Immunocompromised children and young people are at no increased risk of severe COVID-19

H. Chappell[1], R. Patel[2], C. Driessens[3], A.W. Tarr[4,5], W.L. Irving[4,5], P.J. Tighe[4,5], H.J. Jackson[5], T. Harvey-Cowlishaw[5], L. Mills[1], M. Shaunak[1], D. Gbesemete[1,2], A. Leahy[6], J.S. Lucas[1,2,6], S.N. Faust[1,2,6], H. de Graaf[1,2,6], On behalf of the ImmunoCOVID19 study group (Appendix A)

1. NIHR Southampton Clinical Research Facility and Biomedical Research Centre, University Hospital Southampton NHS Trust, Southampton, SO16 6YD, UK
2. Faculty of Medicine and Institute for Life Sciences, University of Southampton, Southampton, SO16 6YD, UK
3. NIHR Applied Research Collaboration Wessex, University Hospital Southampton NHS Trust, Southampton, SO16 6YD, UK
4. NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust, and the University of Nottingham, Nottingham, UK
5. School of Life Sciences, University of Nottingham, Nottingham, NG7 2RD, UK
6. Paediatric Medicine, University Hospital Southampton NHS Trust, Southampton, SO16 6YD, UK

Corresponding author: Dr Hans de Graaf, h.de-graaf@soton.ac.uk, Paediatric Rheumatology, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton, SO16 6YD

Running title: Immunocompromised paediatric COVID-19 risk in the UK

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Highlights:

- UK immunocompromised paediatric patients were at no increased risk of severe COVID-19
- Only 4/38 PCR detected infections were admitted to hospital. None had acute severe COVID-19 or died
- Increasing age and immunodeficiency increased reporting of SARS-CoV-2 infection. Worsening of fever, cough and sore throat were associated with reporting SARS-CoV-2 infection
- Serology results suggest there was a proportion of SARS-CoV-2 infections undetected by PCR

Abstract

Objectives: We aimed to prospectively describe the incidence and clinical spectrum of SARS-CoV-2 infection in immunocompromised paediatric patients in the UK.

Methods: From March 2020 – 2021 weekly questionnaires were sent to immunocompromised paediatric patients or their parents. Information, including symptom presentation and SARS-CoV-2 PCR test results, was collected from 1527 participants from 46 hospitals. Cross-sectional serology was investigated in February and March 2021.

Results: Until the end of September 2020 no cases were reported. From September 28th 2020 through March 2021 a total of 38 PCR-detected SARS-CoV-2 infections were reported. Of these, four children were admitted to hospital but none had acute severe COVID-19. Increasing age in association with immunodeficiency increased reporting of SARS-CoV-2 infection. Worsening of fever, cough, and sore throat were associated with participants reporting SARS-CoV-2 infection.

Serology data included 452 unvaccinated participants. In those reporting prior positive SARS-CoV-2 PCR, there were detectable antibodies in 9 of 18 (50%). In those with no prior report of infection, antibodies were detected in 32 of 434 (7·4%).

Conclusions: This study shows SARS-CoV-2 infections have occurred in immunocompromised children and young people with no increased risk of severe disease. No children died.

Introduction

Studies from the United Kingdom and worldwide have shown that children and young people have made up a small proportion of those infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Less than 5% of total case numbers were in children in studies from Italy (1·2%),[1] USA (1·7%),[2] China (2·2%),[3] and UK (3·9%).[4] Due to subclinical and variable presentation in those under 18 years, rates may be under reported in children and so paediatric seroprevalence studies are vital.[5-7] In the UK, seroprevalence rates in children under 18 were estimated to be between 5 – 10% during the pandemic first wave.[7] Seropositivity rates in children have been found to be comparable to overall rates and variable between countries. For example, seroprevalence studies show rates in 0 – 17 year olds in the USA of 2·7% during the first wave compared to 3·4% overall,[8] whereas in China they were found to be 3·6% versus 5·6% overall.[9] In Switzerland the seroprevalence in 5 – 19 year olds after the first wave was 7·3%, compared to 7·9% overall,[10] rising to 20·2% in 0 – 17 year olds after the second wave, compared to 20·5% overall.[11] The UK "What's the STORY" trial reported seroprevalence rates in 1 – 19 year olds of 0% in February and March 2020, rising to 4·2% in April and 4·0% in May.[12]

Large multicentre cohort studies from USA, UK, and Europe show low overall numbers of paediatric hospital admissions due to coronavirus disease 2019 (COVID-19) with a low proportion of these being admitted to paediatric intensive care units.[5,13,14] These cohort studies and national data from USA, UK, Italy, Germany, Spain, France, and South Korea show that COVID-19 mortality risk is low in children and young people.[15]

