COVID-19 vaccine uptake and efficacy in a national immunodeficiency cohort

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To the Editor,

The United Kingdom (UK) government set a target of offering all adults 2 doses of vaccination against the novel pandemic coronavirus (SARS-CoV-2, COVID-19) by 19th July 2021. The success of this national immunisation programme is dependent on both patient engagement and efficacy of the host immune response. Information on these factors remains limited in the setting of primary and secondary immunodeficiency (1,2). Here we report on vaccine uptake and responses in adults under care of the Immunodeficiency Centre for Wales (ICW) revealing heterogenous anti-SARS-CoV-2 spike IgG responses across common diagnostic immunodeficiency sub-groups. With continued community circulation of SARS-CoV-2 and rising case rates, serosurveillance of vulnerable patient groups facilitates prompt and rational access to precision therapies such as monoclonal anti-SARS-COV-2 antibodies.

Vaccine uptake and safety

A postal survey and electronic notes review were conducted up to 31st October 2021. Data on vaccine uptake were available for 302/304 (99%) adults under follow-up for immunodeficiency (Supplementary Figure 1; Supplementary Methods). COVID-19 vaccinations commenced from 8th December 2020, with 287/304 (94.4%) of individuals receiving their first dose by 24th August 2021. Second dose uptake reached 284/304 (93.4%) by 28th September 2021, Figure 1A. The majority of individuals received the AstraZeneca ChAdOx1-S (176/284, 61.3%), with 39.4% receiving mRNA vaccinations (Pfizer, n=111; Moderna, n=1). The median interval between first and second doses was 77 days (inter-quartile range: 50 to 81 days), in line with the UK's strategy for a 3-month interval. At least fourteen individuals declined or deferred two vaccine doses. The commonest cited reason was the personal belief that they would not respond due to underlying immunodeficiency (n=6), with 4 patients who had recovered from SARS-CoV-2 infection also declining. Four individuals had deferred courses reflecting recent haematopoietic stem cell transplant, pregnancy, or age under 18 years at the start of the national vaccination scheme. Vaccinations were well tolerated across the cohort with no severe reactions reported.

By comparison, at time of submission at least 49 adults (approximately 16% of the ICW cohort) have had molecularly-confirmed SARS-CoV-2 infection between 1st March 2020 and 31st October 2021. COVID-19-related mortality in 11 of these 49 exposed individuals (22.4%). The majority of deaths occurred in unvaccinated individuals (9/11, 81.8%) prior to vaccine rollout or invitation. Together this demonstrates vaccination uptake outpaced SARS-CoV-2 infections (Figure 1A), consistent with national policy for shielding extremely vulnerable individuals between March and August 2020. Notably, two deaths occurred despite two doses of mRNA vaccination, in individuals diagnosed with combined immunodeficiency (CID).

Assessment of vaccine efficacy anti-spike SARS-CoV-2 IgG responses

Subsequent to these deaths, an increasing range of monoclonal antibody and antiviral therapies have received regulatory approval. In the UK, these have initially been targeted to symptomatic individuals who have failed to initiate a humoral immune response to the virus (3). We therefore determined anti-spike SARS-CoV-2 IgG responses in patients as part of routine clinical care up to the 2nd September 2021. Primary analysis was undertaken considering samples obtained at least 14 days following completion of two COVID-19 vaccinations (n=156, 51.3% of the cohort). The median interval from second vaccine to sampling was 49 days (interquartile range: 31 to 77 days). As shown in Figure 1B and Supplementary Table 1, vaccine response varied both between and within common clinical diagnostic groups.

Figure 1

Overall, 51/156 (33%) of patients had an undetectable humoral IgG response to the SARS-CoV-2 spike antigen. Considering diagnostic sub-groups, humoral responses were absent in patients with X-linked Agammaglobulinemia (XLA, n=3) and CID (n=8, including both individuals dying from COVID-19 despite vaccination). Failure to seroconvert post-vaccination was common in 16/35 (46%) individuals with secondary hypogammaglobulinaemia (SHG, see online supplementary for full details), and 17/60 (27%) with common variable immunodeficiency (CVID). Conversely, anti-spike IgG responses were consistently observed in individuals with a prior diagnosis of specific antibody deficiency (SPAD, n=8) and with 22q11 deletion syndrome (n=4).

