic disease. Several recent studies have addressed COVID-19 vaccine immunogenicity in patient groups in whom immune function may be impaired (3-6). Recently, Public Health England reported evaluation of serology and clinical outcomes in clinical risk groups derived from primary care databases and found generally high rates of seroconversion (~96-100%) and no evidence of reduced vaccine effectiveness (7). Questions remain, however, as to the level of protection these vaccines afford patient populations with chronic illnesses who have primary or secondary immune deficiencies either arising from profound immune impairment or significant immunosuppressive therapeutic regimens. Detailed immunologic evaluation of these groups that might inform such questions and future vaccination strategies is limited.

The OCTAVE trial (Observational Cohort Trial-T-cells Antibodies and Vaccine Efficacy in SARS-CoV-2) is an ongoing, prospective trial that seeks to investigate the immune responses to approved SARS-CoV-2 vaccines as they are implemented in the UK national vaccination programme in patient cohorts with a range of chronic diseases that either intrinsically, and/or as a result of the associated therapies have impaired immunity. Between 17th February and 23rd August 2021, 2,592 patients were recruited to the OCTAVE trial, including 1,000 patients with end-stage renal disease requiring haemodialysis (HD) without or with immunosuppression (HD-IS), 567 with hepatic disease (HepD) and inflammatory bowel disease [IBD) disease, 139 solid cancer (SC; breast and lung) and haematological malignancies (HM; acute myeloid leukaemia and multiple myeloma), 726 immune-mediated inflammatory rheumatic (IA) diseases including (rheumatoid arthritis [RA], psoriatic arthritis [PsA], ANCA-associated vasculitis [AAV] and 160 haemopoietic stem cell transplant (HSCT) recipients. These disease states are likely to modulate immune responses to SARS-CoV-2 vaccines as a result of (a) the function of their underlying pathophysiology and associated immune dysregulation, or (b) due to their requisite management with immune modifying

medications, including biologics, disease-modifying anti-rheumatic drugs (DMARDs), broad spectrum immune suppressants and glucocorticoids.

Given the current imperative to inform policy decisions concerning vaccine effectiveness in these vulnerable patient sub-groups, we report herein the findings of an unplanned interim analysis for 655 patients recruited into the deep immunotyping OCTAVE group for whom serological and/or T cell immune evaluation is available.

Materials and Methods

2.1 Trial design and oversight

The OCTAVE trial is a multi-centre, multi-disease, prospective cohort trial of the immune response to SARS-CoV-2 vaccination in patients receiving COVID-19 vaccination as part of routine publicly funded National Health Service (NHS) care. OCTAVE is designed to determine the phenotype and function of SARS-CoV-2 vaccine-induced immune responses in clinically vulnerable groups across the UK, including patients with chronic diseases and/or secondary immunodeficiency, compared to each other in OCTAVE and to healthy controls in parallel studies. The impact of distinct immune therapeutic drug classes on the development of humoral and cellular immune responses to SARS-CoV-2 following vaccination is also evaluated. The trial is a collaboration between the Universities of Birmingham, Glasgow, Imperial College London, Oxford, Leeds, Sheffield and St George's University NHS Foundation Trust, and is coordinated by the Cancer Research UK Clinical Trials Unit at the University of Birmingham; the sponsor. The trial is conducted in accordance with the principles of the Good Clinical Practice (GCP) guidelines. It was approved by the UK Medicines and Healthcare Products Regulatory Agency on the 5th February 2021 and the London and Chelsea Research Ethics Committee (REC Ref:21/HRA/0489) on 12th February 2021, with subsequent amendments approved on 3rd March 2021, 19th April 2021 and 26th April 2021). The trial is registered on ISRCTN 12821688. Written informed consent was obtained from all the participants.

Participants had a diagnosis of end stage kidney disease, liver disease (i.e., liver cirrhosis, liver transplant recipients and autoimmune liver disease on immune suppressive therapy) or gastrointestinal disease on immune suppressive therapy, cancer, immune-mediated rheumatic diseases or were haematopoietic stem cell transplant recipients and were receiving the SARS-CoV-2 vaccines as part of the national vaccination programme. Participants who had not a received the second dose of vaccine (booster) were eligible for the "Deep Immunophenotyping Group" measuring T cell and humoral (antibody responses)

before and after vaccines. The basic demographics of this cohort are described in Table 1. Participants who were within 21-56 days post-booster were eligible for the "Serology Group" measuring antibodies and are not reported here. All participants had an anticipated life expectancy of ≥6 months.

Up to 3,250 participants will be recruited. Between 100 and 200 participants per disease cohort will be recruited for full immune response analysis (Deep Immunophenotyping Group) and between 150 and 850 participants per disease cohort will be recruited for serology analysis (Serology Group). Patients will be followed up for 12 months in accordance with standard clinical practice for the relevant disease cohort. Full details of the trial are available on the trial website: https://www.birmingham.ac.uk/research/crctu/trials/octave/index.aspx

2.2 Intervention

Vaccine (BNT162b2 (Pfizer/BioNTech) or ChAdOx1 Vaccine) was administered in line with its temporary authorisation under Regulation 174 of the Human Medicines Regulations 2012, the national recommendations, and guidance of the Joint Committee on Vaccination and Immunisation (JCVI) and current standard NHS practice. The trial has no influence on the type of vaccine given, or the timing of the booster vaccine delivery. Vaccines were administered both through NHS pathways and by OCTAVE study investigators. The second dose vaccines are delivered in accordance with national recommendations and the guidance of the JCVI.

2.3 Sample Collection

Serum samples were collected 4 weeks post-second dose (-7/+14 days) for all participants, alongside whole blood for the Oxford Immunotec assay, peripheral blood mononuclear cells (PBMC), and plasma, when feasible. Where available, baseline (pre-vaccine samples, including samples that may have been collected prior to recruitment to OCTAVE) or pre-second dose samples taken any time after the first vaccination but before the second dose were included. Thereby, we have created a comprehensive biobank to facilitate future analyses. All samples were collected in accordance with national regulations and requirements including standard operating procedures for logistics and infrastructure. Samples were taken in appropriately licensed premises, stored, and transported in accordance with the Human Tissue Authority guidelines and NHS trust policies.