Parents, clinicians, and public health bodies globally have remained concerned about risk of SARS-CoV-2 infection to children and young people living with chronic health conditions. In the absence of paediatric data, many immunocompromised children and young people in the UK were initially deemed "extremely vulnerable" to the effects of SARS-CoV-2 infection. Against the advice of many specialist clinicians and NICE,[16] many individuals were advised to adopt specific precautionary "shielding" measures, were subject to school closures, and have had reduced access to healthcare, causing significant burden on both them and their families.[17,18]

Evidence on the risks of SARS-CoV-2 in immunocompromised paediatric patients is beginning to emerge. A large systematic review with meta-analysis and a large retrospective cross sectional study, found paediatric patients with chronic health conditions were at higher risk of severe COVID-19 compared to those without.[19,20] However, rates of serious disease (relative risk ratio 1·79 (95% CI 1·27 – 2·51))[19] were very small in proportion to other causes of morbidity and mortality in children[15] and only 26/9353 children with comorbidities had immune

disorders.[19] To accurately understand and assess the risk in cohorts of immunocompromised paediatric patients, further population and serology studies are required. Currently there are a limited number of studies reporting seroprevalence in immunocompromised paediatric patients[21-25] although some studies have not yet been reported.[26,27]

We aimed to prospectively describe the incidence and clinical spectrum of SARS-CoV-2 infection in a UK-wide cohort of immunocompromised children and young people. A secondary aim was to characterise risk factors and predictive symptoms for SARS-CoV-2 infection in this cohort.

Materials and Methods

This prospective cohort study was carried out over one year (16th March 2020 – 14th March 2021) and included immunocompromised children and young people under the age of 19 years. Immunocompromise was defined as having any medical indication for an annual influenza vaccine, in keeping with UK public health guidelines.[28] Participants were recruited from 46 hospitals across the UK between March – July 2020. Participants and parents received information sheets electronically with a link to an online consent form. They received electronic reminders and were removed from the study database after three weeks in the absence of consent. Participants who had consented to participate in the study were asked to complete an online questionnaire every week, with questions based on the ISARIC and WHO COVID-19 Case Report Form.[29] Information was collected regarding symptom presentation, test results, health care attendance, hospital admission, and the effects of COVID-19 on daily life. Results from the first four months of the study have been published.[18]

Participants self-reported when a SARS-CoV-2 PCR test was carried out and found to be positive. These tests were sought according to UK government guidelines with testing capacity increasing through the study period. Initially testing was limited to hospital admissions. From 18th May 2020 those aged over five years with symptoms could seek a test and from 27th May 2020 testing was expanded to those under five years and contact tracing begun.[30,31] Participants reporting positive PCR swabs were emailed to clarify result and clinical outcomes.

The study gained ethical approval from the Yorkshire and the Humber – Leeds West NHS Research Ethics Committee (IRAS 281544).

Cohort

1645 participants consented to the study. Of these, 1527 successfully completed at least one weekly questionnaire. A further 505 were withdrawn during the study period (Figure 1). The

commonest reason for withdrawal was not completing the survey for three successive weeks. At week 32, the study team started contacting participants who had not completed questionnaires for three successive weeks regarding ongoing participation. This led to a sharp rise in withdrawals. Median age was 11 years (range 0 – 18). 55·1% of participants were female. Baseline characteristics are displayed in Table 1.

Serology

Between December 2020 – January 2021 all participants (n=1073) were invited to take part in an optional serology sub-study. They were provided with information sheets electronically with a link to an online consent form. Consenting participants were sent sampling kits via post between February – March 2021. Participants collected a dried blood sample using a safety lancet and Mitra® sampling device. Validated in-house enzyme-linked immunosorbent assays (ELISA) were carried at the virology laboratories of the University of Nottingham to detect SARS-CoV-2 anti-nucleocapsid and anti-spike IgG antibodies, as previously described.[32] All assays were performed on Opentrons OT-2 Precision liquid handling robots (full protocol available on request). Original assay validations were performed on a separate sample set using commercial anti-S1 (Euroimmun) and anti-N assays (Roche) and conducted at the Rare & Imported Pathogens Laboratory at Public Health England using manufacturers' protocols.

Antibodies were first extracted from dried samples to a 1:15 dilution by shaking for 2h in 150μL phosphate buffered saline (PBS) containing 0·1% Triton-x100 and 0·05% sodium azide. Extracted samples were diluted to 1:120 with 3% skimmed milk powder in PBS containing 0·05% Tween 20 and 0·05% sodium azide.