A multivariate linear regression model examining the influence of age, time since vaccination, endogenous IgA and IgM levels, CD19+ cell count, vaccine type, immunological diagnosis, and molecularly-confirmed SARS-CoV-2 infection preceding the date of vaccine response assessment is presented online (Supplementary Table 2). Increasing time since vaccination was associated with falling titres, consistent with waning (p=0.041). Combined deficiency of IgA and IgM (p=0.01) or a CD19+ B-cell count less than 50 x 10^6/L (p<0.001) were both independently associated with impairment of the humoral vaccine response. Controlling for other variables, post-vaccination titres were greater in recipients of Pfizer mRNA vaccinations (p=0.012), equating to a 50% increase, relative to a modelled similar individual receiving the ChAdOx1-S. Conversely, a history of molecularly-confirmed SARS-CoV-2 infection prior to vaccination or age were not associated with significant differences in post-vaccine titre.

Anti-spike SARS-CoV-2 IgG within immunoglobulin replacement therapy products

The presence of anti-SARS-CoV-2 antibodies within immunoglobulin replacement therapy (IgRT) products has been predicted to interfere with assessment of humoral vaccine immunity (4). Evaluation of 13 distinct IgRT products (with a total of 87 unique lots) manufactured between December 2018 and March 2021 is shown in Figure 1B and Supplementary Figure 2. This confirms increasing levels of IgG with reactivity to the SARS-CoV-2 spike protein in products manufactured since the onset of the pandemic from multiple suppliers. However, at dilutions commonly used to model bioavailability of IgRT therapy, these results fall short of the assay cut-off for a positive immune response. At dilution factors simulating higher replacement or immunomodulatory doses, this threshold was crossed (Supplementary Figure 3). Together, this suggests the results of vaccine serosurveillance in a cohort receiving replacement-dose IgRT reflect the endogenous humoral response.

Summary

In conclusion, we observed a high rate of engagement with COVID-19 vaccination programme in our national cohort of immunodeficient individuals. Whilst of modest size, it compares favourably to existing reports (1,2). To our knowledge we are the first to examine rates and reasons for vaccine hesitancy in this patient group. We show a detectable IgG response to the viral spike protein was absent in approximately 1 in 3 patients, but with marked variation between and within clinical diagnostic groups. Importantly, a diagnosis of CVID, one of the most common primary immunodeficiency disorders, was associated with a detectable vaccine response in two-thirds of individuals. Therefore, our results may also help encourage hesitant individuals, particularly given emerging evidence for T-cell mediated immunity in similar cohorts (1,2,4). Following adjustment for demographic and diagnostic factors, mRNA vaccination was associated with a statistically greater humoral response relative to the AstraZeneca ChAdOx1-S. Whilst consistent with the emerging literature (5), the clinical significance of this remains unclear, given failure of seroconversion following both vaccine types and observed mortality in 2 individuals with CID despite two mRNA vaccinations. Further studies are required to determine the nature and durability of both cellular and humoral immune responses following mixed booster vaccine regimens. By systematically profiling a range of IgRT products manufactured over the past 2 years, we reveal low but increasing levels of anti-SARS-CoV-2 IgG. When administered at replacement doses these are unlikely to confer significant protection. Given the severe consequences of vaccine failure in individuals observed in our cohort, our findings support

115 increased access to precision therapies such as monoclonal anti-SARS-COV-2 antibodies (3,4).
116 Continued serosurveillance may help identify individuals with waning immunity who may benefit from
117 booster vaccinations, whilst prioritising vaccine non-responders to receive pre-exposure prophylaxis
118 and post-exposure interventions.

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On behalf of the Immunodeficiency Centre for Wales **

Author Contributions

MJP and SJ conceived the study. KE, FMG, EMC, RB and MJP conducted the postal survey and electronic notes review. EC and EMC collected IgRT samples and collated dates of manufacture. MJP performed anti-SARS-CoV-2 spike IgG testing on IgRT samples supervised by KB and LG. SW, TES, RC, AP, EC, CRP EMC, and SJ supported patient care and clinical testing for anti-SARS-CoV-2 spike IgG response. KE and MJP collated results. MJP conducted statistical and graphical analyses with supervision from DF. MJP wrote the first manuscript draft. All authors provided critical input and have approved the final version.

Ethical Approval

This work was performed as a service evaluation. In line with the Health Research Authority (HRA) decision tool this does not constitute research and requirement for formal ethical application was waived.