2.4 Outcome measures

The primary outcome measures for the humoral immunity are quantity of Anti-SARS-CoV-2 Abs detected following vaccination measured using the Roche Elecsys® Anti-SARS-CoV-2 S and Roche Elecsys® Anti-SARS-CoV-2 N assays by the Public Health England Laboratories at Porton Down. The Roche assay measures the presence and amount of serum antibodies to the spike (S) antigen of SARS-CoV-2. Seroconversion is defined as a response equal to or greater than 0.8 U/ml, and no response is defined as less than 0.8 U/ml. Whole blood samples were sent to Oxford Immunotec and the T-SPOT Discovery SARS-CoV-2 assay used to evaluate SARS-CoV-2-specific T-cell responses. In brief, peptide pools representing the full Spike (S) proteins, subunits S1 and S2, Nucleocapsid and Membrane, plus positive (phytohaemagglutinin) and negative controls were used to stimulate 250,000 PBMCs. Interferon-gamma (IFNγ) secreting T cells were enumerated on an automated plate reader. Final values were calculated by subtracting the negative control and multiplying by 4 to define the number of IFNγ secreting T cells / 10^6 PBMCs. Values $\geq$24 IFNγ secreting T cells / 10^6 PBMCs were defined as a positive response. In the HD and HD-IS group the full spike peptide pool was not included in the assay at all time points due to timing of recruitment. To generate equivalent data the S1+S2 values were combined and a cut-off of 40 IFNγ secreting T cells / 10^6 PBMCs was used for positivity, as previously described (15).

2.5 Statistical Methods

Roche anti-SARS-CoV-2 and T cell data from the cohort, alongside data derived from the PITCH healthy volunteer study (see section 2.6) have been analysed and results within this report. Data on prior COVID-19 infection were captured at patient recruitment. Each data set and disease subgroups have been analysed to present summary descriptive statistics giving number of observations (n), median and interquartile range (IQR), dot and box plots to show data distributions. To aid data visualisation, data from the assays were transformed to log10.

2.6 Control Group

For the healthy control group, serum samples from the UK PITCH (Protective Immunity from T cells in Healthcare workers) study were used. PITCH is a prospective multi-centre study, with the goal of undertaking a deeper mechanistic study, including T cell responses, of immunity induced by natural infection and vaccination (8, 9). Healthcare worker participants received SARS-CoV-2 vaccination as part of workplace programmes. PITCH is a sub-study of the SIREN study, which was approved by the Berkshire Research Ethics Committee, Health Research 250 Authority (IRAS ID 284460, REC reference 20/SC/0230), with PITCH recognised as a sub-study on 2 December 2020. SIREN is registered with ISRCTN (Trial ID:252

ISRCTN11041050). Some participants were recruited under aligned study protocols. In Oxford, participants were recruited under the GI Biobank Study 16/YH/0247, approved by the Yorkshire & The Humber - Sheffield Research Ethics Committee on 29 July 2016, which was amended for this purpose on 8 June 2020. In Liverpool some participants were recruited under the "Human immune responses to acute virus infections" Study (16/NW/0170), approved by the North West - Liverpool Central Research Ethics Committee on 8 March 2016, and amended on 14th September 2020 and 4th May 2021. In Sheffield, participants were recruited under the Observational Biobanking study STHObs (18/YH/0441), which was amended for this study on 10 September 2020. The study was conducted in compliance with all relevant ethical regulations for work with human participants, and according to the principles of the Declaration of Helsinki (2008) and the ICH and GCP guidelines. Written informed consent was obtained for all patients enrolled in the study.

Results

Serum drawn prior to first vaccination (pre-vaccine; baseline), pre-second vaccination (pre-boost) and 4 weeks post boost vaccination were tested for anti-Spike (S) antibody titres using the Roche Elecsys® Anti-SARS-CoV-2 S assay. In the PITCH study 100% of 93 tested HC seroconverted (i.e. ≥ 0.8 U/ml) whilst in the overall OCTAVE cohort, seroconversion for anti-S antibody was observed in 406/455 (89%) of patients after two doses of vaccine. Importantly, the overall 11% non-seroconversion was not equal across all the discrete disease sub-groups (Table 2). Of note only 8/29 (27.6%) of AAV patients seroconverted whereas 98.2% of IA patients, 94.6% of HD patients, 83.3% of HD-IS, 83.3% of HepD patients and 100% of IBD patients, 100% of SC patients, 88.9% of HM patients and 88.1% of HSCT patients exhibited seroconversion at 4 weeks post-second inoculation (Table 2).

Examination of the quantitative anti-S reactivity across disease groups 4 weeks after the second vaccine compared to those observed in the PITCH healthy control (HC) group, revealed that the median responses in the disease groups after both first and second dose of the vaccine were below the level of HC (Figure 1 and Table 3). This was most notable in the AAV, IA and HepD cohorts. For instance, in the IA cohort the median level of anti-S reactivity 4 weeks post-second dose was more than a log order lower that HC (Figure 1A, Table 3); 331 U/ml [166-815] (median [IQR]) and 11,514 U/ml [3,324-23,302] respectively. In addition to the decreased median, it was also observed that the range of reactivity across the cohorts was substantially different from HC. This is most notable in HD patients, where although the median level of response was to some degree equivalent to HC, the range of reactivity was substantially different (HD,

6,123 U/ml [554-29,502]; HC 11,514 U/ml [3,324-23,302]) (Figure 1A, Table 3). Moreover, these data also reveals that there are a substantial proportion of patients across the disease groups (90% of AAV, 54% of IA, 21% of HD, 42% of HD-IS, 52% of HepD, 17% of SC, 39% of HM and 33% of HSCT) that have an anti-S titre that falls below the lowest titre achieved in the PITCH study (i.e., 380 U/ml after second dose of vaccine) (Table 4). This is notable after both the first and second dose of vaccine (Figure 1A&B).

To understand how prior COVID infection impacts the level of response, the PITCH and disease groups were split into those with or without reported prior infection. Comparing individuals that **had not** reported prior COVID infection, the disease groups still displayed a lower median anti-S titre and wider range of reactivity than the previously uninfected HC (Figure 2A&B, Table 5). Furthermore, the second dose of vaccine generally resulted in an increase in the median anti-S titre. For example, in the IA cohort the median level of anti-S reactivity after one dose of vaccine (pre-boost) was lower than the level at 4 weeks post-second dose (Figure 2A, Table 5); 14.8 U/ml [4.8-45.9] (median [inter quartile range (IQR)) and 316 U/ml [162-806.5] respectively.

In the individuals that **had** reported prior COVID infection, the observed median level of reactivity was different across the disease groups. In the case of IA, vaccination did increase the median anti-S titre, however, the levels achieved did not correspond to those seen in HC; in the IA cohort the range of responses seen after booster vaccine in those previously infected were in the same range as previously uninfected HC (Figure 2C, Table 5). In comparison, in HD, HepD and SC the median anti-S titres were similar to HC (Figure 2C&D, Table 5). For example, in HD after one dose of vaccine (pre-boost) the median anti-S titre was comparable to the level observed in HC (Figure 2C, Table 5); 15,914 U/ml [1,775-48,050] (median [inter IQR]) and 14,602 U/ml [9,499-20,438] respectively. It was also noted that in certain disease groups (i.e., AVV, IA, HD, HepD) the administration of a second dose of vaccine did not increase the anti-S titre beyond what was seen following the first vaccine (Figure 2C&D, Table 5). For instance, in HD the median level of anti-S reactivity after one dose of vaccine (pre-boost) was equivalent to the level at 4 weeks post-second dose (Figure 2C, Table 5); 15,914 U/ml [1,775-48,050] (median [IQR]) and 15,877 U/ml [4,002-44,497] respectively. Finally, we also observed in some patient groups (e.g., AAV, IA, HD, HD-IS) that median anti-S titres in prior infected patients were higher after one dose of vaccine than in those un-exposed patients who had received two doses of the vaccine (Table 5).