ELISAs were performed by coating 384 well NUNC maxisorp plates (Thermofisher) with either 20μL/well of 0·5μg/mL of SARS-CoV-2 spike protein S1 subunit (His tagged; Sinobiologicals, GmbH) or SARS-CoV-2 Nucleocapsid (His Tagged; Sinobiologicals, GmbH) in carbonate-bicarbonate buffer (CBC; Merck UK), sealing with foil film and incubating overnight at 4°C. Wells were then washed three times with 100μL PBS with 0·05% Tween 20 (PBST) using a Thermofisher Wellwash Versa plate washer with a final aspirate. Wells were immediately filled with 100μL of 3% skimmed milk powder (w/v) in PBS and 0·05% sodium azide, foil sealed and blocked overnight at 4°C. Assay plates were then washed three times as before and duplicate wells filled with 20μL of the 1:120 diluted sample, diluted in 3% skimmed milk powder (w/v) in PBS and 0·05% sodium azide.

Control samples included duplicates of a 1:120 dilution of a pool of sera derived from 32 individuals previously identified as having high nucleocapsid & high spike S1 reactivity. Three negative samples, each derived from a separate pool of 21 pre-covid sera were added to separate wells in duplicate. Wells containing only dilution buffer were used as non-serum

blank. After 15 minutes incubation at room temperature (21°C), the plate was washed three times in PBST. This was followed by addition to each well of 20µL of gamma chain-specific anti-human IgG-HRP conjugate (Sigma A0170-1ML) at 1:30,000 dilution in PBST and incubation for 15 minutes at room temperature. Wells were then washed three times in PBST. 40 µL of One-step ultraTMB substrate solution (Thermofisher) was added to each well. After 20 minutes incubation at room temperature, 40µL of 2N H2SO4 was added to each well and the 384 well plate read at 450nm absorption in a GlowMax Explorer microplate reader (Promega Corp.). Data from absorbance measurements were output to Excel data sheets and subsequently imported into Graphpad Prism for basic analysis. More detailed statistical analysis was then carried out on SPSS.

Seropositivity was indicated according to the ratio method (i.e. ratio of the average sample optical density/average Negative optical density). According to this approach a ratio of >=1·1 was classified as positive and a ratio of <1·1 was classified as negative.

Statistical analysis

Data cleaning, formatting, and analyses were performed with SAS 9.4 (SAS Institute INC, Cary NC). Survival analysis techniques were used to explore the risk of SARS-CoV-2 infection, as measured by PCR testing, to participants throughout the first year of the study. The semi-parametric methodology of Cox regression (Cox, 1972) was employed. Factors associated with the risk of SARS-CoV-2 infection were determined. In addition, the symptoms uniquely experienced at time of SARS-CoV-2 infection were determined. For analysis purposes we have treated infection as a non-repeated event. Data was collected on a weekly basis, creating ties in the data. Parameters are therefore estimated using the estimation method developed by Efron (1977). Participant information was only collected from participants during the study period from recruitment to the last data received (when they may have chosen to withdraw formally or informally). Data prior to the first questionnaire and beyond the last questionnaire received per participant is unknown and is described as having been censored. Every individual was considered at risk of SARS-CoV-2 infection when they entered the study until they either were infected or were censored. To control for late entry, participants' risk for infection was determined between study entry and withdrawal or finish time. We assume that censoring due to withdrawal is non-informative, but receiving "other immunosuppressants" (azathioprine, tacrolimus or mycophenolate mofetil) has been included in the survival model as participants receiving these treatments were less likely to withdraw from the study.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

PCR confirmed cases

Participants reported a total of 1355 PCR tests through the study period. The majority of participants (919, 60·2%) did not report any PCR tests. 576 (37·8%) reported between 1 – 5 tests and 2% reported between 6 – 20 tests. During the government advised shielding period (March – August 2020) no SARS-CoV-2 infections were reported. The first positive SARS-CoV-2 PCR test was in week 30 (28th September – 5th October). Further positive tests were subsequently reported, with peaks in rates in weeks 36 (9th – 15th November 2020) and 42 (21st – 27th December 2020) with five and six cases respectively (Figure 2). There were a total of 38 PCR detected SARS-CoV-2 infections, giving an incidence rate of 3·7% (n=1022). Of these six were asymptomatic, 28 had symptoms managed at home, and four reported hospital admission. Those reporting hospital admissions are described in Table 2. These participants all had varying presentations and significant underlying co-morbidities and therapies; two were transplant patients, one had acute lymphoblastic leukaemia, and one had X-linked agammaglobulinemia. Clinical presentation was varied but none reported acute severe COVID-19 or paediatric multisystem inflammatory syndrome. None were admitted to paediatric intensive care units or died.