Conflict of interest statement

SJ has received support for conferences, speaker, advisory boards, trials, data and safety monitoring boards, and projects with CSL Behring, Takeda, Swedish Orphan Biovitrum, Biotest, Binding Site, Grifols, BPL, Octapharma, LFB, Pharming, GSK, Weatherden, Zarodex, Sanofi, and UCB Pharma. TE has received support for education, speaker, advisory boards, and/or research from Allergy Therapeutics, CSL Behring, Mylan, Novartis, Pharming, Takeda, and Thermo Fisher. None of these conflicts relates to the current work. The remaining authors have no potential relevant conflicts of interests to declare.

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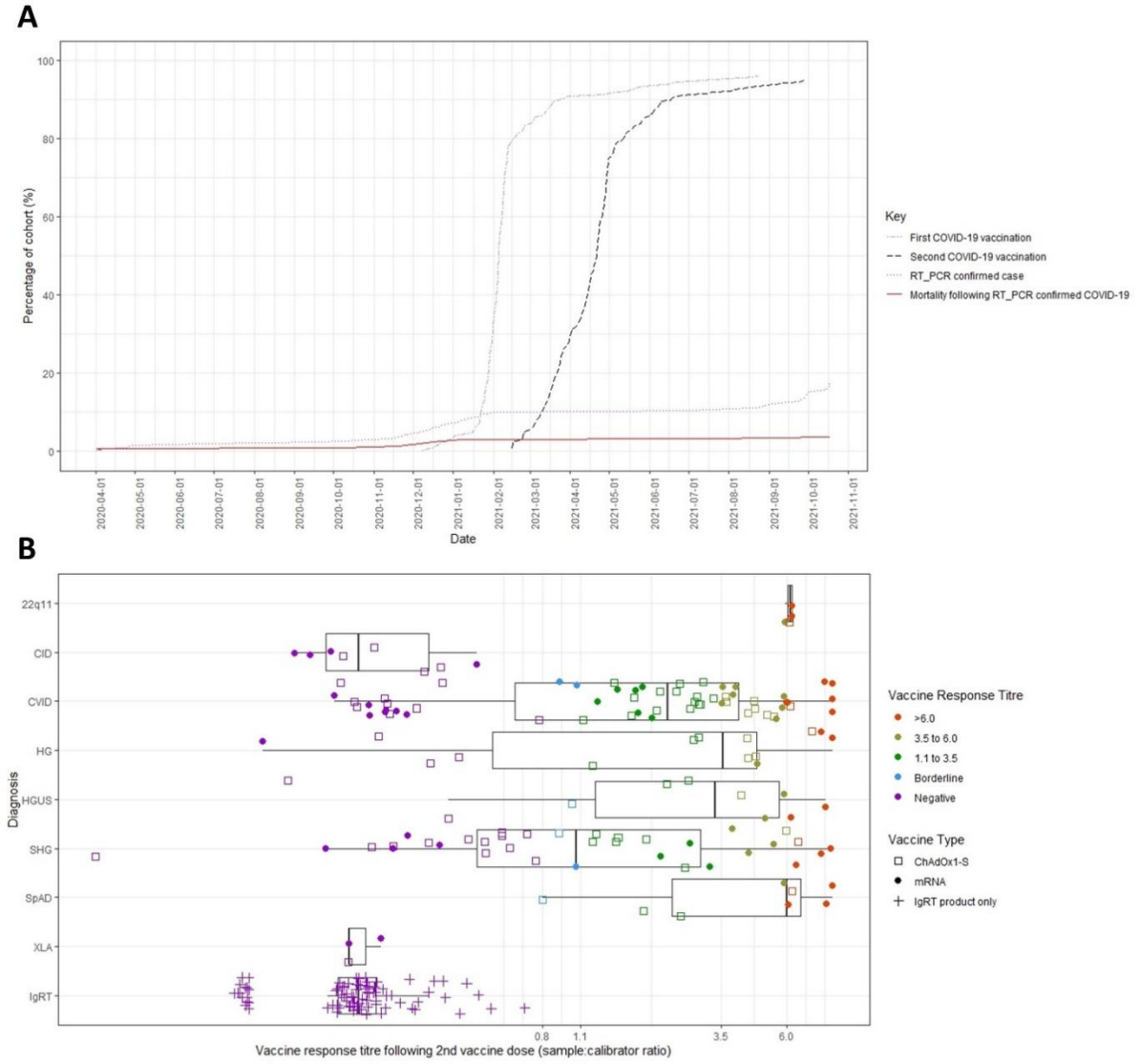
Figure 1: Uptake and serological response following 2 doses of COVID-19 vaccination in adults under care of the Immunodeficiency Centre for Wales