T cell responses were also evaluated prior to first vaccination, pre-second vaccination and 4 weeks post boost vaccination using the Oxford Immunotec T-SPOT Discovery SARS-CoV-2 assay. Analysis included 489 patients recruited where data were available at baseline, pre-second vaccine dose (boost) and/or 4 weeks post second dose, alongside 194 PITCH HC. In general, the level of T cell responses was similar across the disease groups and in comparison with the HC (Figure 3, Table 6 & 7). However, it is worth highlighting that in some disease groups (e.g., IA, HepD, IBD) a second dose of vaccine did not lead to an overall increase in the median T cell response (Figure 3A and Table 6 & 7). For instance, in IA the median level of IFNγ secreting T cell / 10^6 PBMCs after one dose of vaccine (pre-boost) was equivalent to the level observed at 4 weeks post-second dose (Figure 3A, Table 6); 48 IFNγ secreting T cell / 10^6 PBMCs [16-108] (median [IQR]) and 48 IFNγ secreting T cell / 10^6 PBMCs [16-108] respectively. In comparison, and similar to HC, other disease groups did show an increase in T cell response after a second dose of vaccine (e.g., AAV, SC, HM, HSCT)(Figure 3A&B, Table 6). For example, in AAV the median level of IFNγ secreting T cell / 10^6 PBMCs after 1 dose of vaccine (pre-boost) was lower than the level observed at 4 weeks post-second dose (Figure 3A, Table 6); 56 IFNγ secreting T cell / 10^6 PBMCs [20-182] (median [IQR]) and 98 IFNγ secreting T cell / 10^6 PBMCs [40-178] respectively. It should also be noted that although AAV patients (who all received rituximab; B cell depleting therapy) generate a measurable T cell response (Figure 3A) the majority of these patients did not seroconvert (Figure 1A, Table 3).

Discussion

OCTAVE comprises a prospective study undertaking deep immune profiling in subjects exposed to the SARS-CoV-2 vaccine and who have underlying medical conditions that might confer immune vulnerability and increased susceptibility to viral infection. Since these patient sub-groups exhibit a higher prevalence of co-morbidities and risk factors for potentially poorer outcomes upon infection and development of native COVID-19 (10), our data provide fundamental insights as to the qualitative and quantitative nature of immune responses on a background of underlying medical conditions and immunosuppressant medication and could inform the approaches to overcoming immune incompetence and guide re-boosting strategies. The demonstration of a 100% seroconversion rate for anti-S antibodies in the tested healthy controls from the PITCH study support the findings of clinical trials (11, 12) and real-world data that these vaccines are highly immunogenic in healthy populations. Whilst many patient groups in the current study also seroconverted, there is a group of just over 11% of immune vulnerable patients who do not mount a measurable serology response. This is in contrast to prior studies that have suggested that seroconversion in individuals in clinical risk groups is $\geq$96% (7). Furthermore, a significant group of patients in each disease

cohort have serological responses that are lower than those observed in healthy volunteers. Interestingly, evaluation of T cell responses demonstrated that in comparison to healthy volunteers these patient groups are mounting an equivalent response, suggesting that the observed suppression of immunologic activity within a proportion of these patients is specific for the development of S antibodies after vaccination with spike antigen.

This preliminary analysis has not formally compared quantitative anti-S responses across disease subgroups though we note that AAV and a proportion of hemodialysis patients exhibit remarkably low numerical responses, compatible with the immunosuppressant regimes (e.g. rituximab) that they are currently receiving to maintain their disease activity control. Moreover, a substantial proportion of patients in each group mount titres below the lowest measured in the healthy control PITCH study after two vaccine dose exposures. This is also evident after a single dose exposure when compared with healthy controls at the same time point. It does not necessarily follow that lower titres will offer poorer protection, especially against Wuhan strain but as variants of concern emerge, there is consensus that higher titres may be advantageous for clinical protection or disease severity mitigation (13). This may be particularly important in patients with co-morbidities that render them at higher risk of severe disease or death in the event of COVID-19 infection.

OCTAVE is an on-going study with participants still accruing and in follow up, and therefore we have not been able to provide an in-depth formal analysis of all aspects including but not limited to the impact of medication on vaccine response. Moreover, we do not yet have clinical infection data, though such data will be available over time as NHS linkage records are interrogated for this cohort. As such we are unable to draw functional protection conclusions from this dataset. There is no current functionally validated cut-off for antibody titre using this assay that correlates robustly with clinical protection, however, the lowest titres in the healthy control group all exceed 380 U/ml, which is consistent with the range seen in other studies that have evaluated titres across age groups (7). Across disease subgroups 87% of AAV, 51% of IA, 29% of HD, 42% of HD-IS, 36% of HepD, 10% of SC, 33% of HM and 17 % of HSCT fall below this lowest titre level generated in healthy individuals after two vaccine doses. This indicates that overall, the quantitative serological responses in a significant proportion of these disease groups are lower than in the healthy population, which may be important as antibodies wane with time (8), and for cross protection against variants of concern such as delta (14). In contrast, the observed T cell response between disease groups and HC was similar. We cannot yet, however, draw functional conclusions on these observations,

but it is feasible that in the absence of a serological response the T cell response may confer some level of protection from severe outcomes to natural infection.

We wish to clearly highlight the strengths and limitations of this report. The strengths of our study include its relatively large size, a wide range of diseases, UK geographical spread, robust standardised procedures and assays allowing comparison between disease and healthy cohorts, standardization of timepoints and availability of a control group. Weaknesses are several fold and include: (i) The rapid delivery of the vaccination programme to clinically vulnerable groups that meant it was not possible to obtain baseline (pre-vaccination) data on all participants, or fill each disease group equally; this reflected the commencement date of the OCTAVE trial. This can, however, potentially be managed by imputation in due course; (ii) our use of the PITCH control group, whilst empiric and via use of shared standard operating procedures, facilitatory to data comparison, comprises a female predominance (as expected from healthcare workers) and poorly matched age group for comparison. In mitigation we point out that age has not proven a significant diminution factor in serology vaccine quantitation thus far (15, 16), and this cohort represents optimal responses; (iii) We recognise that within disease categories there is heterogeneity in terms not only of disease duration, disease severity and vaccine received but also therapeutic regimens and intercurrent co-morbidities, which may all potentially impact vaccine response. Future analysis will take these into account; (iv) Anti-S antibodies and T cell responses to spike antigen offer only limited measures of immunity – our further studies will explore neutralising antibodies, additional T cell-function responses, measures of innate lymphoid and related pathways; and (v) no formally statistical comparison of the groups, as we are continuing to accrue data. This is one of many attractive features of the OCTAVE study that will offer unparalleled insight to the mechanisms that support effective seroconversion and robust quantitative responses and critically those that do not. In turn this can inform strategizing clinical approaches to maximize vaccine effectiveness as has been achieved with other vaccines in these disease groups through judicious therapeutic cycling and vaccine timing choices.