Hazard Analysis

Assuming that hazard remained constant between August 2020 – March 2021, an estimate of hazard across the whole cohort is 0·00148 or 38/25,687 (number of cases/ total number of answered questionnaires). This is equivalent to a positive SARS-CoV-2 PCR test once every 676 weeks. This hazard was in the context of varying disease incidence during the pandemic, and varying approaches of participants to shielding or not. While NHS electronic systems sent text messages telling children and young people designated "at risk" to shield based on adult diagnostic categories and the assumed risk, many specialist clinicians advised school attendance to children with all but the most severe immune problems.[16]

The significance of different demographic (sex, age, geographical region), diagnosis and medication use covariates, as well as time-dependent symptom covariates were tested. The best multivariate model is presented in Table 3. Schoenfeld residuals were checked to determine any violations in the proportional hazard assumption. OLS regression models of the

residuals for age and immune deficiency disorder did not show departure from proportionality for those variables.

The Cox regression model indicates for each additional year of age the hazard of infection goes up 13%. Having an immunodeficiency increases hazard of infection almost three times. Those individuals who reported positive PCR tests were more likely than other participants to report worsening of fever, cough, and sore throat symptoms during the same week.

Serology

478 participants provided serology samples and their baseline characteristics are displayed in Table 4. However, participants in this cohort were not representative of those overall. Young people over ten years, those with "other diagnoses" or diabetes; and those on "other drugs", biologics or methotrexate were more likely to take part in this sub-study. There was also geographical variation in participation. Rates by vaccination status in all and by sex, age, and prior PCR status in those unvaccinated are displayed in Table 5.

26 participants reported receiving a first dose of a COVID vaccine prior to serology. Of these, six (23·1%) were serologically positive with a mean of 23 days between vaccination and sampling (range 14 – 33). Three of these were positive for only anti-S1 IgG and three positive for both anti-S1 and anti-N IgG. Those who were negative had a mean of 15·65 days between vaccination and sampling (range 1 – 42). Vaccinated participants were excluded from further analysis.

Of 452 unvaccinated participants, anti-N and/or anti-S antibodies were detected in 41 samples (9·1%). Of those participants reporting a prior positive PCR test 18 took part in the serology sub-study and of these, antibodies were detected in nine (50%). Four of these were positive for only anti-N IgG, one positive for only anti-S1 IgG, and four positive for both anti-N and anti-S1 IgG. In those with no previous positive PCR test, antibodies were detected in 32 of 434 (7·4%). Seventeen of these were positive for only anti-N IgG, six positive for only anti-S1 IgG, and nine positive for both anti-N and anti-S1 IgG. Associations were tested and are shown in Table 4. Detection of antibodies was associated with being female and over ten years old. Associations were also found with having had a transplant and being on immunosuppressants or corticosteroids. In those with prior positive PCR tests no associations were found between serology result and interval between positive test and serology test.

Discussion

We have demonstrated that this cohort of immunocompromised paediatric patients were at no increased risk of severe COVID-19 during the first two waves of the COVID-19 pandemic in the UK, supporting current NICE guidance.[16]

During the government-advised shielding period during the first wave of the pandemic, no participant reported a positive test for SARS-CoV-2, suggesting that shielding measures were effective or testing capacity was insufficient. Subsequently, the peaks in cases in mid-November and late December in our cohort, correspond to peaks in overall UK prevalence and in paediatric prevalence in England during the second wave of the pandemic.[33,34] The majority of those who did report positive PCR tests were managed at home. The four participants who reported hospital admission had diverse clinical presentations with none reporting admission due to acute severe COVID-19 or paediatric multisystem inflammatory syndrome (Table 2). No clear patterns or risk factors for admission are evident from data on those admitted. The presentations of anaemia in the participant with acute lymphoblastic leukaemia and delayed COVID lung changes in the participant with X-linked agammaglobulinemia supports ongoing vigilance for atypical COVID presentations in this diverse cohort. The reason participants were not at increased risk of severe disease is unclear. Children in general seem to be less affected and a potential additional factor may be that the participants chronic health conditions or medications, often immunosuppressive, reduce the risk of the excessive immune response that is a hallmark of severe COVID-19.