A: *Uptake of first (grey, dot-dashed) and second (black, dashed) COVID-19 vaccination; cumulative total of patient cohort with molecularly-confirmed SARS-CoV-2 infection (purple, dotted) and subsequent mortality (red, solid). Shielding of clinically extremely vulnerable individuals in Wales was implemented between March and August 2020, directing such individuals to stay at home to protect themselves.*

B: *Anti-SARS-CoV-2 spike IgG serum responses elicited by 2 doses of COVID-19 vaccination in individuals under care of the Immunodeficiency Centre for Wales (ICW) assayed using the semi-quantitative EUROIMMUN IgG assay. Vaccine response indicated on the x-axis by sample: calibrator ratio. Titre grading shown reflects assay cut-off and reported criteria used for selection of convalescent plasma therapy. Patients are sub-grouped by clinical diagnosis (22q11- DiGeorge 22q11 deletion syndrome; CID- Combined Immunodeficiency (without defined molecular diagnosis, including Good's syndrome); CVID- Common Variable Immunodeficiency Syndrome; HG- Hypogammaglobulinaemia (insufficient to meet criteria for CVID); HGUS- Hypogammaglobulinaemia of Uncertain Significance (not requiring immunoglobulin replacement therapy); SHG- Secondary Hypogammaglobulinaemia; SpAD- Specific Antibody Deficiency; XLA- X-linked Agammaglobulinaemia; IgRT- Immunoglobulin Replacement Therapy Products, diluted to simulate infusion at replacement dosing. Vaccine type indicated by open squares (ChAdOx1-S, Astra-Zeneca) and filled circles (mRNA, Pfizer).*

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Online Supplementary Material

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Supplementary Methods:

A service evaluation utilising postal survey and electronic notes review were conducted to assess compliance with the UK government's goal of vaccinating adults and vulnerable individuals against COVID-19. Vaccine efficacy is routinely measured clinically to support diagnosis and management of individuals under care or investigation of the Immunodeficiency Centre for Wales. Information on molecularly-confirmed SARS-CoV-2 diagnoses were extracted from our virtual COVID-19 ward record, considering individuals alive on 1st March 2020 (the start of UK shielding of clinically-vulnerable individuals) and at risk of COVID-19 exposure. COVID-19 related mortality was defined by death within 28-days of diagnosis, listed as a certified cause of death (where this information was available) or deemed as probable/likely contributor to death by a member of the ICW clinical team.

Information on vaccine uptake considered individuals alive at availability of the first UK COVID-19 vaccine (8th December 2020). Vaccine type and dates were cross-checked with the electronic patient record where an individual indicated they were unsure on the postal survey response. Data collection was performed up to the 31st October 2021.

Serosurveillance results were employed to direct clinical use of monoclonal antibody therapy in the event of subsequent COVID-19 diagnosis. In line with the Health Research Authority (HRA) decision tool this does not constitute research and requirement for formal ethical application was waived.

Immunological diagnoses were extracted from electronic medical records and validated by an independent clinician. Diagnostic sub-groups were assigned in line with the European Society of Immunodeficiency (ESID) working diagnostic criteria. The term "Hypogammaglobulinaemia of underdetermined significance" (HGUS) refers to individuals with immunoglobulin measurements below the 95% centile without a significant infection history and who have been commenced on immunoglobulin replacement therapy. "Hypogammaglobulinaemia" (HG) is used for individuals receiving IgRT not meeting specific diagnostic criteria e.g. for CVID or SPAD and without a genetically-defined immunodeficiency.

Causes of secondary hypogammaglobulinaemia included: haematological malignancy (13/35, 33.3%), disease modifying anti-rheumatoid medications (13/35, 33.3%), anti-epileptic medications (4/35, 10.3%), long-term systemic steroid use (3/35, 7.7%), or immunomodulation for neurological conditions (2/35, 5.1%).

Determination of anti-SARS-CoV-2 Spike IgG response

Serum IgG responses to the SARS-CoV-2 spike protein using the EUROIMMUN assay according to manufacturer instructions in a United Kingdom Accreditation Service (UKAS) accredited laboratory. Serum samples were obtained from individuals attending for routine outpatient assessment. Given peak vaccine responses have been reported after 14 days following vaccination, only samples obtained beyond this time point (n = 155) were considered in the primary analysis. An anti-spike IgG response was detectable in an additional 11/17 (65%) of patients where a serum sample was available only following a single vaccine dose or within 14 days of a second dose (data not shown).