Our study, even at a preliminary stage, offers some clear findings that are helpful to policy decisions particularly as they pertain to further boosting strategies. They do not, however, show functional protection and comprise an evaluation of immune activity only. Moreover, we are currently comparing and contrasting the observed T cell responses across disease subgroups with serologic quantitation. This

is particularly important, as the current observations, especially those seen in AAV, suggest that absent antibody responses do not necessarily indicate an inadequate response in the T cell compartment.

We conclude there is an imperative to further study patients in both the non-response category and those in the lower end of the anti-S titre response level (falling below the lower limit of that reached in our healthy control arm) after two inoculations. We note preliminary findings that for some disease types, like infection-naïve HD patients, a disappointing titre after two doses, should be compared to the higher titres observed in the same patient groups but in whom previous COVID-19 infection was observed. Similar trends were noted in the current study. We will shortly provide similar data for other disease cohorts. Some of these data are already available in pre-print format (17). Thereby, it is possible that three dose exposures may be functionally better than two – on the other hand we may not be able to recapitulate native infection even with a third dose. In instances where appropriate seroconversion is not achieved, it may be advisable to use alternative strategies such as monoclonal antibody cocktails (e.g. Ronapreve/REGEN-COV) alongside early intervention on diagnosis of SARS-CoV-2 as therapeutic management of COVID-19 continues to develop (18-21). Further studies are now required across a broad range of vulnerable disease groups including patients with primary and secondary immune compromise who have been identified as having sub-optimal responses to COVID-19 vaccinations.

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Figure Legends.

Figure 1. Anti-spike (S) responses at pre-vaccine, pre-second dose and 4 weeks post-second dose across disease groups in OCTAVE and PITCH Healthy controls. Anti-S titre at baseline (pre-vaccine), following first-dose (pre-boost) and 4 weeks post second-dose vaccine (Post-Boost) in **(A)** Healthy Controls (HS), ANCA-associated vasculitis (AAV), Inflammatory arthritis (IA; rheumatoid arthritis and psoriatic arthritis), Haemodialysis (HD), and Haemodialysis on Immunosuppression (HD-IS), **(B)** Healthy Controls (HS), Hepatic disease (HepD), inflammatory bowel disease (IBD), solid cancer (SC; Breast and Lung) and haematological malignancies (HM; Acute Myeloid Leukaemia and Multiple Myeloma), and Haemopoietic Stem Cell Transplant (HSCT) patients. For visualisation data was placed on a log scale and groups were split across two graphs with the same HC on both. Bars represent median/IQR.

Figure 2. Anti-spike (S) responses at pre-vaccine, pre-second dose and 4 weeks post-second dose in individuals with or without prior COVID infection. Anti-S titre at baseline (pre-vaccine), following first-dose (pre-boost) and 4 weeks post second-dose vaccine (post-Boost) in **(A and B)** infection-naïve patients and **(C and D)** patients with reported prior infection. **(A and C)** Healthy Controls (HC), ANCA-associated vasculitis (AAV), Inflammatory arthritis (IA; rheumatoid arthritis and psoriatic arthritis), Haemodialysis (HD), and Haemodialysis on Immunosuppression (HD-IS), **(B and D)** Healthy Controls (HC), Hepatic disease (HepD), inflammatory bowel disease (IBD), solid cancer (SC; Breast and Lung) and haematological malignancies (HM; Acute Myeloid Leukaemia and Multiple Myeloma), and Haemopoietic Stem Cell Transplant (HSCT) patients. For visualisation data was placed on a log scale and groups were split across two graphs with the same HC on both. Bars represent median/IQR.

Figure 3. Spike specific IFNγ T cell responses at pre-vaccine, pre-second dose and 4 weeks post-second dose across disease groups in OCTAVE and PITCH Healthy controls. IFNγ T-cell responses to Full Spike peptide pool **(A and B)** or Spike 1 + Spike 2 peptide pool **(C)** of SARS-CoV-2 at baseline (pre-vaccine), following first-dose (pre-boost) and 4 weeks post second-dose vaccine (Post-Boost). **(A)** Healthy Controls (HC), ANCA-associated vasculitis (AAV), Inflammatory arthritis (IA; rheumatoid arthritis and psoriatic arthritis), Hepatic disease (HepD), inflammatory bowel disease (IBD), **(B)** Healthy Controls (HC), solid cancer (SC; Breast and Lung) and haematological malignancies (HM; Acute Myeloid Leukaemia and Multiple Myeloma), and Haemopoietic Stem Cell Transplant (HSCT) patients. **(C)** Healthy Controls (HC), Haemodialysis (HD), and Haemodialysis on Immunosuppression (HD-IS). For visualisation data was placed on a log scale and in **(A and B)** groups were split across two graphs with the same HC on both. PMBC, peripheral blood mononuclear cell. Bars represent median/IQR.

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IM, PK, CSG, SS, EB, SJD, MW, DT, AK, PK, PM, TdS, DR and GC, conceived and developed the idea for this trial; IM, PK, CSG, SS, EB, MW, DT, PM, TdS, DR, GC, SB, SM, AK and AH were involved in writing and revising the trial protocol; AP, AH, SB and SM wrote the IRAS application; AP and AH submitted the REC, HRA, MHRA and local R&D applications; SJD and PK Chief Investigator of the PITCH Study; LT major contribution of PITCH data; EB, ML, SD, SM, TM, ZW, SI and GM recruited and vaccinated patients and developed data packages and analysis and SI and GM established laboratory pipeline and data packages at Oxford; AK developed the statistical plan; AK, CG and SP collated and analysed the data.

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Conflict of interest

None

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Table 1. OCTAVE and PITCH participant demographic information.