Increased hazard of SARS-CoV-2 infection with age is in keeping with overall paediatric rates reported in England and USA.[2,35] This may represent increased symptom burden with age, as in the general paediatric population a bimodal distribution of severity has been observed with peaks in those under one year and over ten years.[2,14] It may also represent increased social mixing with age.

While immune deficiency was found to increase hazard of infection, there was no increased risk of admission in this group. This is a novel observation and has not been observed from initial[36] or more recent data (Dr AM Shields, personal communication, July 2021) from the United Kingdom Primary Immunodeficiency Network. An Italian registry study including 1396 paediatric patients with primary immunodeficiency over one year from February 2020, found a lower incidence of infection (33, 2·36%) compared to the general paediatric population.[37] In a separate cohort, only three of 582 paediatric hospital admissions with SARS-CoV-2 infection had immunodeficiency with none admitted to intensive care.[14]

Recognising symptoms of COVID-19 is a challenge in this population, due to symptom variability and overlap with those of chronic medical conditions. This study shows that in immunocompromised children, worsening of fever, cough, and sore throat were associated

with a positive PCR test in the same week. Symptoms of fever and cough are common with SARS-CoV-2 infection and sore throat has been reported as being more common with the delta variant.[38]

Serology

While 9·1% (41/452) of unvaccinated children and young people tested positive for antibodies reactive to SARS-CoV-2 in the serology sub-study, only 2·5% (38/1527) reported positive SARS-CoV-2 PCR during the survey study. This suggests a proportion of participants had infection which was not confirmed by PCR test. Only 50% (9/18) of participants included in the serology sub-study who reported prior positive SARS-CoV-2 PCR tested positive for antibodies reactive to SARS-CoV-2. Half of PCR positive participants were not serologically positive when tested and some seroconverted with no prior detected infection. This may mean SARS-CoV-2 incidence was higher than reported here with participants having an infection undetected by PCR and serology.

Rates reported in this UK cohort are comparable to those (6·9%, 68/992) reported in a cohort of children of UK healthcare workers during the first wave of the pandemic 2020.[39] Other UK paediatric seroepidemiology studies have yet to be formally reported.[26,27]

The serology rates are comparable to a cross-sectional study in Madrid from September 2020 to February 2021 in paediatric rheumatology patients where 5·7% (6/105) had PCR positive cases and 20·0% (21/105) had serology positive cases with no overlap between these groups.[22] Our results are comparable to initial data from a prospective Belgian cohort study which reported 6·0% (15/250) serology positive participants in paediatric patients with chronic medical conditions. Only one seropositive participant, with a diagnosis of cystic fibrosis, required hospital admission while the rest were either asymptomatic or had mild symptoms.[21]

These rates are higher than observed in a cross sectional study from the USA from April 2020 to May 2020 and June 2020 to July 2020. In immunocompromised paediatric patients there were 1% (5/485) serology positive cases and 0·4% (2/485) PCR positive cases with one of these in both groups.[25]

The reason for PCR positive cases not having detectable antibodies has not been established in our study and no associations are evident. Some evidence from inflammatory bowel disease patients suggests infliximab and other cytokine inhibitors may reduce seroconversion.[23,40] Of participants with negative serology tests but prior PCR confirmed SARS-CoV-2 infection, five had juvenile idiopathic arthritis, one immunodeficiency, and one type one diabetes. The remaining two are described in Table 2 as they reported admission with SARS-CoV-2 infection.

Limited conclusions can be drawn from serology in those who received a prior dose of a COVID vaccine given the single time point and short interval between vaccination and antibody testing.

Limitations

Limitations of our study include random censoring, due to late entry or withdrawal, which was experienced by 60% of participants. Due to this level of censoring, less confidence should be placed in results than the calculated confidence intervals. Questionnaire data is patient or parent reported and subject to recall bias, although we tried to minimize this by sending the questionnaire every week. Symptom over-reporting is possible, particularly in weeks when participants reported positive PCR tests. Symptom under-reporting is possible, particularly in participants with a baseline of symptoms from chronic disease, although less likely due to levels of anxiety in this cohort.[18] Hazard of infection is likely over-estimated due to self-selection bias with participants presumably responding to surveys more frequently in weeks they reported a positive PCR swab. The shielding precautions taken will have varied both between individuals and through the course of the pandemic, so the individual hazard of SARS-CoV-2 infection will vary. The serology sub-study cohort was not representative of the overall study as described in the results section.

Following the study period reported here, in May 2021 the predominant strain in the UK became the Delta variant. There has been concern about the increased transmissibility and severity found in adults infected with the Delta variant.[41] Fortunately, children have been shown to not be at increased risk of severe disease from it[42]. This emphasises the need for ongoing surveillance of the impact of variant strains on the risk to immunocompromised children.