Aliquots of immunoglobulin replacement therapy (IgRT) products were obtained at the time of routine infusions and stored at +4C until analysis. Dates of manufacture were obtained from product packaging or from the product manufacturer representatives. To simulate physiological bioavailability following infusion, products were diluted according to concentration as follows: 5% products – 1 in 7.5; 10% products – 1 in 15; 20% products- 1 in 30 (Supplementary Figure 2). Serial dilutions were performed on 4 randomly selected 10% products manufactured immediately prior to and following the SARS-CoV-2 pandemic (Supplementary Figure 3).

Data was curated in Microsoft Excel. All analyses were performed using R v4.0.5 in R Studio Version 1.4.1106.

Supplementary Table 1: Anti-SARS-CoV-2 spike IgG responses assessed in 156 individuals at a minimum of 14 days following 2 COVID-19 vaccine doses.

Diagnostic subgroup	Total, N	Antibody response (optical density ratio)				
		Negative	Borderline (0.8 to 1.1)	1.1 to 3.5	3.5 to 6.0	>6.0
Common variable immunodeficiency (CVID)	60	16 (27%)	2 (3%)	21 (35%)	14 (23%)	7 (12%)
Secondary Hypogammaglobulinaemia (SHG)	35	16 (46%)	2 (6%)	9 (26%)	4 (11%)	4 (11%)
Hypogammaglobulinaemia (HG)	14	4 (29%)	0	3 (21%)	4 (29%)	3 (21%)
Hypogammaglobulinaemia of Undetermined Significance (HGUS)	10	2 (20%)	1 (10%)	2 (20%)	3 (30%)	2 (20%)
Combined Immunodeficiency (CID) without molecular diagnosis	8	8 (100%)	0	0	0	0
Specific Antibody Deficiency (SpAD)	8	0	1 (12.5%)	2 (25%)	1 (12.5%)	4 (50%)
"DiGeorge" 22q11 deletion syndrome	4	0	0	0	1 (25%)	3 (75%)
X-lined Agammaglobulinemia (XLA)	3	3 (100%)	0	0	0	0
Signal Transducer And Activator Of Transcription 1 (STAT1) Gain-of-Function	2	0	1 (50%)	1 (50%)	0	0
Autoimmune regulator (AIRE) deficiency	1	0	0	0	1 (100%)	0
CD40-ligand deficiency	1	1 (100%)	0	0	0	0
X-linked Chronic Granulomatous Disease (CGD)	1	0	0	0	1 (100%)	0
CTLA4-deficiency	1	0	0	1 (100%)	0	0
Complement C2 deficiency	1	0	0	0	1 (100%)	0
Adenosine Deaminase 2 (ADA2) Deficiency	1	0	0	0	0	1 (100%)
Interferon-gamma receptor (IFNGR1) deficiency	1	0	0	0	1 (100%)	0
NF-kappa B Essential Modulator (NEMO) deficiency	1	0	0	1 (100%)	0	0
Cartilage hair hypoplasia (CHH)	1	0	0	0	0	1 (100%)
Signal Transducer And Activator Of Transcription (STAT3) dominant negative. Post haematopoietic stem cell transplantation.	1	0	0	0	0	1 (100%)
Idiopathic T-cell Lymphopenia	1	1 (100%)	0	0	0	0
Wiskott-Aldrich Syndrome (WAS)	1	0	0	0	0	1 (100%)