	Disease Sub-group																	
	HC (231)		AAV (30)		IA (119)		HD (138)		HD on IS (12)		HepD (86)		IBD (85)		SC (78)		HM (21)		HSCT (80)	
Sex																				
Female	156	(68%)	16	(53%)	80	(67%)	56	(41%)	8	(67%)	41	(48%)	30	(35%)	70	(90%)	8	(38%)	36	(45%)
Male	75	(32%)	14	(47%)	39	(33%)	82	(59%)	4	(33%)	45	(52%)	55	(65%)	8	(10%)	13	(62%)	34	(43%)
Missing Data	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	10	(13%)
Age Risk Group																				
18-49	186	(81%)	10	(33%)	57	(48%)	22	(16%)	1	(8%)	24	(28%)	72	(85%)	21	(27%)	1	(5%)	25	(31%)
50-64	37	(16%)	12	(40%)	53	(45%)	42	(30%)	6	(50%)	42	(49%)	13	(15%)	30	(38%)	11	(52%)	34	(43%)
65+	7	(3%)	8	(27%)	9	(8%)	74	(54%)	5	(42%)	20	(23%)	0	(0%)	27	(35%)	9	(43%)	21	(26%)
Missing Data	1	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Ethnicity																				
Black	1	(0%)	0	(0%)	1	(1%)	36	(26%)	4	(33%)	0	(0%)	1	(1%)	6	(8%)	0	(0%)	1	(1%)
East Asian	4	(2%)	0	(0%)	0	(0%)	3	(2%)	0	(0%)	3	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Mixed Race	0	(0%)	1	(3%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(2%)	0	(0%)	0	(0%)	0	(0%)
South Asian	13	(6%)	0	(0%)	0	(0%)	47	(34%)	2	(17%)	2	(2%)	7	(8%)	0	(0%)	1	(5%)	0	(0%)
White	144	(62%)	26	(87%)	108	(91%)	40	(29%)	6	(50%)	79	(92%)	74	(87%)	55	(71%)	19	(90%)	65	(81%)
Other†	13	(6%)	1	(3%)	9	(8%)	10	(7%)	0	(0%)	2	(2%)	1	(1%)	14	(18%)	0	(0%)	3	(4%)
Not Applicable	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)	0	(0%)	0	(0%)
Unknown	0	(0%)	2	(7%)	0	(0%)	2	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(5%)	3	(4%)
Missing Data	56	(24%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	8	(10%)
BMI																				
Underweight	5	(2%)	0	(0%)	1	(1%)	8	(6%)	1	(8%)	2	(2%)	2	(2%)	0	(0%)	0	(0%)	3	(4%)
Healthy Weight	107	(46%)	7	(23%)	31	(26%)	35	(25%)	4	(33%)	28	(33%)	52	(61%)	11	(14%)	7	(33%)	26	(33%)
Overweight	55	(24%)	8	(27%)	47	(39%)	31	(22%)	2	(17%)	26	(30%)	17	(20%)	8	(10%)	6	(29%)	18	(23%)
Obese	5	(2%)	12	(40%)	31	(26%)	38	(28%)	4	(33%)	23	(27%)	8	(9%)	5	(6%)	7	(33%)	7	(9%)
Very Obese	0	(0%)	3	(10%)	7	(6%)	5	(4%)	0	(0%)	4	(5%)	0	(0%)	4	(5%)	1	(5%)	0	(0%)
Missing Data	59	(26%)	0	(0%)	2	(2%)	21	(15%)	1	(8%)	3	(3%)	6	(7%)	50	(64%)	0	(0%)	26	(33%)
Prior Covid																				
No	131	(57%)	28	(93%)	113	(95%)	85	(62%)	10	(83%)	80	(93%)	81	(95%)	40	(51%)	9	(43%)	61	(76%)
Yes	94	(41%)	2	(7%)	6	(5%)	52	(38%)	2	(17%)	5	(6%)	4	(5%)	12	(15%)	1	(5%)	4	(5%)
Unknown	5	(2%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	8	(10%)	11	(52%)	5	(6%)
Not applicable	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	18	(23%)	0	(0%)	0	(0%)
Missing Data	1	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	10	(13%)
Vaccine Type																				
AstraZeneca	63	(27%)	30	(100%)	119	(100%)	86	(62%)	10	(83%)	84	(98%)	85	(100%)	24	(31%)	14	(67%)	43	(54%)
Moderna	2	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Pfizer	165	(71%)	0	(0%)	0	(0%)	52	(38%)	2	(17%)	2	(2%)	0	(0%)	47	(60%)	4	(19%)	20	(25%)
Missing Data	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	6	(8%)	2	(10%)	16	(20%)
Unknown	1	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(5%)	0	(0%)

HC – Healthy controls (PITCH study), AAV – ANCA-associated Vasculitis, IA – Inflammatory arthritis (rheumatoid arthritis and psoriatic arthritis), HD – Haemodialysis, HD-IS – Haemodialysis on Immunosuppression, HepD - Hepatological Disease, IBD - Inflammatory Bowel Disease, SC – Solid cancer (Breast & Lung), HM - Haematological malignancies (Acute Myeloid Leukaemia & Multiple Myeloma), HSCT - Haemopoietic Stem Cell Transplant

† Other Ethnicities given as: African (n=1); Arabic (n=2); Arabic (British) (n=1); Asian (n=1); Asian British (n=5); Asian Indian (n=4); Asian Other (n=3); Bangladeshi (n=1); British (n=1); British Pakistani (n=1); Chinese (n=1); Hispanic (n=2); Lithuanian (n=1); Mauritian (n=1); Pilipino (n=1); Polish (n=1); Scottish (n=1); Somali (n=1); South East Asian (n=3); Syrian (n=1); White Mixed (n=1); Not Specified (n=18) & Unknown (n=1)

Table 2. Anti-Spike seroconversion at 4 weeks post-boost in OCTAVE and PITCH Healthy controls.

	HC (93)	AAV (29)	IA (114)	HD (129)	HD on IS (12)	HepD (60)	IBD (4)	SC (47)	HM (18)	HSCT (42)
Response (N (%))										
No	0 (0.0)	21 (72.4)	2 (1.8)	7 (5.4)	2 (16.7)	10 (16.7)	0 (0.0)	0 (0.0)	2 (11.1)	5 (11.9)
Yes	93 (100.0)	8 (27.6)	112 (98.2)	122 (94.6)	10 (83.3)	50 (83.3)	4 (100.0)	47 (100.0)	16 (88.9)	37 (88.1)

Table 3. Anti-Spike antibody responses presented as U/ml [Median (IQR)] across disease groups in OCTAVE and PITCH Healthy controls.