Conclusion

Though cases of COVID-19 occurred in UK immunocompromised children and young people following the cessation of shielding measures, there was no increased risk of severe SARS-CoV-2 infection in this large prospective national cohort. The serology results suggest that asymptomatic or unproven infection is quite common. Increasing age and immunodeficiency increased hazard of SARS-CoV-2 infection. Worsening of fever, cough, and sore throat were predictive of positive SARS-CoV-2 PCR.

Contributors

HC, RP, and HdG drafted and revised the manuscript. All authors reviewed and approved the final manuscript as submitted. HC, RP, CD, LM, MS, DG, AL, JSL, SNF, and HdG contributed to the recruitment of participants. CD completed statistical analysis and contributed to the statistical analysis section and tables of the manuscript. AT, WI, PT, HJ, and TH-C completed laboratory analysis of serology samples and AT, WI, and PT contributed to the serology sections of the manuscript.

Competing interests

All authors have completed ICMJE disclosure forms. HdG received grant funding from the BPAIIG for the submitted work; there are no other relationships or activities that could appear to have influenced the submitted work.

Dissemination declaration

We plan to disseminate the results to study participants and their parents.

Data sharing statement

Research data may be made available upon reasonable request, wherever legally and ethically possible.

Transparency declaration

The Corresponding Author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted. Any discrepancies from the study as planned have been explained.

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Figures and Tables

Figure 1: Weekly participant numbers and weekly questionnaire response rate (16th March 2020 – 14th March 2021)
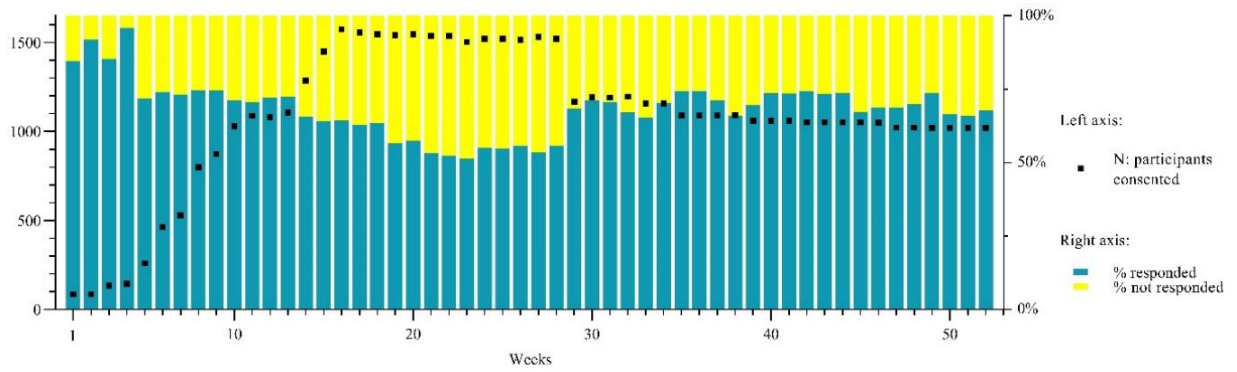

Left axis:

■ N: participants consented

Right axis:

■ % responded
■ % not responded

Table 1: Characteristics of participants referred to the ImmunoCOVID study

	Referred but not participating	Withdrawn participants	Currently active participants	COVID positive (subset)
Sample size	1373	505	1022	38
Female	53·8%	54·5%	55·1%	55·3%
Teenagers	64·4%***	55·6%	55%	68·4%
Age	11·9 + 4·3***	10·8 + 4·4	10·7 + 4·3	12·6 + 4·2**
UK geography	***	*		
South	9·9%	16·6%	21·4%	18·4%
Middle	44·0%	41·1%	42·1%	47·4%
North	46·1%	42·3%	36·5%	34·2%
Treatment team				
Rheumatology	42·8%	48·2%	48·7%	52·6%
Immunology	8·1%	10·4%	9·3%	13·2%
Respiratory	7·7%	6·3%	5·1%	5·3%
Oncology	5·3%	2·6%	4·3%	7·9%
Gastroenterology	7·5%	8·3%	9·7%	2·6%
Nephrology	11·7%	12%	10·7%	7·9%
Neurology	3·1%	3·9%	2·2%	0%
Haematology	3·7%	1·6%	2·3%	2·6%
Neonatology	0·3%	0·2%	0·2%	0%
Diabetes	7·3%	5·1%	5·3%	5·3%
Infection	2·0%	0·4%	0·4%	2·6%
Dermatology	0·5%	0·8%	0·9%	0%
Heart and Lung	0·1%	0·2%	0·6%	0%
Diagnosis				
Gastroenterology		10·7%	13·1%	0%*
Nephrology		11%	9%	10·8%
Transplants		7·4%	7·6%	13·5%
Diabetes		6·4%	6·5%	5·4%
Immunodeficiency		10·3%	8·7%	18·9%
Oncology		5·6%	7·7%	10·8%
Respiratory		7·2%	8·5%	8·1%
Other		29·1%	26·7%	29·7%
Juvenile Idiopathic Arthritis		37·4%	35·4%	40·5%
Other immune condition		15·5%	18·5%	16·2%
Medication				
Other drugs		49%	53·7%	58·8%
Chemotherapy		0·9%	0·8%	0%
Antibiotics		16·6%	16%	16·7%
Other immunosuppressants		16·7%*	21·6%	23·7%
Systemic corticosteroids		17·5%	19%	16·7%
Biologics		34·7%	35·1%	25%
Methotrexate		27·2%	29·3%	27·8%