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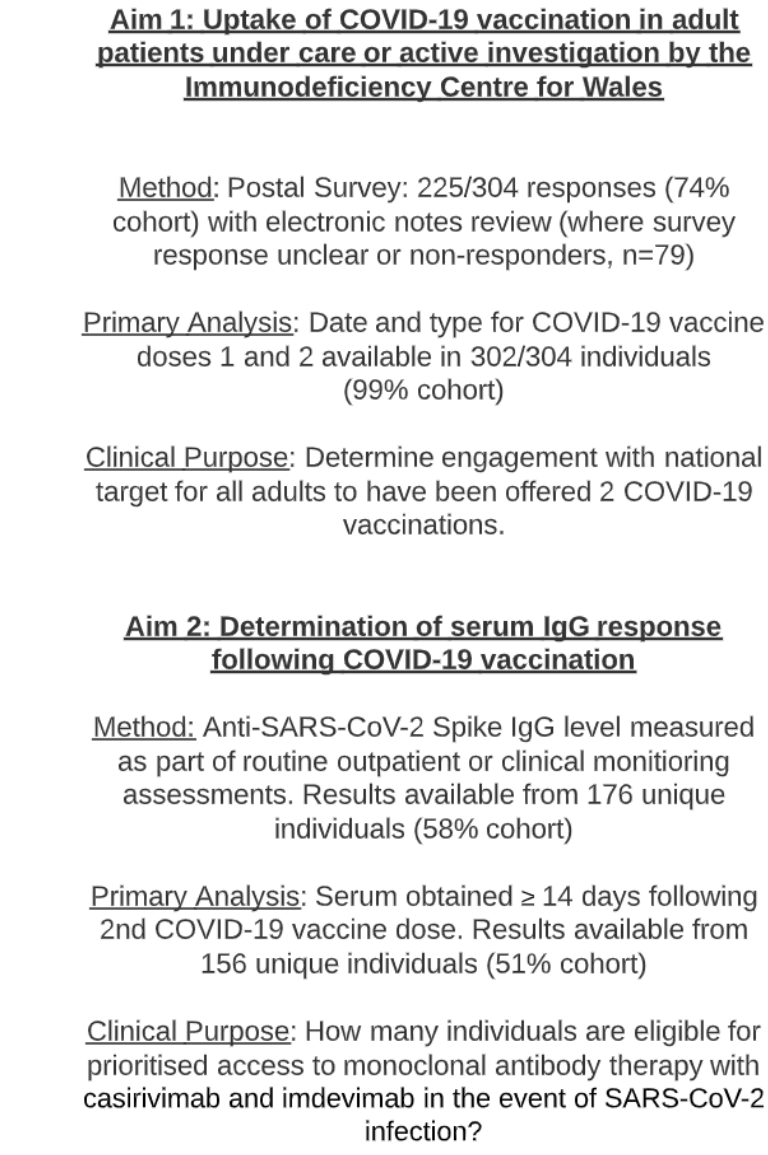
Supplementary Table 2: Multivariate Linear Regression Model

Anti-SARS-CoV-2 spike IgG response in 154 individuals (measured at least 14 days following second vaccine dose) modelled with diagnostic sub-group, time elapsed between second vaccine dose and serum sampling (in days), age (years), history of molecularly-confirmed infection, absence of IgA and IgM, CD19+ B-cell count, and vaccine type included as explanatory variables. Patients with 22q11deletion syndrome were selected as the reference category. Vaccine response titre is considered using a log-transformed scale.