Disease Sub-Group	Baseline (N)	Baseline	Pre-Boost (N)	Pre-Boost	Post-Boost (N)	Post-Boost
HC	21	0.4 (0.4, 130.0)	91	333.0 (74.9, 11085.0)	93	11514.0 (3324.0, 23302.0)
AAV	6	0.4 (0.4, 1.3)	30	0.4 (0.4, 0.4)	29	0.4 (0.4, 24.5)
IA	108	0.4 (0.4, 0.4)	118	16.4 (5.6, 56.4)	114	331.0 (166.0, 815.0)
HD	135	0.4 (0.4, 491.0)	130	69.4 (0.6, 23018.0)	129	6123.0 (554.0, 29502.0)
HD on IS	11	0.4 (0.4, 0.8)	11	0.8 (0.4, 1.5)	12	798.0 (3.2, 3992.5)
HepD	17	0.4 (0.4, 0.4)	80	12.6 (0.5, 38.8)	60	283.5 (18.8, 1552.5)
IBD	83	0.4 (0.4, 0.4)	82	28.9 (8.7, 80.0)	4	733.0 (458.0, 1006.5)
SC	10	0.4 (0.4, 0.4)	70	23.4 (5.8, 118.0)	47	4101.0 (655.0, 10819.0)
HM	0	. (., .)	20	18.0 (1.6, 65.6)	18	1011.5 (17.3, 3877.0)
HSCT	6	0.4 (0.4, 0.4)	59	14.9 (0.4, 77.0)	42	980.0 (91.9, 5129.0)

Table 4. Number and percentage of patients with Post-boost anti-S antibody response lower than the lowest reported result in PITCH.

Disease Sub-Group	Number Recruited	Available Post Boost Assay Results	Number of patients with results lower than PITCH lowest result*	Percentage
AAV	30	29	26	89.7%
IA	119	114	61	53.5%
HD	138	129	28	20.7%
HD on IS	12	12	5	41.7%
HepD	86	60	31	51.7%
IBD	85	4	0	0%
SC	78	47	8	17%
HM	21	18	7	38.8%
HSCT	80	42	14	33.3%

* Lowest reported result in PITCH was 380 U/ml

Table 5. Anti-Spike antibody responses presented as U/ml [Median (IQR)] across disease groups in OCTAVE and PITCH Healthy controls with or without prior COVID infection.

Disease Sub-Group	Prior Covid	Baseline (N)	Baseline	Pre-Boost (N)	Pre-Boost	Post-Boost (N)	Post-Boost
HC	No	14	0.4 (0.4, 0.4)	56	90.3 (49.0, 196.0)	59	10451.0 (1516.0, 17206.0)
	Yes	7	164.0 (94.9, 402.0)	33	14602.0 (9499.0, 20438.0)	31	23302.0 (9511.0, 30233.0)
	Unknown	0	. (., .)	2	3190.5 (1825.0, 4556.0)	3	13460.0 (3472.0, 22386.0)
AAV	No	4	0.4 (0.4, 0.4)	28	0.4 (0.4, 0.4)	27	0.4 (0.4, 0.4)
	Yes	2	29.1 (1.3, 57.0)	2	49.4 (45.2, 53.6)	2	38.0 (24.5, 51.4)
IA	No	102	0.4 (0.4, 0.4)	112	14.8 (4.8, 45.9)	108	316.0 (162.0, 806.5)
	Yes	6	15.5 (2.9, 62.6)	6	1371.0 (563.0, 2687.0)	6	1080.0 (794.0, 1534.0)
HD	No	83	0.4 (0.4, 0.4)	80	3.8 (0.4, 203.5)	79	1664.0 (150.0, 10568.0)
	Yes	51	238.0 (1.3, 1105.0)	49	15914.0 (1775.0, 48050.0)	49	15877.0 (4002.0, 44497.0)
	Unknown	1	0.4 (0.4, 0.4)	1	0.4 (0.4, 0.4)	1	116.0 (116.0, 116.0)
HD on IS	No	9	0.4 (0.4, 0.4)	10	0.6 (0.4, 1.4)	10	340.1 (0.9, 1060.0)
	Yes	2	795.5 (207.0, 1384.0)	1	24797.0 (24797.0, 24797.0)	2	63456.0 (32395.0, 94517.0)
HepD	No	16	0.4 (0.4, 0.4)	75	11.4 (0.5, 29.9)	57	250.0 (19.4, 1324.0)
	Yes	1	0.4 (0.4, 0.4)	4	11439.5 (4613.0, 15325.5)	2	12521.5 (8668.0, 16375.0)
	Unknown	0	. (., .)	1	0.4 (0.4, 0.4)	1	14.0 (14.0, 14.0)
IBD	No	79	0.4 (0.4, 0.4)	78	27.9 (8.2, 71.1)	4	733.0 (458.0, 1006.5)
	Yes	4	2.1 (0.6, 11.3)	4	499.5 (189.5, 1125.5)	0	. (., .)
SC	No	3	0.4 (0.4, 0.4)	39	12.9 (5.6, 56.3)	28	4386.5 (665.0, 9150.0)
	Yes	3	590.0 (0.4, 2006.0)	10	3974.0 (23.2, 15536.0)	5	7549.0 (2776.0, 13070.0)
	Unknown	4	0.4 (0.4, 0.4)	21	24.4 (4.0, 68.8)	14	3005.5 (497.0, 18519.0)
HM	No	0	. (., .)	8	18.0 (3.1, 44.8)	8	1510.0 (9.9, 3437.0)
	Yes	0	. (., .)	1	234.0 (234.0, 234.0)	0	. (., .)
	Unknown	0	. (., .)	11	15.0 (0.4, 75.9)	10	576.0 (127.0, 5670.0)
HSCT	No	6	0.4 (0.4, 0.4)	48	15.3 (0.4, 58.0)	38	1000.5 (98.0, 5129.0)
	Yes	0	. (., .)	3	83.6 (14.9, 37993.0)	2	14970.0 (694.0, 29246.0)
	Unknown	0	. (., .)	8	5.1 (0.4, 130.4)	2	0.4 (0.4, 0.4)

Table 6. Spike specific IFNγ T cell responses presented as IFNγ secreting T cell / 10^6 PBMCs [Median (IQR)] across disease groups in OCTAVE and PITCH Healthy controls.