Statistical significance is calculated with Chi-Square statistics. If one or more cells in the contingency table had an expected count of less than five the Fisher's exact statistic was calculated. Group differences in age were calculated with F test. * significant at 0·05 level; ** significant at 0·01 level; *** significant at 0·001 level

Table 2: Description of PCR positive SARS-CoV-2 infection reporting hospital admission

Week of PCR	Week of admission	Age in years	Sex	Admission Details	Past Medical History	Baseline Medication
42	42	17	Male	Admitted with negative PCR, symptoms of bowel obstruction and underwent laparotomy. Asymptomatically tested positive prior to discharge. Subsequently readmitted with fever and abdominal pain for three days before symptom resolution. Subsequent serology negative.	liver transplant, atypical haemolytic uraemic syndrome, chronic kidney disease, and superior vena cava stenosis	prednisolone, sirolimus, mycophenolate mofetil, hydralazine, doxazosin, amlodipine, losartan, atenolol, allopurinol, and desloratadine
42	44	12	Male	Initially tested positive with only symptom being abdominal pain. Subsequently admitted for two days with bacterial chest infection. Put down to post viral immunosuppression. Admission swab negative. Subsequent serology negative.	heart transplant	sirolimus, mycophenolate mofetil, pravastatin, and melatonin
43	52	17	Male	Tested positive, initially managed at home with antibiotics. Subsequently had persistent fever leading to investigation with bronchoscopy which showed changes consistent with SARS-CoV-2 infection. Five day admission for remdesivir giving symptom resolution.	X-linked agammaglobulinemia	human normal immunoglobulin
45	45	6	Male	Household tested positive two weeks prior but no test sought at time for participant. Admission with anaemia for two days with positive PCR swab. Received one unit of blood. Tests for leukaemia relapse negative.	acute lymphoblastic leukaemia, asthma, and autism	mercaptopurine, co-trimoxazole, gabapentin, fluticasone with salmeterol, montelukast, methotrexate, macrogol, and esomeprazole

Figure 2: Number of participant SARS-CoV-2 infections by week (16th March 2020 – 14th March 2021)
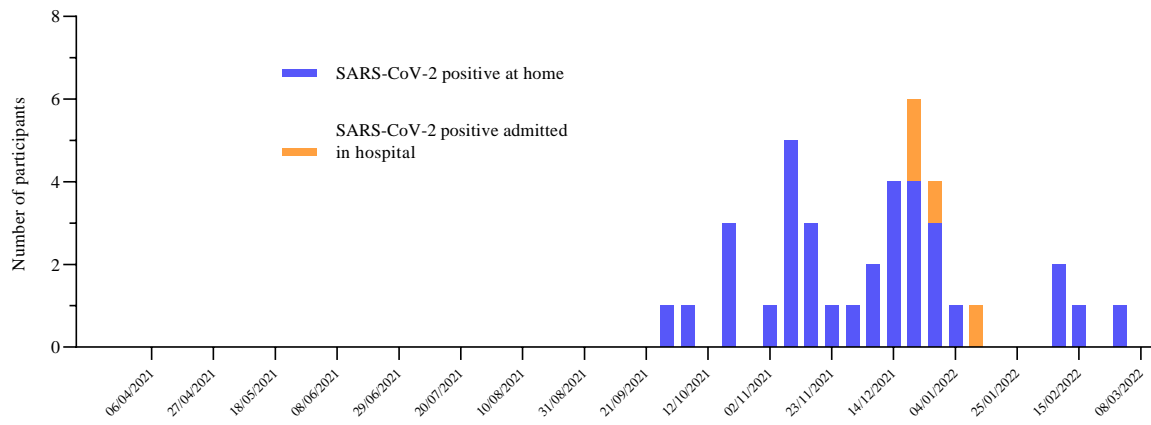
Table 3: Cox hazard estimates for SARS-CoV-2 infection (controlling for other immunosuppressant treatment)