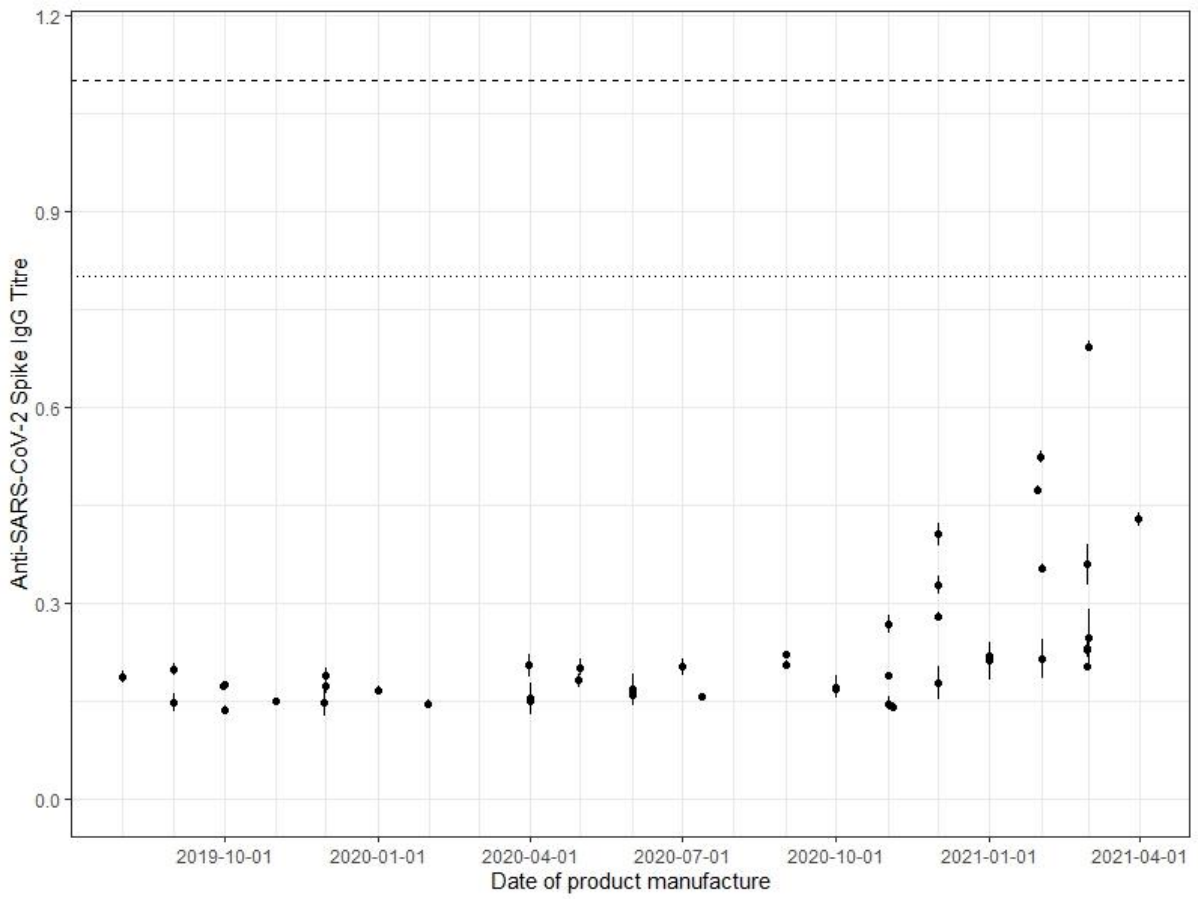
	Log_e(Anti-SARS-CoV-2 Spike IgG Titre)		
Explanatory variable	*Estimate*	*95% Confidence Interval*	*p-value*
(Intercept)	2.27	0.91 – 3.63	0.001
Sampling interval (vaccine to assay), days	**-0.01**	**-0.01 – -0.00**	**0.041**
Age, years	-0.01	-0.02 – 0.01	0.277
CD19+ B-cells < 50 x10^6/L (TRUE)	**-1.09**	**-1.68 – -0.51**	**<0.001**
Molecularly-confirmed SARS-CoV-2 infection prior to serology (TRUE)	0.34	-1.00 – 1.69	0.612
IgA <0.05 and IgM < 0.1 g/L (TRUE)	**-0.68**	**-1.19 – -0.16**	**0.01**
Pfizer mRNA Vaccine received (TRUE)	**0.51**	**0.12 – 0.91**	**0.012**
Autoimmune regulator (AIRE) deficiency	-0.05	-2.63 – 2.52	0.967
CD40-ligand deficiency	-3.53	-6.10 – -0.96	0.007
X-linked Chronic Granulomatous Disease (CGD)	0.69	-1.91 – 3.29	0.601
Combined Immunodeficiency (CID)	-2.35	-3.87 – -0.82	0.003
Complement C2 deficiency	-0.29	-2.84 – 2.27	0.825
CTLA4-deficiency	-1.3	-3.87 – 1.26	0.316
Common variable immunodeficiency (CVID)	-0.94	-2.19 – 0.31	0.138
Adenosine Deaminase 2 (ADA2) Deficiency	-0.01	-2.58 – 2.57	0.996
Hypogammaglobulinemia (HG)	-1.02	-2.38 – 0.33	0.138
Hypogammaglobulinemia of Undetermined Significance (HGUS)	-1.02	-2.41 – 0.36	0.145
Interferon-gamma receptor (IFNGR1) deficiency	0.01	-2.55 – 2.57	0.994
NF-kappa B Essential Modulator (NEMO) deficiency	-1.18	-3.74 – 1.38	0.364
Cartilage hair hypoplasia (CHH)	0.3	-2.27 – 2.87	0.818
Secondary Hypogammaglobulinemia (SHG)	-1.24	-2.50 – 0.02	0.053
Specific Antibody Deficiency (SpAD)	-0.47	-1.90 – 0.96	0.514
Signal Transducer And Activator Of Transcription 1 (STAT1) Gain-of-Function	-1.33	-3.33 – 0.66	0.187
Signal Transducer And Activator Of Transcription (STAT3) dominant negative; post-HSCT.	-0.48	-3.03 – 2.07	0.711
Idiopathic T-cell Lymphopenia	-2.04	-4.64 – 0.56	0.123
Wiskott-Aldrich Syndrome (WAS)	-0.9	-3.79 – 1.99	0.539
X-linked Agammaglobulinemia (XLA)	-1.97	-3.88 – -0.06	0.043
Observations, N	154*		
R^2 / R^2 adjusted	0.442 / 0.328		

* CD19+ B-cell count not available for 2 individuals.