Disease Sub-Group	Baseline (N)	Baseline	Pre-Boost (N)	Pre-Boost	Post-Boost (N)	Post-Boost
HC	20	6.0 (0.0, 8.0)	135	32.0 (12.0, 112.0)	194	60.0 (20.0, 136.0)
AAV	6	6.0 (4.0, 44.0)	28	56.0 (20.0, 182.0)	28	98.0 (40.0, 178.0)
IA	98	4.0 (0.0, 12.0)	117	48.0 (16.0, 108.0)	113	48.0 (16.0, 108.0)
HepD	10	0.0 (0.0, 4.0)	71	20.0 (8.0, 80.0)	60	20.0 (12.0, 134.0)
IBD	76	0.0 (0.0, 8.0)	74	24.0 (12.0, 84.0)	47	32.0 (12.0, 92.0)
SC	15	4.0 (0.0, 12.0)	58	12.0 (0.0, 52.0)	48	32.0 (8.0, 112.0)
HM	2	36.0 (4.0, 68.0)	12	10.0 (0.0, 14.0)	14	54.0 (20.0, 164.0)
HSCT	36	8.0 (0.0, 24.0)	22	4.0 (0.0, 8.0)	31	32.0 (8.0, 108.0)

Table 7. Spike1 + Spike 2 specific IFNγ T cell responses presented as IFNγ secreting T cell / 10^6 PBMCs [Median (IQR)] across HD and HD-IS groups in OCTAVE and PITCH Healthy controls

Disease Sub-Group	Baseline (N)	Baseline	Pre-Boost (N)	Pre-Boost	Post-Boost (N)	Post-Boost
HC	20	8.0 (12.0, 120.0)	135	28.0 (12.0, 72.0)	194	36.0 (16.0, 120.0)
HD	94	20.0 (16.0, 248.0)	98	74.0 (16.0, 544.0)	124	36.0 (10.0, 248.0)
HD on IS	9	0.0 (4.0, 88.0)	9	8.0 (4.0, 24.0)	11	16.0 (0.0, 88.0)

Figure 1

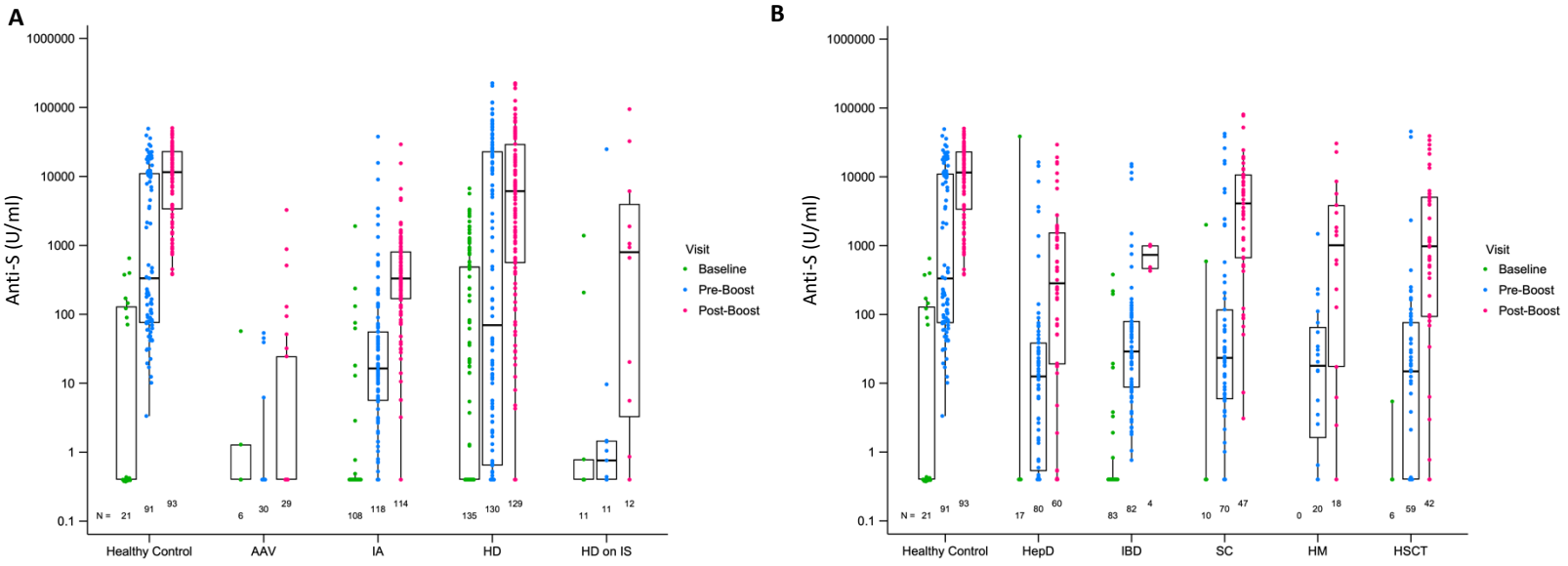

A
B
Anti-S (U/ml)
1000000
100000
10000
1000
100
10
1
0.1
N = 21 91 93
6 30 29
108 118 114
135 130 129
11 11 12
Healthy Control
AAV
IA
HD
HD on IS
17 80 60
83 82 4
10 70 47
0 20 18
6 59 42
HepD
IBD
SC
HM
HSCT
Visit
Baseline
Pre-Boost
Post-Boost