Covariate	Coefficient	Standard error	P-value	Hazard Ratio	95% confidence interval HR
Age	0·13	0·05	0·006	1·14	1·04-1·25
Immune deficiency	1·05	0·45	0·02	2·87	1·18-6·94
Worsening of fever in week of infection	3·25	0·75	<0·0001	25·79	5·94-112·01
Worsening of cough in week of infection	2·42	0·69	0·0005	11·29	2·91-43·73
Worsening of sore throat in week of infection	2·00	0·69	0·0037	7·41	1·92 - 28·61

Table 4: Characteristics of participants participating in serology testing

		No serology	Serology	Positive serology	Negative serology
Sample size		1167	478	47	431
Female		53·6%	56·4%	68·1%	55·1%
Teenagers		52·7%	61·0%**	80·9%**	58·8%
Age		10·5 + 4·5	11·3 + 4·2***	13·5 + 3·7***	11·1 + 4·1
UK geography					
South		18·6%	22·5%*	23·4%	22·4%
Middle		41·3%	43·3%	59·6%*	41·5%
North		40·1%	34·2%*	17·0%*	36·1%
Diagnosis					
Gastroenterology		12·3%	12·5%	17·0%	12·0%
Nephrology		9·9%	7·6%	12·8%	7·0%
Transplants		7·3%	7·8%	17·0%*	6·8%
Diabetes		6·0%	8·7%*	8·5%	8·7%
Immunodeficiency		9·9%	7·2%	4·3%	7·5%
Oncology		6·9%	7·2%	6·4%	7·3%
Respiratory		8·0%	9·3%	6·4%	9·6%
Other		25·4%	30·0%	25·5%	30·5%
Juvenile Idiopathic Arthritis		35·9%	35·5%	38·3%	35·2%
Other immune condition		16·5%	19·0%	19·2%	19·0%
Medication					
Other drugs		45·2%	56·6%***	59·5%	56·3%
Chemotherapy		0·9%	0·9%	0%	1·0%
Antibiotics		15·2%	15·1%	11·4%	15·5%
Other immunosuppressants		17·6%	21·0%	31·9%*	19·8%
Systemic corticosteroids		16·6%	18·9%	27·3%	18·0%
Biologics		29·3%	40·9%***	43·2%	40·7%
Methotrexate		24·6%	32·1%**	22·7%	33·2%

Statistics significance is calculated with Chi-Square statistics. If one or more cells in the contingency table had an expected count of less than five the Fisher's exact statistic was calculated. Group differences in age were calculated with F test. * significant at 0·05 level; ** significant at 0·01 level; *** significant at 0·001 level

Table 5: Serology rates by vaccination status, sex, age group, and prior PCR status (only unvaccinated in the latter three tables)

Prior vaccination status	anti-N IgG positive	anti-S1 IgG positive	Both positive	Seronegative	Totals	Total seropositive (%)
Vaccinated	0	3	3	20	26	6 (23·1)
Non-vaccinated	21	7	13	411	452	41 (9·1)
Totals	21	10	16	431	478	47 (9·8)
Sex	anti-N IgG positive	anti-S1 IgG positive	Both positive	Seronegative	Totals	Total seropositive (%)
Female	15	4	10	223	252	29 (11·5)
Male	6	3	3	188	200	12 (6)
Totals	21	7	13	411	452	41 (9·1)
Age group	anti-N IgG positive	anti-S1 IgG positive	Both positive	Seronegative	Totals	Total seropositive (%)
0-5 years	0	0	0	26	26	0 (0)
6-10 years	5	0	2	125	132	7 (5·3)
11-15 years	7	2	5	167	181	14 (7·7)
16+ years	9	5	6	93	113	20 (17·7)
Totals	21	7	13	411	452	41 (9·1)
Prior PCR status	anti-N IgG positive	anti-S1 IgG positive	Both positive	Seronegative	Totals	Total seropositive (%)
PCR positive	4	1	4	9	18	9 (50·0)
PCR negative	17	6	9	402	434	32 (7·4)
Totals	21	7	13	411	452	41 (9·1)

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