Supplementary Figure 1: Study Flowchart

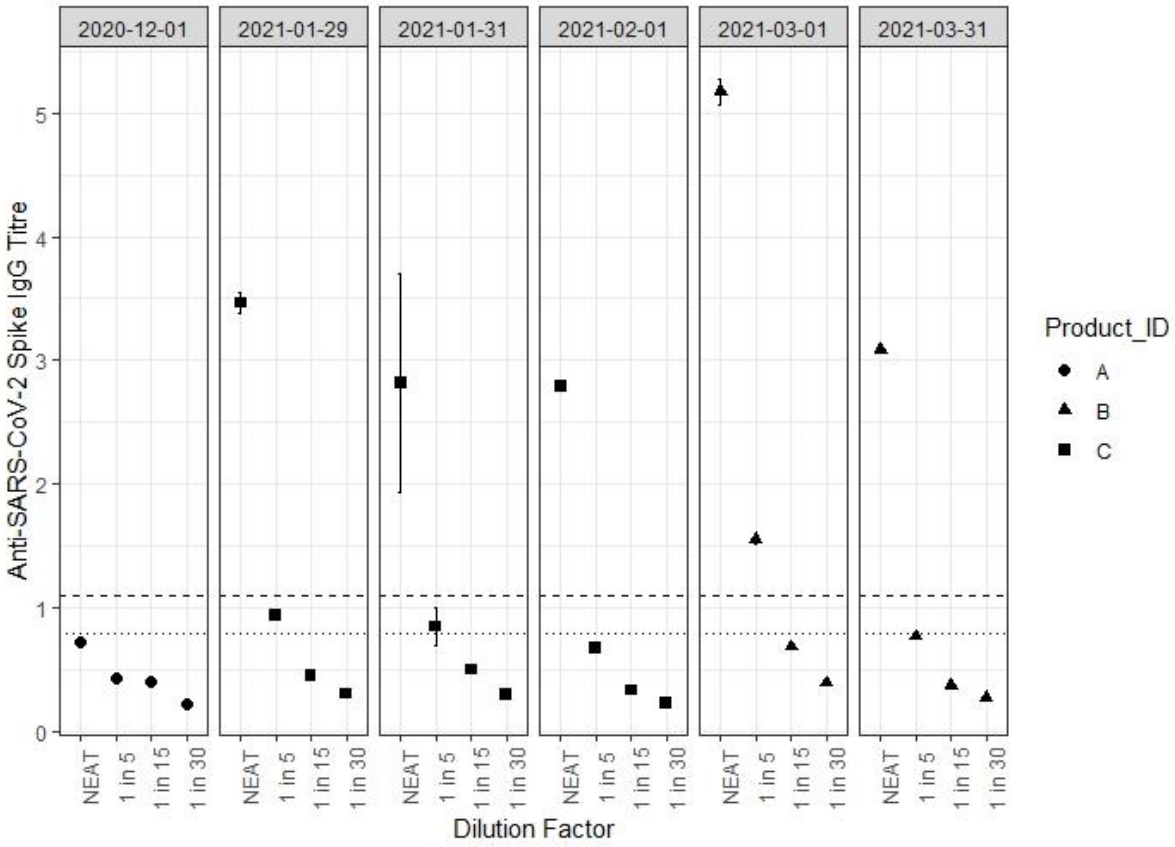


Supplementary Figure 2: Rising levels of IgG reactive to SARS-CoV-2 Spike in Immunoglobulin Replacement Therapy (IgRT) products manufactured since 2020.



Anti-SARS-CoV-2 spike IgG responses assessed using EUROIMMUN assay. Immunoglobulin Replacement Therapy (IgRT) products were diluted according to concentration as follows: 5% products – 1 in 7.5; 10% products – 1 in 15; 20% products- 1 in 30. Manufacture stated assay cut-offs for borderline (dotted, ≥0.8) and positive (dashed, ≥1.1) results are indicated. Points represent mean value for an individual product lot, obtained from a minimum of 3 measurements. Error bars represent 1 standard error of the mean (SEM).

Supplementary Figure 3: Anti-SARS-CoV-2 IgG levels in serially diluted Immunoglobulin Replacement Therapy (IgRT) products



Anti-SARS-CoV-2 spike IgG titre measured using the EUROIMMUN assay in 3 products manufactured during 2020 and 2021. All products were available for clinical use in 2021. Values from product lots manufactured in 2021 are repeated a minimum of twice. Error bars represent 1 standard error of the mean (SEM). The manufacture stated assay cut-offs for borderline and positive results are indicated by dotted (≥0.8) and dashed (≥1.1) lines, respectively.