Figure 2

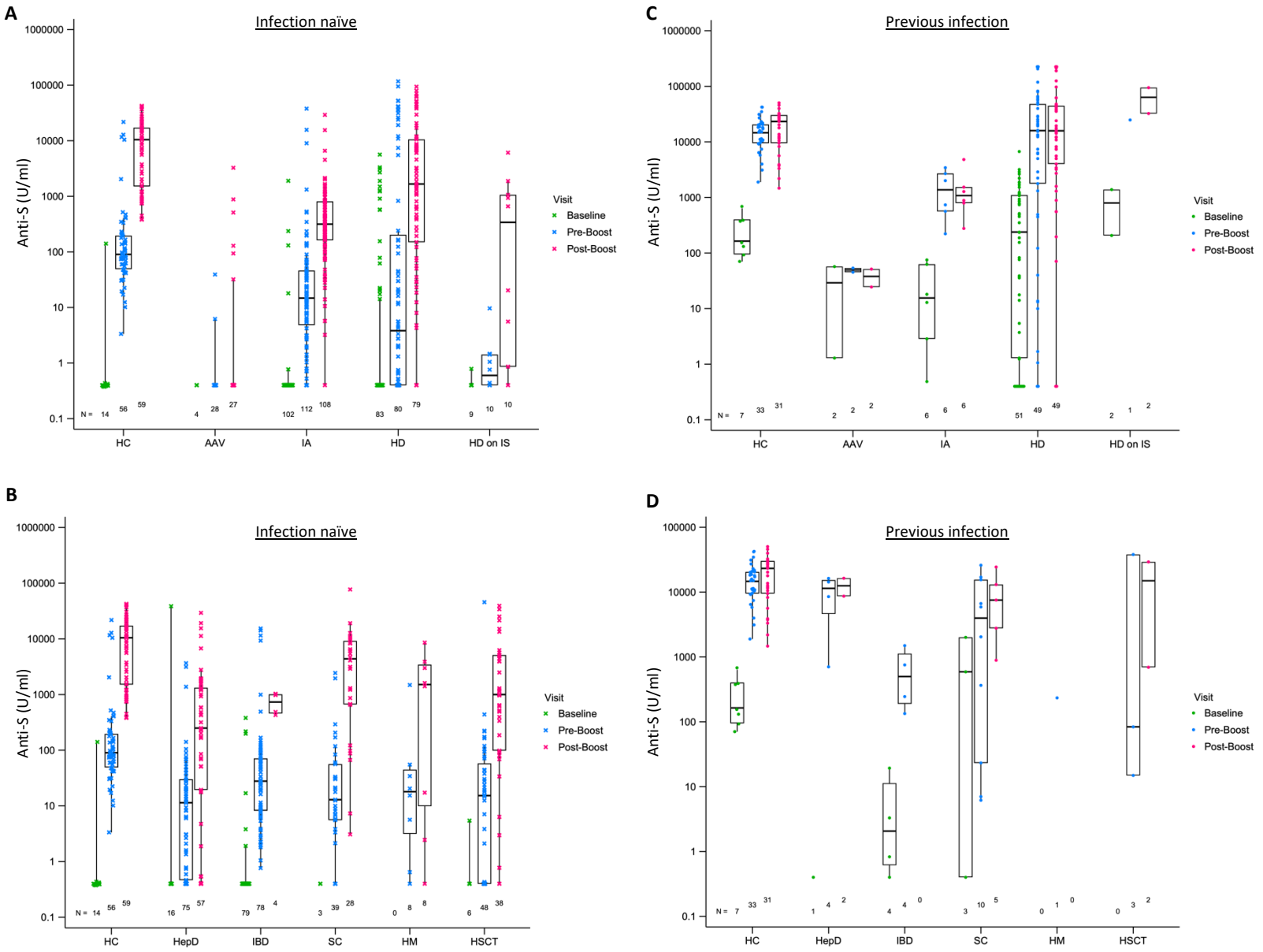
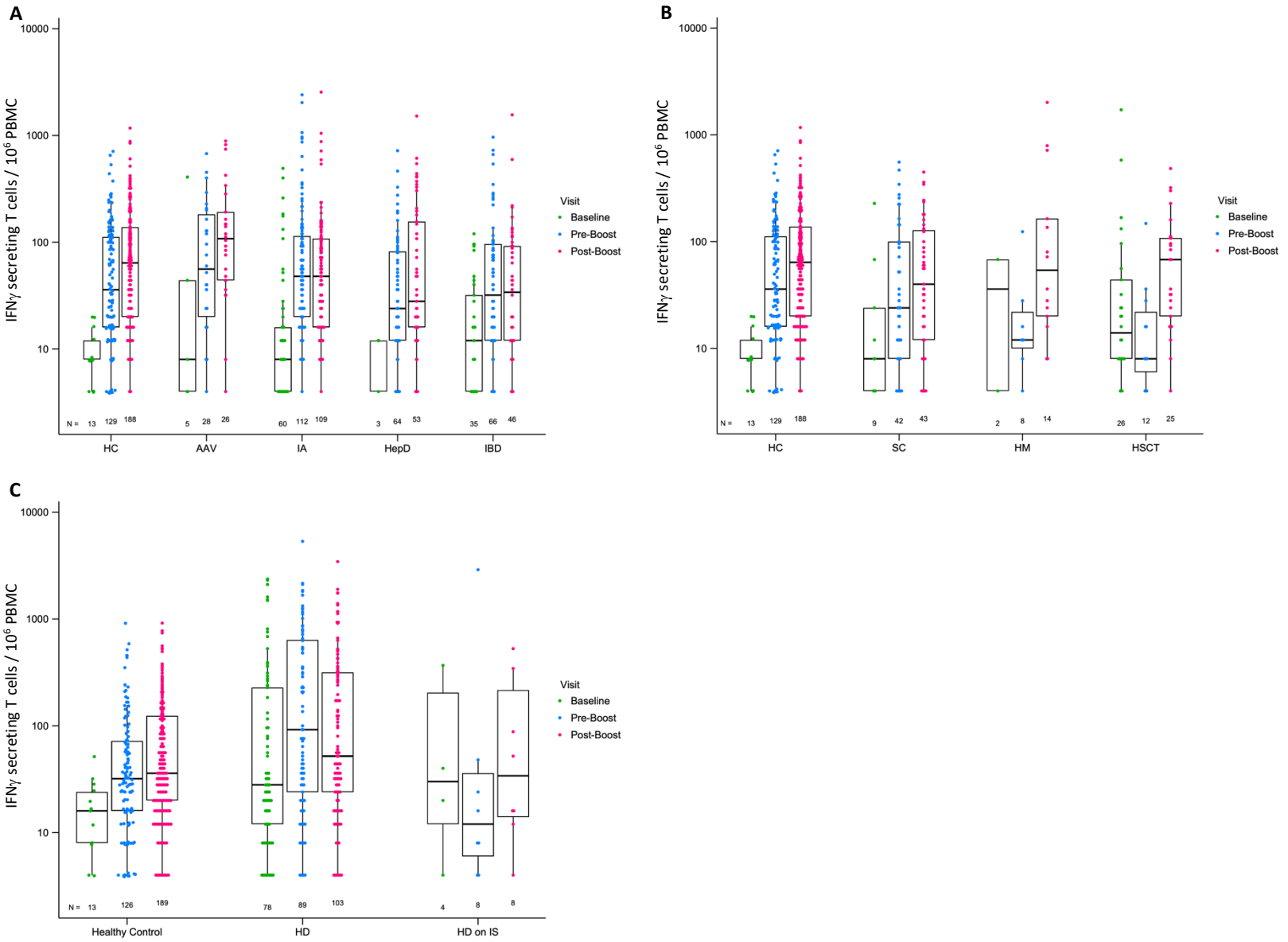

A
Infection naïve
Anti-S (U/ml)
1000000
100000
10000
1000
100
10
1
0.1
N = 14 56 59
4 28 27
102 112 108
83 80 79
9 10 10
HC
AAV
IA
HD
HD on IS
Visit
Baseline
Pre-Boost
Post-Boost
C
Previous infection
N = 7 33 31
2 2 2
6 6 6
51 49 49
2 1 2
B
Infection naïve
N = 14 56 59
16 75 57
79 78 4
3 39 28
0 8 8
6 48 38
HC
HepD
IBD
SC
HM
HSCT
D
Previous infection
N = 7 33 31
1 4 2
4 4 0
3 10 5
0 1 0
0 3 2

Figure 3


A
B
C
IFNγ secreting T cells / 10^6 PBMC
10000
1000
100
10
Visit
Baseline
Pre-Boost
Post-Boost
N = 13 129 188
5 28 26
60 112 109
3 64 53
35 66 46
HC
AAV
IA
HepD
IBD
N = 13 129 188
9 42 43
2 8 14
26 12 25
HC
SC
HM
HSCT
N = 13 126 189
78 89 103
4 8 8
Healthy Control
HD
HD on IS